DISSERTATION FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Pharmacovigilance study of anti-seizure medications among people living with epilepsy and the potential impact of complementary and alternative medicine regarding outcome

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List of abbreviations

95% CI = 95% confidence interval

ADRs = Adverse Drug Reactions

AE = Adverse Drug Effect

ASMs = Anti-Seizure Medications

ATC = Anatomical Therapeutic Chemical

BRV = Brivaracetam

BW = Body Weight

CAM = Complementary and Alternative medicine

CBZ = Carbamazepine

CLB = Clobazam

CNB = Cenobamate

CZP = Clonazepam

DM = Diabetes mellitus

EEA = European Economic Area

EMA = European Medicines Agency

ESL = Eslicarbazepine

ESM = Ethosuximide

EV = EudraVigilance

FBM = Felbamate

FEN = Fenfluramine

GBP = Gabapentin

HIC = High-Income Countries

ICSRs = Individual Case Safety Reports

ILAE = International League Against Epilepsy

LCM = Lacosamide

LEV = Levetiracetam

LMIC = Low- and Middle-Income Countries

LTG = Lamotrigine

MAHs = Marketing Authorization Holders

MedDRA = Medical Dictionary for Regulatory Activities

NCAs = National Competent Authorities

NCCAM = National Center for Complementary and Alternative Medicine

NIH = National Institutes of Health

ROR = reporting odds ratio

OXC = Oxcarbazepine

PB = Phenobarbital

PER = Perampanel

PGB = Pregabalin

PHT = Phenytoin

PRM = Primidone

PRR = Proportional Reporting Ratio

PTs = Preferred Terms

PV = Pharmacovigilance

PWE = patients with epilepsy

RTG = Retigabine

RUF = Rufinamide

sADRs = Suspected Adverse Drug Reactions

SOC = System Organ Classes

STP = Stiripentol

SUDEP = Sudden Unexpected Death in Epilepsy

SUL = Sultiame

T2DM = Type 2 Diabetes Mellitus

TCM = Traditional Chinese Medicine

TGB = Tiagabine

TPR = Topiramate

VGB = Vigabatrin

VPA = Valproic acid and Sodium Valproate

WHO = World Health Organization

ZNS = Zonisamide

1. Introduction

1.1. Epilepsy and anti-seizure medications

Epilepsy is a disease needing life-long treatment affecting millions of people. It is a challenge for people living with epilepsy (PWE), their relatives and epileptologists as well to acquire the best treatment in different life stages being aware of its morbidity and mortality (1). Numerous risk factors are known in association with the onset of epilepsy. Prevalence is different between male and female, higher among men. Also elderly people are commonly affected and some neurological disorders show higher frequency (stroke, neurodegenerative diseases and tumours) (1).

On the market, a lot of anti-seizure medications (ASMs) on different targets is accessible in the world. Nevertheless, the old ASMs are still necessary because of their mechanism of action, despite their adverse drug reactions (ADR) (2).

Regarding the trends in age-specific incidence over the last decades, it showed a decrease in the youngest age-groups. Nevertheless, it should not be forget that the morbidity and mortality of this age group improved enormously thanks to better perinatal care and better control of infectious diseases (3). There was an increase in the elderly possibly due to improved life expectancy accompanied by increased epileptogenic conditions such as stroke, tumours and neurodegenerative disorders (4). Epilepsy usually needs life-long treatment, even after epilepsy surgery. ASMs are important for most PWE.

ASMs can be classified as old and new types. Although many new type ASMs were made available, no considerable improvement in tolerability and efficacy had been proved (5). Still multiple traditional ones continued to be employed widely (2). However, this provided more therapeutic options (6), but still adverse drug reactions (ADRs), interactions and hypersensitivity reactions were not eliminated (7).

1.2. Pharmacovigilance and some related definitions

According to the World Health Organization (WHO), adverse drug effect (AE) can be defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (8). Adverse drug reactions (ADRs) contribute outstandingly to debilitation of health quality and treatment failure in PWE (9). Many efforts were exerted to quantify ASMs drug toxicity and lower their burden.

According to the WHO, pharmacovigilance (PV) can be defined as “the science and activities relating to the detection, assessment, understanding and prevention of the adverse effects of drugs or any other possible drug-related problems” (10). We have to face the increase the ADRs , therefore PV supports proper and safe use of drugs, through increasing reporting rates (11). VigiBase and EudraVigilance (EV) are good examples from the past decades for marked development in drug safety measurement with the advantage of large PV databases and offering automation of statistical methods and safety signal detection (12). The EV database was launched in 2001 and quickly became of paramount importance in the management of suspected ADRs (sADRs) reports and safety evaluation of authorized medicines in the European Economic Area (EEA) (13). Marketing authorisation holders (MAHs) and sponsors of clinical trials have obligations to report sADRs during phases of medicinal products development and after getting authorized in the EEA. EV supports electronic exchange of sADRs using Individual Case Safety Reports (ICSRs) between the European Medicines Agency (EMA), National Competent Authorities (NCAs), MAHs and sponsors of interventional clinical trials and non-interventional studies in the EEA. With the help of EV, early detection of possible safety signals, monitoring and evaluation of potential safety issues and decision making process in the frame of EU Risk Management Strategy became possible (14, 15).

1.3. Complementary and alternative medicine in epilepsy

According to the National Center for Complementary and Alternative Medicine (NCCAM) and National Institutes of Health (NIH), “complementary and alternative medicine or modalities (CAM)” was defined as health care approaches with a history of use or origins outside of mainstream medicine (16). Healthcare professionals have to be aware of increased CAM consumption in the last decades, so it should be taken in consideration. Among people living with chronic disease publication showed a significant rise in use of them (17). Patients usually turn to CAM in case of disappointment from conventional therapies, by the choice media, family and friends are the most important informants. Among the elderly, parallelly conventional treatment CAM is used often, including using herbal supplements. In the background, fear of ADRs caused by polypharmacy, ignoring physiological changes in old people in the choice of therapy, like altered organ functions that may lead to increased sensitivity to some medications (18). CAM therapy is thought to be safe among patients, and common misbelieve is that they are free from ADRs. In the publication of Bello et al, it has been shown unsafe, hidden CAM use increased the

risk of admission to intensive care unit (19). However, CAM therapy has its value and the place in the treatment for example conventional therapy is not effective enough or when therapy escalation is not possible or no other therapeutic options could be given for severely ill patients (20).

CAM therapies can alter the drug metabolism and drug disposition leading to ADRs ineffectiveness and may have toxic consequence. CAM may have unfavourable interactions with antidiabetics. Herbals, as an example of CAM, can affect clinical safety and efficacy via additive/synergistic or antagonistic interactions among the herbal components and drug molecules. Whilst negative or harmful interactions tend to receive more attention due to safety considerations, additive/synergistic effects induced by herbal drug interactions may result in an enhancement of desired pharmacological effects (21).

For example, the antagonistic interactions of *Gymnema sylvestre* was studies in a chemically-induced diabetic rat model, taking metformin. As a consequence, the metformin concentration in the plasma decreased, parallelly blood glucose level increased by rats given both agents. (22).

In western-based medical system applying countries, CAM is utilized by PWE as a preventive tool in seizures, or to mitigate the ADRs or because of the treatment of comorbidities, beside maintaining good general health (23). The most frequently taken products, e.g. St. John's wort, have not been reported to have either beneficial or detrimental effects on seizures, however their activity on the P450 system can lead to interactions with ASMs metabolised by the liver. Moreover, melatonin and kava kava were also associated with the aggravation of epilepsy. Ephedra and caffeine have been linked to proconvulsive effects. Some infrequently used products have shown beneficial effects on seizures, epilepsy comorbidities or complications of epilepsy including skullcap, grapefruit juice, hops and omega-3 fatty acids. Other countries have widely practiced forms of traditional medicine, among which Ayurveda and traditional Chinese medicine (TCM) are the best known. In Ayurveda, epileptic patients are prescribed mixtures of natural products, containing herbal extracts (like *Acacia arabica*, Acoruscalamus, Bacoppamonnieri), as well as animal ghee, honey and milk. Likewise, TCM involves mixtures of different herbal extracts (each containing many active compounds), either to treat the seizure disorder directly or to maintain the general wellbeing of a patient.

In many instances, herbal drugs are used simultaneously with modern drugs. Generally, all drugs with a narrow therapeutic index may either have increased adverse effects or be less effective when used in conjunction with herbal products (24). The interactions between the herbal remedies and

active pharmaceutical ingredients can be additive/synergistic or antagonistic altering the efficacy and clinical safety (21).

2. Aims of the study

Our study had two main foci.

I. Firstly, we conducted a pharmacovigilance study to examine ADRs reported in ASMs in EudraVigilance (EV) database. This gave us an opportunity to compare old and new ASMs and outcomes covering a ten-year period. Our aim was also to investigate the seriousness of reported preferred terms (PT) and their System Organ Classes (SOC) of sADRs. Furthermore, we aimed to find the possible associations between ASMs and occurrences of sudden unexpected death in epilepsy (SUDEP).

II. Secondly, we studied CAM in PWE with a self-developed questionnaire. Since CAM therapy has not been mapped in our region, our intention was to have an insight on it. Therefore, our aim was to determine the prevalence of CAM use; to identify factors that may lead to CAM use; and to measure the outcome and adherence in order to improve care.

3. Literature review

3.1. Definition of epilepsy

Epileptic seizure can be defined as: “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (25). It is a disorder of the brain which is identified by predisposition towards epileptic seizures generation (26). Earlier, it was defined as at least two unprovoked seizures with more than twenty-four hours apart. Later, this definition got modified practically to even after only one unprovoked seizure in individuals having other factors that can contribute to persistently reduced seizure threshold leading to higher recurrence risk. In 2014, the term ‘disease’ was found preferable in definition of epilepsy rather than ‘disorder’ to emphasize its importance and impact.

3.2. Epidemiology of epilepsy

Epilepsy is a stigmatizing disease affecting millions of both sexes and all age groups in the world. In terms of its epidemiology, its morbidity and mortality are noteworthy. It shows slightly higher prevalence and incidence in men. Higher frequency of stroke, neurodegenerative diseases and tumours among elderly are the most common underlaying pathophysiology of epilepsy (1). Focal seizures tend to more common in both children and adults if compared to the generalized ones. There is higher incidence and prevalence in low- and middle-income countries (LMIC) where about 80% of the affected patients live, which can be justified by more abundance of risk factors like head trauma, CNS infections and perinatal injuries in these regions (27). Despite being a treatable disease, more than 75% of patients in poor regions of the world are not treated (28). The pooled incidence rate of epilepsy was 61.4 per 100,000 person-years (95% CI 50.7–74.4) according to a systematic review and meta-analysis of incidence studies (29), while the overall lifetime prevalence of epilepsy was 7.60 per 1,000 population (95% CI 6.17–9.38). Looking over the trends in age-specific incidence over the last decades, it showed a decrease in the youngest age-groups due to improvements in perinatal care, better sanitation, and increased control of infectious diseases (3), whereas it increased in the elderly possibly due to improved life expectancy accompanied by increased epileptogenic conditions such as stroke, tumours and neurodegenerative disorders. In high-income countries (HIC), standardized mortality ratio was found to range from 1.6 to 3.0 (10); whilst in LMIC, it was found to be 19.8 (95% CI 9.7–45.1) (30).

3.3. Pathophysiology of epilepsy

Over several decades, there has been excessive effort dedicated for understanding pathophysiological mechanisms of epilepsy. Epileptic seizures emerge from an excessively synchronous and sustained discharge of a group of neurons (31), where persistent rise in neuronal excitability is the common feature of all epileptic syndromes. Various causative factors like trauma, oxygen deprivation, tumours, infection, and metabolic derangements may be associated with abnormal cellular discharges. Disorders of neuronal migration are the major developmental disorders that can provoke epilepsy. These abnormal patterns of neuronal migration produce varied forms of agyria or pachygyria; whereas milder failure degrees of neuronal migration can prompt neuronal heterotopia in the subcortical white matter. Such cortical malformations can elicit epileptogenic foci and alter brain development diffusing hyperexcitability of the cortical networks (32). Examples for disorders are tuberous sclerosis, periventricular heterotopia and double cortex syndrome. Almost 40% of PWE have a contributing genetic background (33); for instance, most familial epilepsies like juvenile myoclonic epilepsy and childhood absence epilepsy have a fx inheritance mode that involves interaction of many loci together with environmental factors (34). Many studies using experimental models and even in clinical settings featured the possible contribution of inflammatory processes in the brain to the etiopathogenesis of seizures and chronic epileptic focus precipitation (35). Overexpression of prototypical inflammatory cytokines like IL-1b, TNF-a and IL-6 were found in brain areas of seizure generation and propagation by glia and neurons. These cytokines mediated changes can be justified by functional interactions between cytokines and classical neurotransmitters like glutamate and GABA. There are many theories for interictal-ictal transition; which can be either non-synaptic mechanisms like alteration in the ionic microenvironment, decrease in size of extracellular space or failure of ion transport; or synaptic mechanisms like depression of GABAergic inhibition or NMDA receptor activation.

3.4. Risk factors and prevention of epilepsy

There are dozens of risk factors which are significantly associated with onset of epilepsy (36). Irreconcilable levels of evidence for risk of onset included family history of epilepsy, history of febrile seizures, alcohol consumption, CNS and other infections, brain trauma, head injury, perinatal stroke, preterm birth and three genetic markers. A decreased odds of seizure emission was found with little evidence in symptomatic epilepsy, focal seizures/syndromes, slow waves on EEG, higher seizure frequency, high stress or anxiety, and lack of sleep. SUDEP has higher

incidence in patients with chronic epilepsy and in particular among those with refractory seizures (37); moreover, many studies investigated the potential association between certain ASMs and polytherapy with increased SUDEP. Modifiable risk factors that are linked to childhood or adult onset epilepsy, such as alcohol consumption, acquired brain injuries or CNS infections can be the target of prevention efforts and strategies.

3.5. Diagnosis of epilepsy and classification of seizures

Having an epileptic seizure together with brain demonstration of pathologic and enduring tendency to have recurrent seizures can mean that epilepsy exists (26). More specific diagnostic criteria of epilepsy include having at least two unprovoked or reflex seizures with more than twenty-four hours apart; or one unprovoked or reflex seizure with probability of having another seizure similar to the general recurrence risk after two unprovoked seizures (≥60%) over the next 10 years; or an epilepsy syndrome. Epileptiform activity on EEG or a potential epileptogenic abnormality on brain imaging are examples of evidence that can increase the probability of additional seizure occurrence. Epilepsy resolution is defined by either exceeding certain age in a patient with an age-dependent epilepsy syndrome; or being seizure free for ten or more years and having stopped all anti-seizure medications for 5 or more years. Based on onset, seizures can be classified to focal which is synonymous with partial, generalized (both hemispheres are activated potentially asymmetrically at onset of the seizure according to behaviour and EEG), unknown, or unclassifiable (38). The level of awareness and defining the onset as either motor or non-motor are taken into consideration in the basic classification of focal seizures. The term “focal to bilateral tonic-clonic seizures” is used to describe secondarily generalized seizures to differentiate it from seizures of generalized onset. Awareness is impaired in most generalized seizures; accordingly, it is omitted while classifying them. In contrast, designation of “motor” or “non-motor (absence)” is applied in generalized seizures. Furthermore, both generalized motor seizures and unknown onset seizures can be classified to “tonic-clonic” or “other motor”.

3.6. Complications of epilepsy

Many complications are known to occur in PWE. Like other brain conditions, epilepsy is associated with many psychiatric illnesses which is sometimes associated with brain activity associated with abnormal seizures, such as the ictus itself, or during postictal mental state changes, or at other times they can be so closely intertwined with to the extent that it may be not possible

to separate their aetiologies (4). Examples for ictal psychiatric disturbances are ictal mood changes, anxiety, depression, psychosis, violence and aggression for which adequate seizure control together with ASMs or surgical procedures are focus of therapy. Periictal psychiatric disturbances can be classified to either postictal (like postictal delirium, psychosis and mania) or preictal disturbances (like increased irritability, depression or psychosis). Maintaining patient safety is the main focus in immediate management of periictal psychiatric disturbances especially when agitated or destructive behaviour exists. Interictal psychiatric disorders include interictal mood disorders, major depression, bipolar disorders, anxiety disorders and others. It is widely accepted to resort to surgery in case of drug-resistant focal epilepsy. Epilepsy surgery, either definitive resective procedure for removal of the epileptogenic focus or invasive monitoring for localization of the epilepsy focus, can cause variety of medical and neurologic complications like CSF leak, intracranial hematomas, aseptic meningitis, bacterial infection and others (39). The majority of these complications lead to only temporary impairment and resolve over time.

3.7. Available ASMs

Despite of many new ASMs developed, well-functioning old ASMs with different mechanisms of actions are prescribed such as phenytoin (PHT), ethosuximide (ESM), carbamazepine (CBZ), valproate (VPA) and certain benzodiazepines (2). Phenobarbitone (PB) acts by prolonging the opening of post-synaptic cell membrane chloride ion channels within GABA-A receptors causing the neuronal cell membrane to be hyperpolarized. PHT's chemical structure is related to barbiturates and its main mechanism of action is likely to be blocking frequency and use of voltage dependent neuronal sodium channels, accordingly limiting the repetitive firing of action potentials. ESM is a succinimide derivative that blocks thalamic T-type calcium channels which is a mutual effect in drugs effective against absence seizures. CBZ, which blocks voltage dependent sodium ion channels in cell membranes, was introduced in the early 1960s for trigeminal neuralgia and later it became the first choice in focal epilepsies. Sodium VPA has a complex mechanism of action involving elevation of brain GABAergic inhibitory activity, decreasing cortical excitability, affecting various brain receptors and blocking sodium channels which limits the high-frequency repetitive firing of sodium dependent action potentials. Benzodiazepines bind specifically to GABA-A receptors leading to increased frequency of chloride channels opening which increases inhibitory neurotransmission. There are multiple benzodiazepines that are used mainly in particular situations like diazepam and clonazepam (CZP) in status epilepticus, clobazam (CBZ)

in contingency situations and nitrazepam in some paediatric syndromes. In spite of being widely used as ASMs, older generation ASMs suffer from many influential weakness points like being highly variable, having nonlinear pharmacokinetics, having narrow therapeutic index, suboptimal response rates and tendency to cause significant adverse effects and drug interactions (40). Many new ASMs were produced and became used mainly as adjunctive therapy in the epilepsy treatment for those who are refractory to older ones or even as first line in certain subgroups of patients due to being more tolerable or more easily used. Some of these new ASMs are advantageous in terms of having less variable kinetics and lower interaction potentials like gabapentin (GBP), levetiracetam (LEV) and vigabatrin (VGB). Many of these ASMs are protective against generalized seizure types like lamotrigine (LTG), topiramate (TPM), zonisamide (ZNS) and felbamate (FBM); while others are used in partial epilepsy like VGB, tiagabine (TGB) and GBP. They work by various mechanisms of actions like blockage of voltage dependent sodium channels, GABA transmission potentiation and calcium channels blockade. In terms of the mechanism of action, many of them are similar to the old ones but fundamentally new mechanism of action was discovered. These ASMs, LEV and brivaracetam (BRV) block a synaptic vesicle protein (SV2A).

3.8. General idea about complementary and alternative medicines

Based on NCCAM and NIH definition of CAM (16), more than 1800 CAM therapies are used in both developing and developed countries which can have benefits and risks. Due to their risk, it must be highlighted the role of healthcare providers having a basic understanding of CAM. According to national health statistics report in the USA, it is important to think about the costs of using CAM, for instance, adults with a history of use or origins outside of mainstream medicine spent on such health care methods other than traditional medicine with two-thirds of that amount spent on self-care purchases and one-third on specialist visits (41). NCCAM classified CAM therapies to two main sub groups of natural products and mind-and-body practice, that can be more classified into another five categories of biologically based therapies, mind-body therapies, manipulative and body-based therapies, energy therapies, and systems of care. Biologically based therapies are substances typically found in nature like herbs and essential oils, special diets (e.g., Ayurveda, hot-cold balance), nutritional and food supplements, and other products such as cartilage. Mind-body therapies are interventions that use a variety of techniques to enhance the mind's ability to affect body functions and symptoms and include guided imagery, visualization, progressive muscle relaxation, meditation, prayer, music therapy, light therapy, art therapy,

journaling, story-telling, biofeedback, hypnosis, humour, animal-assisted therapy, t'ai chi, qigong, and yoga. Manipulative and body-based therapies are therapies that apply pressure to, manipulate, or move one or more body parts like chiropractic medicine, osteopathic manipulative medicine, movement therapy, massage, and other body work, such as rolfing. Electromagnetic and biofield energies that are thought to originate in or near the body and on energy from other sources are employed in various energy therapies like healing touch, therapeutic touch, Reiki, acupuncture or acupressure. Other practices exist that do not fit into the previous categories and have evolved from cultural and spiritual traditions earlier than conventional western medicine like Ayurvedic medicine, traditional Chinese medicine, folk medicine, homeopathy, and naturopathy.

3.9. General factors contributing to CAM use

The use and interest in CAM increased over the previous years, which emphasizes the importance of considering various factors contributing to these. Studies showed special increase in CAM use among chronic diseases patients (42). Intention to take as few drugs as possible can be considered as main motivation for CAM use besides the doctor's advice and dissatisfactory results from conventional therapies. Media, family and friends are the main information source for CAM. Elderly persons showed increasing CAM use, including using herbal supplements concomitantly with conventional medications, this can be understood due to various concerns to the elderly like polypharmacy, decreased organ functions and increased sensitivity to some medications (18). Patients who may think that these therapies are safe and those who have limited understanding of the potential adverse effects tend to use CAM more than others which expose them to increased risk for admission to an intensive care unit (19). CAM therapies may be considered to enhance the comfort of life-threatening illness patients when conventional care turns to be unsuccessful or in the case that therapy escalation is deemed to be too risky or no longer beneficial (20).

3.10. CAM use in epilepsy

CAM is utilized by PWE for different purposes. Hungary from the point of view conservative or alternative medicine favouring regions falls into the western based medical system with conservative dominance. So, CAM is used in PWE as a preventive tool in seizures, or to mitigate the ADRs or because of the treatment of comorbidities, beside maintaining good general health (23). According to the literature, the most frequently taken products were ginseng, *Ginkgo biloba*, St. John's wort, echinacea, garlic and soy. Despite these herbs are metabolized in the liver on P450

system resulting unfavourable interactions with ASMs beneficial effects on seizures is missing. Although melatonin, kava kava and valerian cause sleep induction and have anticonvulsant effects according to some reports, but also it was associated with worsening of epileptic symptoms. Beneficial effects on seizures, epilepsy comorbidities or complications of epilepsy were detected in case of skullcap, grapefruit juice, hops and omega-3 fatty acids. Ephedra and caffeine have been linked to proconvulsive effects. In countries where CAM is widespread alongside with different forms of traditional medicine, such as Ayurveda and traditional Chinese medicine (TCM). These are also used by PWE. Ayurveda offers a complex treatment for PWE: mixtures of natural products, containing herbal extracts (like *Acacia arabica*, *Acorus calamus*, *Bacoppa monnieri*), animal ghee, honey and milk. Similarly, PWE choosing TCM will have mixtures of different herbal extracts prescribed (each containing many active compounds), in order to handle the seizure and to maintain the general wellbeing of patient.

3.11. Interactions between CAM and ASMs

The most common interactions between CAM and ASMs will results in modifications such as intrinsic proconvulsant properties, effects on the cytochrome P450 enzymes and P-glycoproteins or changing disposition of ASMs (43). These interactions are hardly predicted, what is more dangerous is that PWE do not report it because they do not consider CAM as a medicine. Many herbs can be associated with induced seizures like toxic effects of wormwood (*Artemesia absinthium*), besides, seizures can result from contamination of the herbal preparations with lead and other heavy metals. Many herbal remedies on market can themselves contain antiepileptic drugs misleadingly (actually as a falsified medicine), which can lead to toxic levels when they are taken concomitantly with other ASMs. Many herbs were reported to contain neurotoxic components that can provoke seizures like Ephedra, *Ginkgo biloba*, star anise and wormwood. Other herbs can alter ASMs disposition, for instance, *Ginkgo biloba* induces CYP2C19, leading to reduced serum levels of PHT and VPA, on the other hand, Saint John's wort (*Hypericum perforatum*) induces CYP enzymes together with induction of P-glycoproteins. Another good example of herbals that later ASMs disposition is Sho-seiryu-to/sho saiko -to that was found to delay gastric emptying in rats which caused increased CBZ levels.

4. Methods

4.1. PV study of ASMs

4.1.1. Data source of adverse drug reactions

EV system was mined to obtain information about sADRs which is based on ICSRs. According to 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 (44-46). Results were exported in the form of Line listings results of reported sADRs with different ASMs (which were considered at the level of chemical structure or active pharmaceutical ingredient) during the period from January 2012 to December 2021 which were extracted in a tabulated format useful for further analyses.

4.1.2. Adverse drug reactions

The SOCs of individual reported preferred terms (PTs) for each sADR were determined using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.

Seriousness is classified into many criteria as per the EV: *'other medically important condition'*, *'caused/prolonged hospitalisation'*, *'congenital anomaly'*, *'disabling'*, *'life threatening'*, and *'results in death'*; whereas *'fatal'*, *'not recovered/not resolved'*, *'recovered/resolved'*, *'recovered/resolved with sequelae'*, and *'recovering/resolving' are the classifications of the outcome* (15).

4.1.3. Antiseizure medications

The Anatomical Therapeutic Chemical (ATC) classification system N03A subgroups was used to obtain list of ASMs (also known as antiepileptics) (47). Aggregate analysis considered Chemical grouping of ATC.

The term established or old was commonly used previously, however currently, both new ASMs and old ones could be included in established ASMs. Thus, there can be a difference regarding this among countries, so we decided to name the groups old and new ASMs. Old ASMs are those introduced to the market before 1990 and fall into the categories of first and second generation ASMs. Both old and new types of ASMs were considered, with their common abbreviations provided in parentheses as follows:

a.) Old types:

Phenobarbital (PB), Barbexaclone, Metharbital, Methylphenobarbital, Primidone (PRM), Clonazepam (CZP), Clorazepate potassium, Carbamazepine (CBZ), Aminobutyric acid, Valproic acid and Sodium Valproate (VPA), Ethotoin, Mephenytoin, Phenytoin (PHT), Beclamide, Phenacemide, Pheneturide, Sultiame (SUL), Paramethadione, Trimethadione, Ethosuximide (ESM), Mesuximide, Phensuximide.

b.) New types:

Clobazam (CLB), Eslicarbazepine (ESL), Oxcarbazepine (OXC), Rufinamide (RUF), Tiagabine (TGB), Vigabatrin (VGB), Fosphenytoin, Brivaracetam (BRV), Cenobamate (CNB), Felbamate (FBM), Fenfluramine (FEN), Gabapentin (GBP), Lacosamide (LCM), Lamotrigine (LTG), Levetiracetam (LEV), Perampanel (PER), Pregabalin (PGB), Retigabine (RTG), Stiripentol (STP), Topiramate (TPR), Zonisamide (ZNS).

4.1.4. Statistical analysis

Data was organized and analysed using Microsoft Office Excel 2019 and SPSS for Windows 21.0 (SPSS Inc., Chicago, USA). To analyse outcomes and seriousness, the following metrics were calculated for various ASMs: Reporting odds ratio (ROR) with its 95% confidence interval (95%CI), proportional reporting ratio (PRR), p-value and chi-square statistic. Significant differences were considered if $p<0.05$.

The number of reported sADRs was pooled into 2 by 2 contingency tables, correlating specific ASMs or ASM pharmacological groups with other ASMs or ASM pharmacological groups, to various outcomes, seriousness criteria, and SUDEP. This was done to calculate ROR, PRR, and chi-square values.

ROR allows for the estimation of relative risk and helps eliminate biases in pharmacovigilance (48).

According to the EMA, a signal of disproportionate reporting can indicate an association between a drug-event pair in the database. This signal can be generated from spontaneous adverse drug reaction reporting systems based on the following criteria (15).

Meeting the following criteria for generating a signal according to EudraVigilance (49):

a) When the PRR is displayed with its 95% confidence interval:

- the lower bound of the 95% confidence interval is greater than or equal to one
- the number of individual cases is greater than or equal to three

b) When the PRR is displayed with $\chi 2$ statistic:

- the PRR > 2
- $\chi 2 > 4$
- the number of individual cases is greater than or equal to three.

PRR serves as a direct measure of signal strength and can assess unexpectedness relative to the background of the entire database. Further insights provided by ROR over PRR can aid in evaluating the associations between drugs and adverse drug reactions (ADRs).(50).

4.2. Questionnaire based study on the use of CAM

4.2.1. Patients

Two self-developed questionnaires, comprising both open-ended and closed-ended questions, were employed to explore the utilization of CAM and its outcomes among 127 adult patients with epilepsy and 100 patients with diabetes mellitus. In both groups, patients had been diagnosed at least one year prior to filling the questionnaire. Patients with epilepsy were previously diagnosed at the Department of Neurology by two senior epileptologists (IF and KF) and were receiving regular check-ups at a tertiary university hospital. Patients with diabetes mellitus were treated at the Departments of Cardiology and Neurology and had already experienced vascular consequences such as stroke or myocardial infarction due to the disease. Consequently, they were admitted to a tertiary university hospital where they underwent percutaneous coronary intervention (angioplasty with stent or thrombolysis). Like epilepsy, diabetes mellitus may require lifelong treatment and attention from family and healthcare providers throughout various stages of life. However, diabetes mellitus is generally more socially accepted and lacks the stigma associated with epilepsy. This distinction is why this population was chosen for comparison.

The following inclusion criteria were applied to both groups: a) Only adult patients were included in this study, b) Patients had to willingly participate on a voluntary basis.

In the epilepsy group, inclusion criteria were as follows: patient was diagnosed with epilepsy according to ILAE classification (26) and participated in regular check-ups prior to being involved in the survey.
In the diabetes mellitus group, the inclusion criteria were: patients with a primary diagnosis of diabetes mellitus and subsequent vascular consequences; and during the study period: the patient was hospitalized to treat a vascular event.
The exclusion criteria were: a) dependent patient, b) Patients with serious medical condition, c) Patients with other major comorbidities.

We compared PWE to DM patients due the potential association between both diseases, comparing patients' adherence to their prescribed medications, CAM use and the impact on patients' satisfaction.

4.2.2. Questionnaire

Patients filled the questionnaire anonymously and voluntarily between December 2018 and September 2019. It included questions about patients' demographics, lifestyle activities, seizure freedom, prescribed ASMs, adherence, satisfaction, reported adverse effects, CAM therapy and quality of life. A patient was classified as a "smoker" if he smoked actively, a "non-smoker" if he had never smoked, and "stopped smoking" if he had quitted smoking at least one year prior to filling the questionnaire. The self-developed questionnaire for DM-sufferers included some questions that were identical to those used in the other study on PWE. Additionally, specific questions for patients with diabetes mellitus addressed topics such as: diabetic diet, owning a glucometer at home, frequency of measuring blood glucose levels, family history of DM, last measured fasting blood glucose, last measured HbA1c%, prescribed antidiabetics, adherence and general satisfaction with therapy.
Both surveys mentioned were developed through collaborative efforts among the authors. They underwent review and discussion by numerous clinicians and experts to ensure face validity.

Data was entered in a database for further evaluation. With the aim to minimize the error risk, data was initially entered into spreadsheet, later two people collaborated in reviewing the merged database.

4.2.3. Outcome

For patients living with epilepsy, achieving a "controlled disease" outcome was defined as declaring themselves seizure-free. For patients with diabetes mellitus, a "controlled disease" outcome was considered if their fasting glucose level was <7.0 mmol/L and/or their HbA1c level was <6.5%.

Adherence to prescribed medication was classified into three categories:

1 – good (if patients had taken at least 90% of their prescribed medicines or maximum three days of drug holiday a month),

2 – less often (if they had taken at least 50-90% of their prescribed medicines) and

3 – poor (if they had taken at least <50% of their prescribed medicines).

Physical activity was defined as any activity that lasted at least 30 minutes per day. The five-point Likert scale was used to measure a patient's overall quality of life, where one meant well-being.

4.2.4. Statistics

Statistical analysis was conducted using the SPSS for Windows 19.0 (SPSS Inc. Chicago, USA) and Microsoft Office Excel 2016. Two-sample T test, and F test were used to analyse the patients'. For categorical variables, analysis was conducted using Pearson's χ^2 test and Fisher's exact test. As per standard pharmacovigilance practices, the values of the reporting odds ratio (ROR) were computed using 2x2 contingency table. Significant differences were considered if $p<0.05$.

5. Results

5.1. Pharmacovigilance study of ASMs

5.1.1. Reports overview

A total of 276,694 reports were in the exported line listings from January 2012 to December 2021, encompassing 1,051,142 individual sADRs reported as PTs. On the whole, the EV database held a total of 22,301,140 sADRs reports by 31st of December 2021 (51), so our exported ASMs line listings constituted 1.24%. Regarding sex distribution in the reports, 106,834 (38.61%) of the reports were from males, whereas 148,957 (53.83%) were from females and sex had not been specified in the remaining reports (20,903, 7.56%). The majority of the reports belonged to the age group between 18 and 64 years old, followed by those aged more than 65 years old group, though two years old children or under had the lowest percentage (Table 1). Of all the reports, 199,956 (72.27%) had healthcare professional as reporter. There were fewer reports from countries within the European Economic Area (EEA) compared to non-EEA countries (99,243 [35.87%] vs 177,271 [64.07%]). Looking at ASM groups based on the ATC classification system, the group of other antiepileptics constituted the vast majority of the reports (167,065, 60.38%), followed by fatty acid derivatives and carboxamides (41,733 [15.08%] and 32,295[11.67%] respectively). The five ASMs with the highest numbers of sADRs reported were PGB (57,497, 20.78%), VPA (35,235, 12.73%), LEV (29,146, 10.53%), CBZ (23,294, 8.42%) and LTG (22,835, 8.25%). Detailed information is listed in Table 1. There were more reports of new ASMs than old ones (Table 2) especially for women, which was statistically significant χ^2 (2, N = 1051144) = 11356.9014, $p < 0.00001$. The average number of PT (number of PTs / numbers of ASMs) for old and new ASMs were found to be 16,202.7 vs. 33,924.1, respectively. If we consider the average PTs per reports, it was found to be 3.72 for newer ASMs and 3.96 for old ASMs.

Table 1 Reports overview of antiseizure medications in EudraVigilance database between 2012-2021

	Number of reports in EudraVigilance (%)
Total number of reports	276,694 (100)
Age groups	
0-2 years	8,977 (3.24)
3-17 years	24,789 (8.96)
18-64 years	131,984 (47.7)
>64	50,291 (18.18)
Not specified	60,653 (21.92)
ASMs (approval in the EU/USA)	
Barbiturates	5,569 (2.01)
Phenobarbital (1912/1912)	4,607 (1.67)
Barbexaclone (1983/1983)	24 (0.01)
Metharbital (1952/1952)	1 (0)
Methylphenobarbital (1932/1932)	172 (0.06)
Primidone (1960/1954)	765 (0.28)
Benzodiazepines	18,931 (6.84)
Clobazam (1975/2011)	4,245 (1.53)
Clonazepam (1968/1976)	14,679 (5.31)
Clorazepate potassium (1972/1972)	7 (0)
Carboxamides	32,295 (11.67)
Carbamazepine (1965/1968)	23,294 (8.42)
Eslicarbazepine (2010/2013)	1,980 (0.72)
Oxcarbazepine (1990/2000)	6,678 (2.41)
Rufinamide (2007/2009)	343 (0.12)
Fatty Acid derivatives	41,733 (15.08)
Aminobutyric acid (undetermined)	19 (0.01)
Tiagabine (1996/1990)	308 (0.11)
Valproic acid and Sodium Valproate (1970/1978)	35,235 (12.73)
Vigabatrin (1989/2009)	6,171 (2.23)
Hydantoins	10,467 (3.78)
Ethotoin (1957/1957)	4 (0)
Fosphenytoin (1998/1996)	713 (0.26)
Mephenytoin (1947/1947)	11 (0)
Phenytoin (1939/1953)	9,739 (3.52)
Other Antiepileptics	167,065 (60.38)
Beclamide (undetermined/1952)	2 (0)
Brivaracetam (2016/2015)	2,944 (1.06)
Cannabidiol (2019/2018)	4,722 (1.71)
Cenobamate (2019/2019)	389 (0.14)
Felbamate (1994/1993)	189 (0.07)
Fenfluramine (2020/2020)	309 (0.11)
Gabapentin (1994/1994)	19,369 (7)
Lacosamide (2008/2009)	10,542 (3.81)
Lamotrigine (1991/1994)	22,835 (8.25)
Levetiracetam (2000/1999)	29,146 (10.53)
Perampanel (2012/2012)	2,413 (0.87)
Phenacemide (1951/1951)	2 (0)
Pheneturide (1951/1951)	2 (0)
Pregabalin (2005/2005)	57,497 (20.78)
Retigabine (2011/2011)	463 (0.17)
Stiripentol (2007/2018)	614 (0.22)
Sultiame (1960/ not approved)	170 (0.06)
Topiramate (1995/1996)	13,214 (4.78)
Zonisamide (2007/2000)	2243 (0.81)
Oxazolidines	10 (0)
Paramethadione (1949/1949)	1 (0)
Trimethadione (1946/1946)	9 (0)
Succinimides	624 (0.23)
Ethosuximide (1958/1960)	580 (0.21)
Mesuximide (1957/1957)	43 (0.02)
Phensuximide (1953/1953)	1 (0)

Table 2 Number of suspected adverse drug reactions of old and new antiseizure medications by sex and year reported

	Number of sADRs (in % of total sADRs)	
	Old ASMs (%)	***New ASMs (%)***
Total	372,660 (35.45)	678,482 (64.55)
Sex		
Male	162330 (15.44)	228844 (21.77)
Female	188410 (17.92)	415526 (39.53)
Not Specified	21922 (2.09)	34112 (3.25)
Year		
2012	27489 (2.62)	59165 (5.63)
2013	36095 (3.43)	56517 (5.38)
2014	37793 (3.6)	56487 (5.37)
2015	31134 (2.96)	58445 (5.56)
2016	27089 (2.58)	55144 (5.25)
2017	46758 (4.45)	73937 (7.03)
2018	29981 (2.85)	65693 (6.25)
2019	40368 (3.84)	79795 (7.59)
2020	42226 (4.02)	76339 (7.26)
2021	53729 (5.11)	96960 (9.22)

sADRs: suspected adverse drug reactions; ASM: antiseizure medications

5.1.2. Reported PTs

The ten most frequently reported PTs were seizure (36,694, 3.49%), drug ineffective (25,873, 2.46%), somnolence (13,903, 1.32%), dizziness (13,562, 1.29%), off label use (11,953, 1.14%), rash (10,877, 1.03%), pain (10,327, 0.98%), fatigue (10,021, 0.95%), toxicity to various agents (9,773, 0.93%) and drug interaction (9,726, 0.93%). In males, the ten most frequently reported PTs were seizure (14,602, 1.39%), drug ineffective (9,106, 0.87%), somnolence (5,117, 0.49%), off label use (4,585, 0.44%), dizziness (4,033, 0.38%), drug interaction (4,006, 0.38%), rash (3,685, 0.35%), epilepsy (3635, 0.35%), toxicity to various agents (3,457, 0.33%) and pyrexia (3,211, 0.31%). In females, the ten most frequently reported PTs were seizure (16,168, 1.54%), drug ineffective (13459, 1.28%), dizziness (8,239, 0.78%), somnolence (7534, 0.72%), pain (6,793, 0.65%), off label use (6,255, 0.60%), rash (6,078, 0.58%), fatigue (5,968, 0.57%), nausea (5,918, 0.56%) and headache (5,765, 0.55%).

The reported PTs for the different SOCs between 2012 and 2021 are presented (Figure 1). Looking at the total number of reported PTs, the highest was recorded in 2021 (150,689 [14.34%]), followed

by 2017, 2019 and 2020 (120,695 [11.48%], 120,163 [11.43%] and 118,564 [11.28%] respectively). In 2016, the lowest number of total reported PTs was recorded (82,232, 7.82%). Similarly, both males and females had the highest number of reported PTs in 2021 (55,245 [5.26%] and 89,625 [8.53%] respectively). In all years, the most frequently reported sADRs belonged to four SOCs: *'nervous system disorders'* (20,2420, 19.26%), *'general disorders and administration site conditions'* (151,240, 14.39%), *'psychiatric disorders'* (118,635, 11.29%) and *'injury, poisoning and procedural complications'* (102,953, 9.79%) (Table 3 and Figure 2), however, the SOC of endocrine disorders had the lowest number of PTs in all years, except for 2012 and 2013, when the SOC of product issues had the lowest frequency. Figure 3 depicts the proportions of SOCs in different ASMs. In a similar way, in both males and females, the highest number of PTs belonged to the SOC of *'nervous system disorders'*, followed by the SOC of *'general disorders and administration site conditions'*. Comparing the old and new ASMs pronounced unfavourable effect can be seen in case of *'blood and lymphatic system disorders'*, *'congenital, familial and genetic disorders'*, and *'hepatobiliary disorders'* (Table 3).

Regarding **barbiturates**, there was a significant positive association with occurrences of PTs that belong to SOCs of '*blood and lymphatic system disorders', 'congenital, familial and genetic disorders', 'hepatobiliary disorders'.*

In **benzodiazepines**, a significant positive association with occurrences of PTs was noticed in SOCs of *'congenital, familial and genetic disorders'*, *'pregnancy, puerperium and perinatal conditions'*.

As for **carboxamides**, a significant positive association with occurrences of PTs was observed in SOCs of *'blood and lymphatic system disorders'*, *'endocrine disorders'*, *'skin and subcutaneous tissue disorders'*, *'pregnancy, puerperium and perinatal conditions'*.

ESL exhibited the least negative impact on SOC. For instance, in case of CBZ *'hepatobiliary disorders'* is common, in case of OXC is half; and ESL is a quarter, ESL having the best ADR profile.

Regarding **fatty acid derivatives**, there was a significant positive association with occurrences of PTs belonging to SOCs of *'congenital, familial and genetic disorders'* (three-fold in males), *'social circumstances'*.

As regards to **hydantoins**, SOCs of *'cardiac disorders'*, *'hepatobiliary disorders'* and *'blood and lymphatic system disorders'* had a noticed significant positive association with occurrences of PTs.

None was notable for **other antiepileptics**.

As for **oxazolidines**, *'blood and lymphatic system disorders'*, *'congenital, familial and genetic disorders'* had a significant positive association generally (same in males) and no association in females.

Regarding **succinimides**, there was a significant positive association with occurrences of PTs belonging to SOCs of *'blood and lymphatic system disorders'*, *'gastrointestinal disorders'*.

Table 3 Number of PTs by SOC and numbers of PTs related to old and new ASMs with their Reporting Odds Ratio (ROR)

SOC	Number of PTs (%)	Number of old ASMs (%)	Number of new ASMs (%)	Reporting Odds Ratio with its 95% confident interval and p-value
Blood and lymphatic system disorders	16,214 (1.54)	8,676 (0.83)	7,538 (0.72)	ROR = 2.12, 95% CI [2.09, 2.15] p<0.0001
Cardiac disorders	18,707 (1.78)	6,253 (0.59)	12,454 (1.18)	ROR = 0.91, 95% CI [0.88, 0.94] p<0.0001
Congenital, familial and genetic disorders	16,644 (1.58)	11,069 (1.05)	5,575 (0.53)	ROR = 3.69, 95% CI [3.66, 3.73] p<0.0001
Ear and labyrinth disorders	6,795 (0.65)	2,282 (0.22)	4,513 (0.43)	ROR = 0.92, 95% CI [0.87, 0.97] p<0.0001
Endocrine disorders	2,680 (0.25)	1,255 (0.12)	1,425 (0.14)	ROR = 1.61, 95% CI [1.53, 1.68] p<0.0001
Eye disorders	247,86 (2.36)	6,089 (0.58)	18,697 (1.78)	ROR = 0.59, 95% CI [0.56, 0.62] p<0.0001
Gastrointestinal disorders	57,747 (5.49)	19,827 (1.89)	37,920 (3.61)	ROR = 0.95, 95% CI [0.93, 0.97] p<0.0001
General disorders and administration site conditions	151,241 (14.39)	47,355 (4.51)	103,885 (9.88)	ROR = 0.81, 95% CI [0.79, 0.82] p<0.0001
Hepatobiliary disorders	11,601 (1.1)	6,111 (0.58)	5,490 (0.52)	ROR = 2.04, 95% CI [2.01, 2.08] p<0.0001
Immune system disorders	7,075 (0.67)	2,261 (0.22)	4,814 (0.46)	ROR = 0.85, 95% CI [0.8, 0.9] p<0.0001
Infections and infestations	27,773 (2.64)	8,579 (0.82)	19,194 (1.83)	ROR = 0.81, 95% CI [0.78, 0.84] p<0.0001
Injury, poisoning and procedural complications	102,953 (9.79)	35,582 (3.39)	67,371 (6.41)	ROR = 0.96, 95% CI [0.94, 0.97] p<0.0001
Investigations	60,734 (5.78)	26,551 (2.53)	34,183 (3.25)	ROR = 1.45, 95% CI [1.43, 1.46] p<0.0001
Metabolism and nutrition disorders	22,989 (2.19)	8,832 (0.84)	14,157 (1.35)	ROR = 1.14, 95% CI [1.11, 1.17] p<0.0001
Musculoskeletal and connective tissue disorders	42,077 (4)	10,419 (0.99)	31,658 (3.01)	ROR = 0.59, 95% CI [0.57, 0.61] p<0.0001
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7,044 (0.67)	1,713 (0.16)	5,331 (0.51)	ROR = 0.58, 95% CI [0.53, 0.64] p<0.0001
Nervous system disorders	202,420 (19.26)	68,629 (6.53)	133,791 (12.73)	ROR = 0.92, 95% CI [0.91, 0.93] p<0.0001
Pregnancy, puerperium and perinatal conditions	7,677 (0.73)	2,669 (0.25)	5,008 (0.48)	ROR = 0.97, 95% CI [0.92, 1.02] n.s.
Psychiatric disorders	118,635 (11.29)	42,193 (4.01)	76,442 (7.27)	ROR = 1.01, 95% CI [0.99, 1.02] n.s.
Renal and urinary disorders	13,630 (1.3)	4,058 (0.39)	9,572 (0.91)	ROR = 0.77, 95% CI [0.73, 0.81] p<0.0001
Reproductive system and breast disorders	4,821 (0.46)	1,748 (0.17)	3,073 (0.29)	ROR = 1.04, 95% CI [0.98, 1.09] n.s.
Respiratory, thoracic and mediastinal disorders	31,058 (2.95)	11,299 (1.07)	19,759 (1.88)	ROR = 1.04, 95% CI [1.02, 1.07] p<0.0001
Skin and subcutaneous tissue disorders	63,215 (6.01)	27,102 (2.58)	36,113 (3.44)	ROR = 1.4, 95% CI [1.38, 1.41] p<0.0001
Social circumstances	7,760 (0.74)	3,607 (0.34)	4,152 (0.39)	ROR = 1.59, 95% CI [1.54, 1.63] p<0.0001
Surgical and medical procedures	6,478 (0.62)	1,535 (0.15)	4,943 (0.47)	ROR = 0.56, 95% CI [0.51, 0.62] p<0.0001
Vascular disorders	13,575 (1.29)	4,994 (0.48)	8,581 (0.82)	ROR = 1.06, 95% CI [1.03, 1.1] p<0.0001
Product issues	4,813 (0.46)	1,970 (0.19)	2,843 (0.27)	ROR = 1.26, 95% CI [1.21, 1.32] p<0.0001
Not Specified	2 (0)	2 (0)	0 (0)	N/C

SOC: System Organ Classes; PT: preferred terms; ASM: antiseizure medication; ROR: Reporting Odds Ratio; CI: confidence interval; n.s.: not significant; N/C: not countable

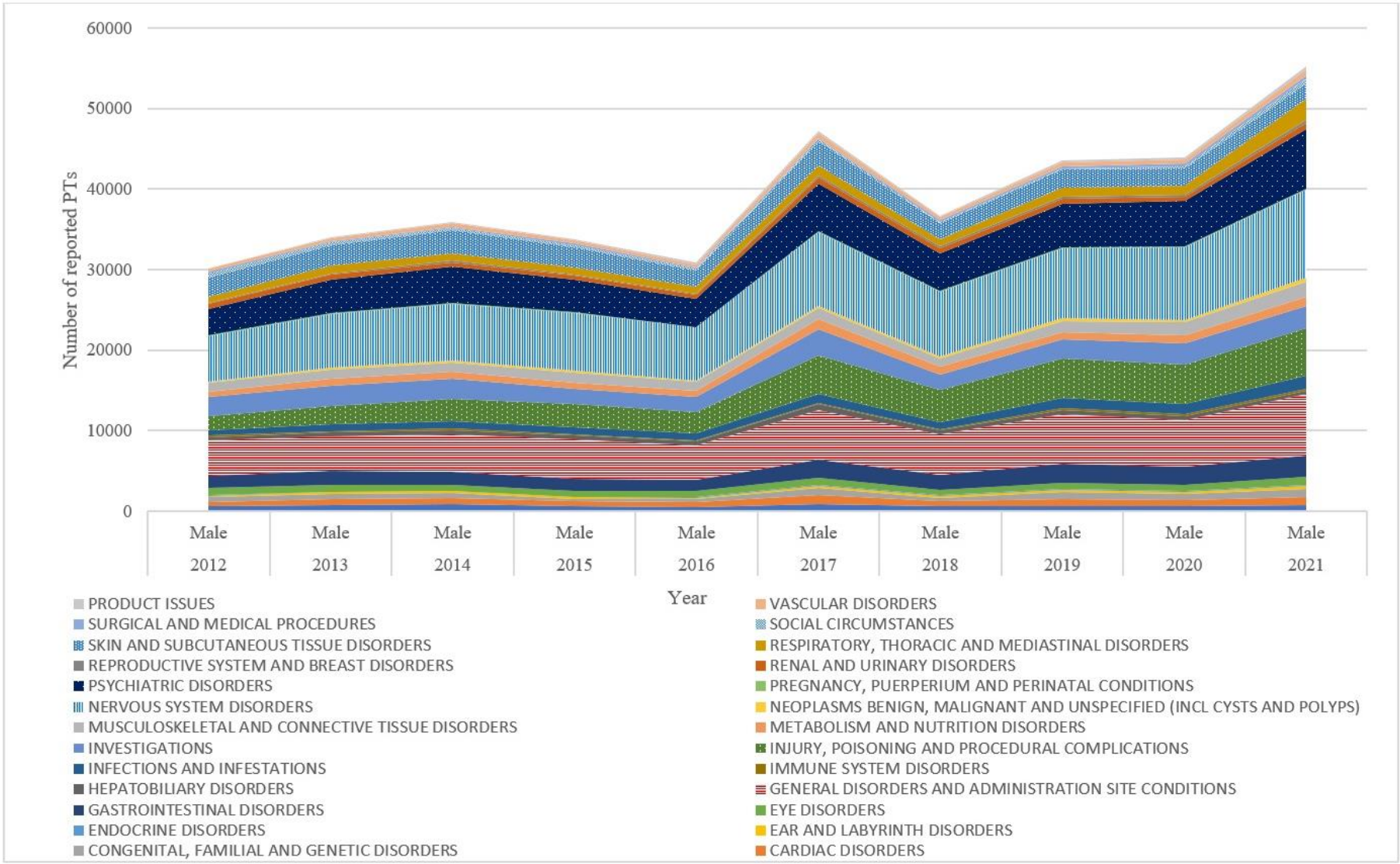

Figure 1A Change in number of reported PTs in different SOCs from 2012 to 2021 among male

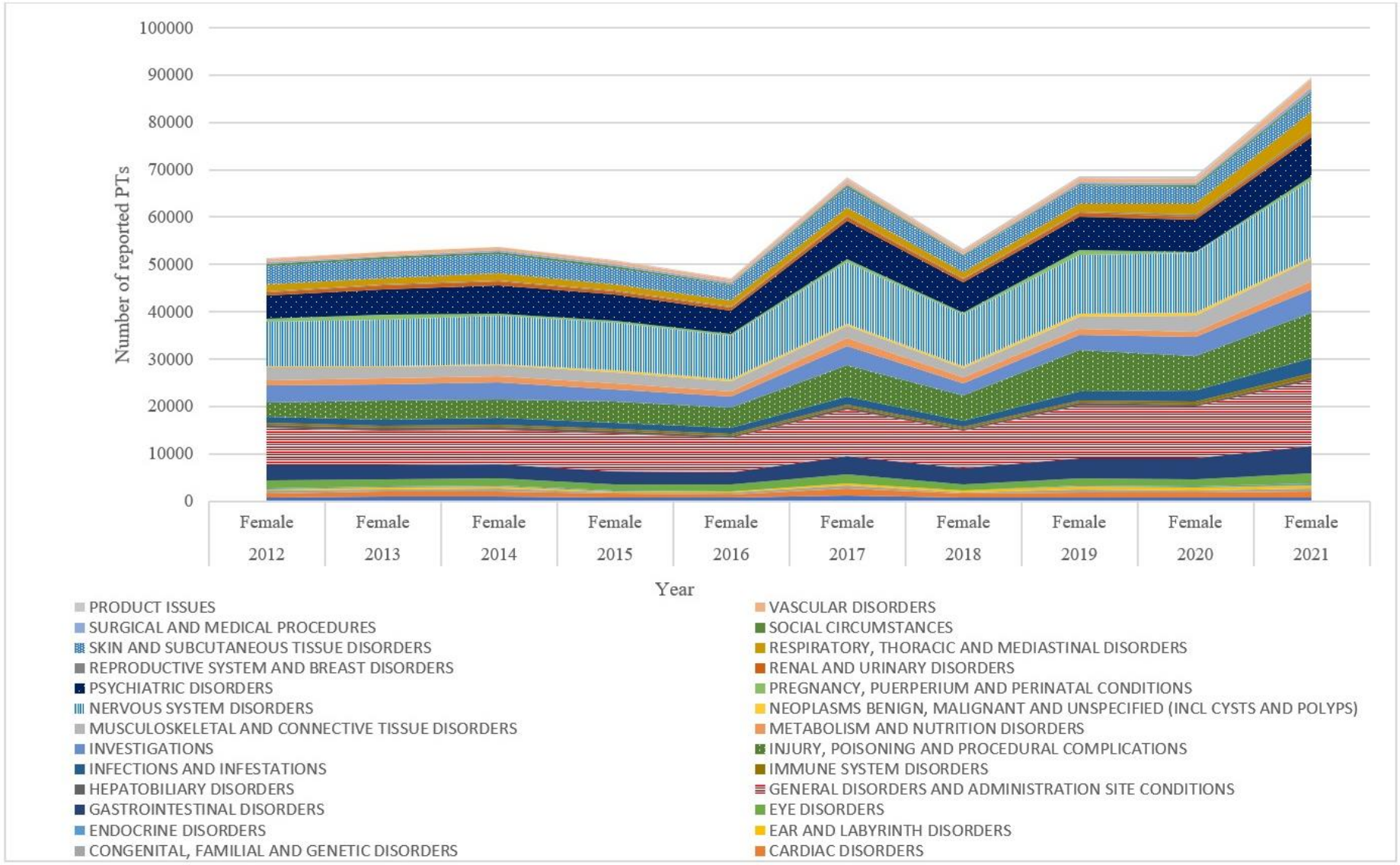

Figure 1B Change in number of reported PTs in different SOCs from 2012 to 2021 among female

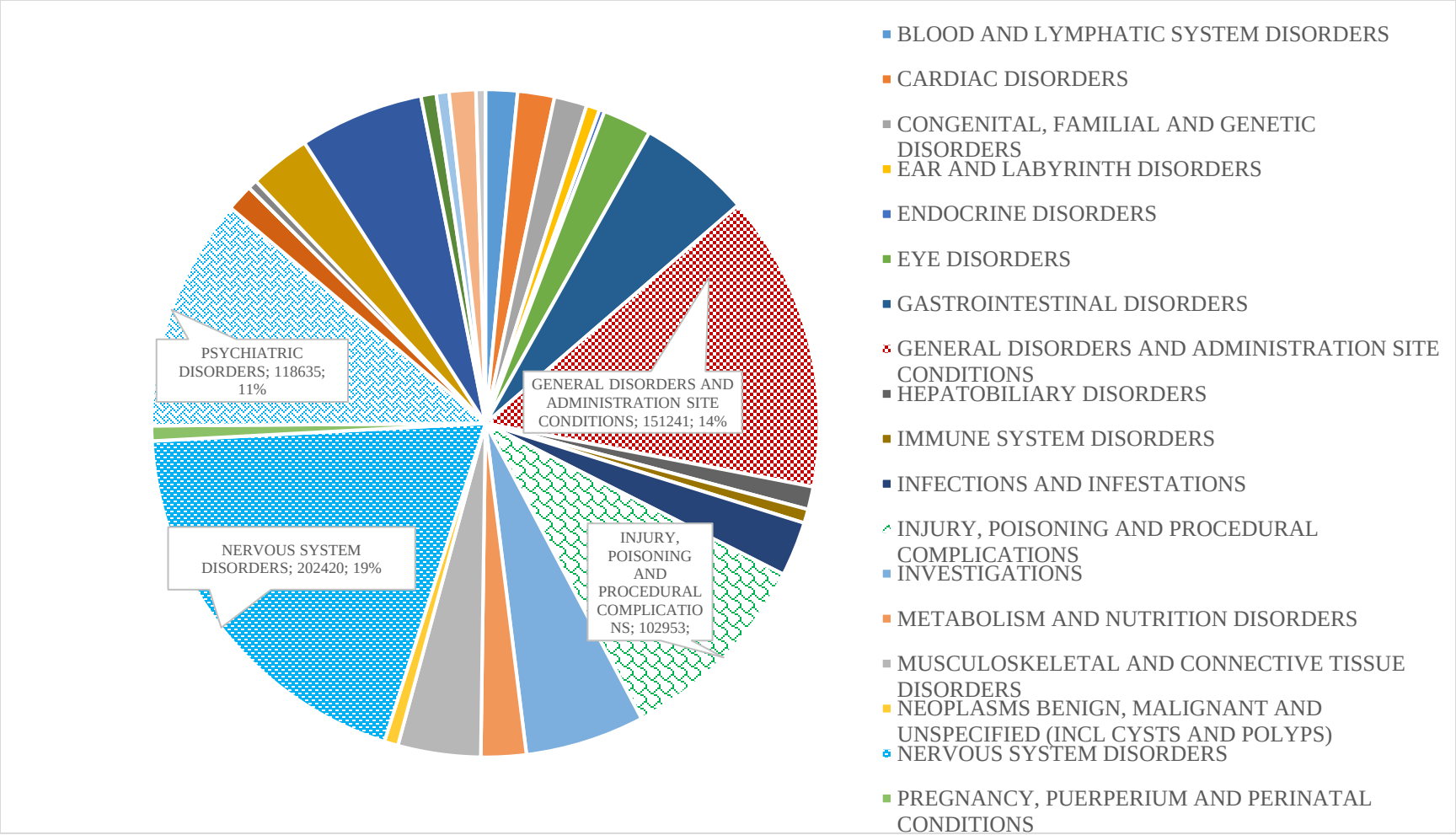

Figure 2 Proportions of different SOCs

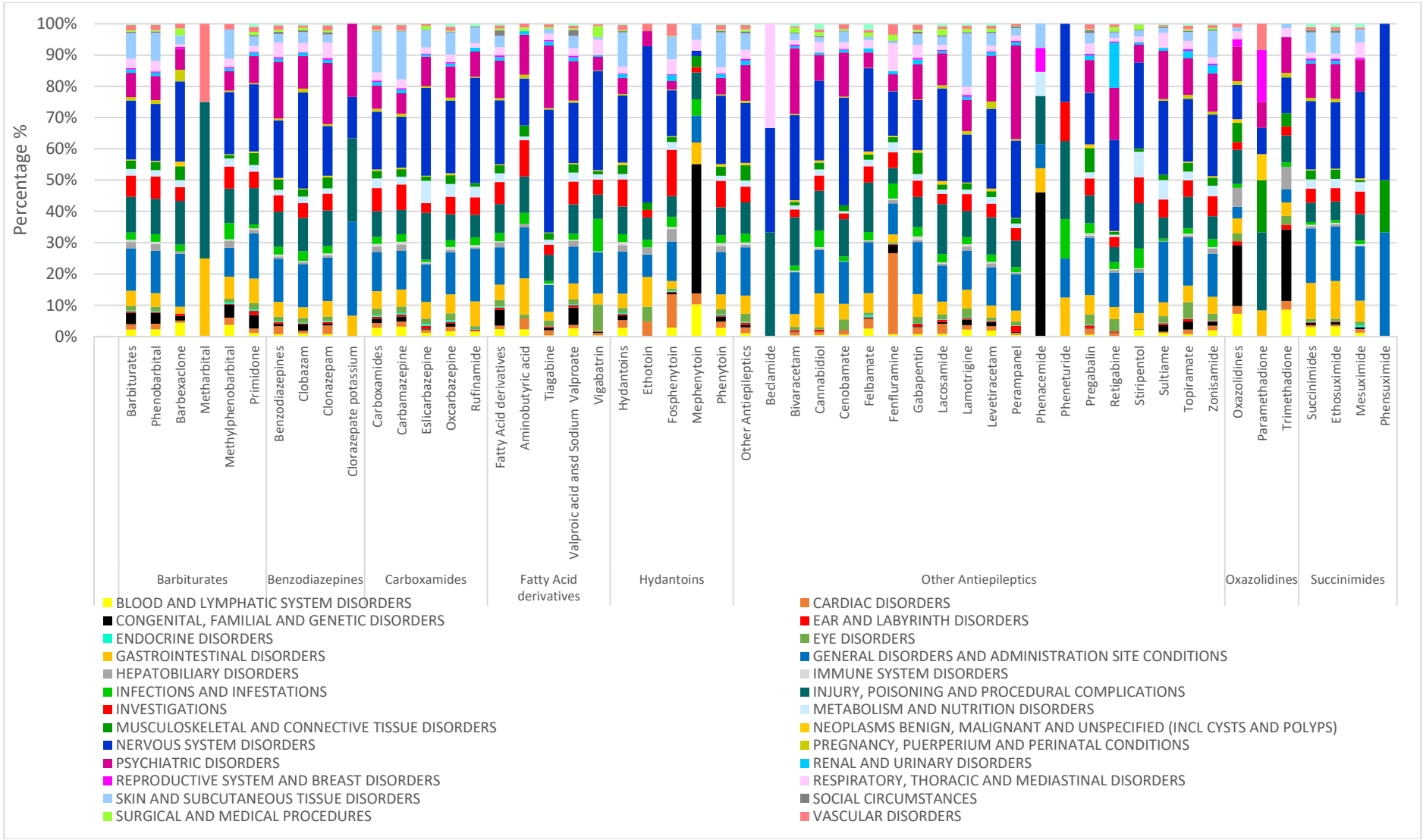

Figure 3 Proportions of SOCs by different ASMs

5.1.3. Seriousness

Out of all the reported PTs, 882,706 (83.98%) were marked as serious, and 621,642 PTs (70.42%) of these were reported by healthcare professionals. The age group of 18 to 64 years old had the highest number of PTs across all seriousness categories (Table 4), with one exception: *'congenital anomaly'* seriousness in which age group of 2 to 17 years had the highest PTs number (11,715, 27.05%) followed by neonates less than 2 years old (5,977, 13.80%).

The most frequently reported seriousness criteria were *'other medically important condition'* (632,691 PTs, 60.19%) followed by *'caused/prolonged hospitalisation'* (371,185 PTs, 35.31%). These trends were consistent in both males (226,702 PTs [57.95%] and 148,947 PTs [38.08%], respectively) and females (371,775 PTs [61.56%] and 212,625 PTs [35.21%], respectively). Additionally, 5.79% of all the reported PTs had the seriousness criterion of *'results in death'* (7.20% in males and 4.87% in females).

In the chemical subgroup of **barbiturates**, in all seriousness criteria, there were significant positive associations across all seriousness criteria, except for *'other medically important condition'* and *'disabling',* which showed negative associations. Notably, mephenytoin stood out in the *'life threatening'* and *'congenital anomaly'* criteria (Table 5). Methylphenobarbital had the highest ROR for the *'results in death'* criterion within the group.

For **benzodiazepines**, there was a significant positive association with the seriousness criteria of *'caused/prolonged hospitalisation', 'life threatening'* and *'results in death'*, while a significant negative association was observed only with the *'congenital anomaly'* seriousness criterion. There was no significant association with the 'other medically important condition' criterion. Clorazepate potassium is notable for its remarkably high positive associations.

The **carboxamides** demonstrated a significant positive association only with *'caused/prolonged hospitalisation'* and *'life-threatening'* seriousness criteria. However, there was a significant negative association with the 'results in death', 'congenital anomaly', 'disabling', and 'other medically important condition' criteria (Table 5).

It is noteworthy that **fatty acid derivatives** showed the highest ROR in the 'congenital anomaly' criterion. Additionally, they exhibited a significant increased association with the 'disabling' criterion. However, there was a significant negative association with the seriousness criteria of

'results in death', 'caused/prolonged hospitalisation', and 'other medically important condition'. VGB demonstrated a significant positive association with the 'results in death' criterion. VPA showed a significant positive association with the 'congenital anomaly' criterion.

Regarding **hydantoins**, there was a significant positive association with *'other medically important condition'*, *'caused/prolonged hospitalisation'*, *'life threatening'* and *'results in death'* seriousness criteria. Conversely, there was a significant negative association with *'congenital anomaly'* seriousness criterion overall. However, upon closer inspection of individual ASMs, mephenytoin exhibited 26-fold higher reported odds for *'congenital anomaly'*. Fosphenytoin showed a significant positive association with the 'results in death' and 'life-threatening' criteria, with reported odds ratios of three-fold and five-fold, respectively.

As regards to **other antiepileptics**, a significant negative association was observed with seriousness criteria of *'congenital anomaly'* (TPM) and *'life threatening'* (LTG, and ZNS). None of these medications demonstrated positive associations with the five specific serious medical conditions among the seriousness criteria, except for 'other medically important condition', which was detailed specifically for PGB, RGB, GBP, and TPM.

Concerning **oxazolidines**, there was a significant positive association with the *'results in death'* seriousness criterion, showing five-fold higher reported odds. Regarding to *'congenital anomaly'*, there was a general 26-fold positive association, while trimethadione exhibited a 34-fold.

Regarding **succinimides**, there was a significant inverse relationship with seriousness criteria of *'other medically important condition'* and *'caused/prolonged hospitalisation'*.

When examining the cases labelled as *'results in death'* (Table 6), the most frequently reported PTs were listed by the following ASMs: PGB (8,407, 13.81%), GBP (8,316, 13.66%) and CLZ (7,877, 12.94%). Among those PTs with *'caused/prolonged hospitalization'*, PGB (66,041, 17.79%), VPA (44,908, 12.10%), CBZ (42,313, 11.40%), LTG (42,300, 11.39%) and GBP (31,626, 8.52%) were the most common. Regarding *'congenital anomaly'*, ASMs having the highest number of reported PTs were VPA (27,330, 62.12%), LTG (3,082, 7.01%), TPM (2,634, 5.99%), CBZ (2,542, 5.78%) and LEV (2,211, 5.03%). Regarding *'disabling'* criteria, the most frequently reported PTs were in case of PGB (9,832, 26.62%), VPA (7,267, 19.68%), GBP (3,756, 10.17%), LTG (3,062, 8.29%) and CLZ (2893, 7.83%). In case of *'life-threatening'* term, the most

frequently reported PTs were by patients taking VPA (6828, 13.85%), PGB (6,477, 13.14%), LTG (6,334, 12.85%), CBZ (5,897, 11.97%) and CLZ (5,438, 11.03%).

Old ASMs (Table 7), demonstrated a significant positive association with *'caused/prolonged hospitalisation'* (ROR=1.32, 95%CI: 1.31-1. 32, p<0.001), *'congenital anomaly'* (ROR=6.05, 95%CI: 6.03-6.07, p<0.001), *'disabling'* (ROR=1.13, 95%CI: 1.10-1.15, p<0.001) (not significant in males), *'life threatening'* (ROR=1.54,95%CI: 1.52-1.56, p<0.001) and *'results in death'* (ROR=1.34,95%CI: 1.32-1.36, p<0.001) seriousness criteria, in contrast, they had a significant negative association with *'other medically important condition'* seriousness criterion (ROR=0.77,95%CI: 0.76-0.78, p<0.001).

New ASMs showed a significant negative association with *'congenital anomaly'* (ROR=0.17, 95%CI: 0.14-0.19, p<0.001) and *'life threatening'* seriousness criteria (ROR=0.65, 95%CI: 0.63-0.67, p<0.001). They exhibited a significant negative association overall and among females, however a significant positive association was detected in males with *'caused/prolonged hospitalisation'* (ROR=0.76, 95%CI: 0.75-0.77, p<0.001) and *'results in death'* (ROR=0.75,95%CI: 0.73-0.76, p<0.001). Generally, there was a significant positive association and among females with *'other medically important condition'* (ROR=1.30, 95%CI: 1.29-1.31, p<0.001), however no significant association could be detected in males. *'Disabling'* seriousness criterion showed a significant negative association (ROR=0.89, 95%CI: 0.87-0.91, p<0.001) (in general and by males), compared to a significant positive association observed among females.

Table 4 Number of reported sADRs in different seriousness criteria by age group

Age Group	Seriousness (Number of sADRs)							
	Other Medically Important Condition	**Caused/Prolonged Hospitalisation**	**Congenital Anomaly**	**Disabling**	**Life Threatening**	**Results in Death**	**Not specified/ Unknown**	**All**
0 - 2 years	15.314	11.599	5.977	997	1.210	1.830	2.133	39,060
3 - 17 years	50.670	37.376	11.715	2.766	5.838	3.366	12.490	124,221
18 - 64 years	330.296	204.658	5.378	21.256	29.574	34.261	85.933	711,356
65 years or older	113.041	82.848	130	5.697	8.671	12.980	34.490	257,857
Not Specified	118.476	29.984	20.114	5.897	2.888	6.920	33.388	217,667
All	627,797	366,465	43,314	36,613	48,181	59,357	168,434	1,350,161

Table 5 A and B Associations of seriousness criteria by ASM chemical subgroups

A Seriousness criterion with positive association of ASM chemical subgroups

Criterion	ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	χ^2
Caused/Prolonged Hospitalisation	Barbiturates	1.43	1.41	1.46	<0.001	1.24	1.23	700.24
	Benzodiazepines	1.24	1.23	1.26	<0.001	1.14	1.14	856.54
	Carboxamides	1.57	1.55	1.58	<0.001	1.31	1.31	5,229.80
	Hydantoins	1.59	1.57	1.61	<0.001	1.32	1.31	2,071.67
Congenital Anomaly	Barbiturates	1.69	1.64	1.74	<0.001	1.64	1.60	386.55
	Fatty Acid derivatives	11.45	11.43	11.47	<0.001	9.59	9.57	83,040.01
	Oxazolidines	24.06	23.62	24.49	<0.001	12.25	12.04	452.35
Disabling	Benzodiazepines	1.11	1.08	1.15	<0.001	1.11	1.07	33.19
	Fatty Acid derivatives	1.49	1.46	1.51	<0.001	1.46	1.44	901.91
Life Threatening	Barbiturates	1.51	1.45	1.56	<0.001	1.47	1.42	235.70
	Benzodiazepines	1.65	1.62	1.68	<0.001	1.60	1.58	1,251.79
	Carboxamides	1.42	1.39	1.44	<0.001	1.39	1.37	730.39
	Hydantoins	1.55	1.51	1.59	<0.001	1.51	1.48	481.40
Other Medically Important Condition	Hydantoins	1.34	1.32	1.36	<0.001	1.11	1.11	751.15
	Other Antiepileptics	1.19	1.18	1.20	<0.001	1.07	1.07	1,835.28
Results in Death	Barbiturates	2.11	2.07	2.15	<0.001	1.98	1.95	1,249.83
	Benzodiazepines	1.99	1.97	2.01	<0.001	1.89	1.87	3,246.13
	Hydantoins	1.74	1.71	1.78	<0.001	1.67	1.64	1,017.93
	Oxazolidines	5.25	4.74	5.75	<0.001	4.21	3.83	51.97

B Seriousness criterion with negative association of ASM chemical subgroups

Criterion	ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	χ^2
Caused/Prolonged Hospitalisation	Fatty Acid derivatives	0.90	0.89	0.91	<0.001	0.93	0.92	346.95
	Other Antiepileptics	0.73	0.73	0.74	<0.001	0.82	0.82	5,547.76
	Succinimides	0.80	0.70	0.89	<0.001	0.86	0.79	20.98
Congenital Anomaly	Benzodiazepines	0.43	0.38	0.48	<0.001	0.44	0.39	1,156.42
	Carboxamides	0.57	0.53	0.60	<0.001	0.58	0.54	910.72
	Hydantoins	0.46	0.39	0.53	<0.001	0.47	0.40	497.05
	Other Antiepileptics	0.17	0.15	0.20	<0.001	0.19	0.16	27,829.44
Disabling	Barbiturates	0.69	0.61	0.78	<0.001	0.70	0.62	72.42
	Carboxamides	0.55	0.51	0.60	<0.001	0.56	0.52	806.86
	Other Antiepileptics	0.97	0.94	0.99	<0.001	0.97	0.95	10.28
Life Threatening	Other Antiepileptics	0.64	0.62	0.65	<0.001	0.65	0.63	2,428.99
Other Medically Important Condition	Barbiturates	0.82	0.80	0.85	<0.001	0.92	0.91	205.15
	Carboxamides	0.85	0.84	0.86	<0.001	0.93	0.93	702.09
	Fatty Acid derivatives	0.79	0.78	0.80	<0.001	0.90	0.90	1,875.13
	Succinimides	0.77	0.68	0.86	<0.001	0.89	0.85	32.94
Results in Death	Carboxamides	0.82	0.80	0.85	<0.001	0.83	0.81	187.29
	Fatty Acid derivatives	0.82	0.80	0.85	<0.001	0.83	0.81	238.79
	Other Antiepileptics	0.75	0.74	0.77	<0.001	0.77	0.75	1,132.85

Table 6 A and B Associations of seriousness criteria by ASMs

A Seriousness criterion with positive association of ASMs

Criterion	ASM	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	χ^2
Caused/Prolonged Hospitalisation	Carbamazepine	1.83	1.82	1.85	<0.001	2.04	2.03	5,172.57
	Clonazepam	1.30	1.29	1.32	<0.001	1.67	1.66	771.59
	Clorazepate potassium	4.27	3.49	5.06	<0.001	2.68	2.45	11.68
	Felbamate	1.30	1.14	1.45	<0.001	1.59	1.50	8.16
	Fenfluramine	1.62	1.51	1.74	<0.001	1.80	1.74	53.41
	Fosphenytoin	1.36	1.27	1.45	<0.001	1.63	1.58	32.29
	Lamotrigine	1.73	1.72	1.75	<0.001	1.99	1.98	4,321.50
	Mesuximide	1.58	1.28	1.89	<0.001	1.78	1.61	6.59
	Methylphenobarbital	2.15	2.01	2.28	<0.001	2.07	2.01	97.10
	Oxcarbazepine	1.04	1.02	1.07	<0.001	1.42	1.40	7.70
	Phenobarbital	1.48	1.45	1.51	<0.001	1.73	1.72	496.45
	Phenytoin	1.60	1.58	1.62	<0.001	1.83	1.82	1,466.58
	Primidone	1.12	1.04	1.19	<0.001	1.45	1.41	6.42
	Tiagabine	2.51	2.40	2.61	<0.001	2.22	2.17	233.30
	Vigabatrin	1.49	1.45	1.52	<0.001	1.73	1.71	347.11
	Zonisamide	1.20	1.15	1.25	<0.001	1.52	1.49	42.65
Congenital Anomaly	Clobazam	1.21	1.14	1.29	<0.001	1.27	1.19	22.45
	Mephenytoin	26.30	25.78	26.82	<0.001	13.31	13.07	336.88
	Methylphenobarbital	1.40	1.12	1.69	<0.001	1.44	1.17	5.23
	Phenacemide	26.71	25.62	27.80	<0.001	13.41	12.90	76.73
	Phenobarbital	1.72	1.67	1.78	<0.001	1.77	1.72	328.83
	Primidone	1.60	1.46	1.74	<0.001	1.63	1.50	40.04
	Topiramate	1.34	1.30	1.38	<0.001	1.44	1.41	189.63
	Trimethadione	34.37	33.89	34.85	<0.001	14.95	14.76	521.92
	Valproic acid and Sodium Valproate	12.96	12.94	12.98	<0.001	12.47	12.45	80,405.04
Disabling	Clonazepam	1.21	1.17	1.25	<0.001	1.33	1.29	83.78
	Fenfluramine	2.89	2.70	3.08	<0.001	2.81	2.63	123.56
	Gabapentin	1.15	1.12	1.19	<0.001	1.30	1.27	58.26
	Pregabalin	1.28	1.26	1.30	<0.001	1.67	1.65	319.34
	Retigabine	1.58	1.35	1.81	<0.001	1.60	1.38	14.48
	Rufinamide	1.36	1.06	1.66	<0.001	1.39	1.10	3.85
	Valproic acid and Sodium Valproate	1.62	1.59	1.65	<0.001	1.89	1.86	1,111.04
Life Threatening	Aminobutyric acid	2.68	2.02	3.33	<0.001	2.60	2.01	8.85
	Carbamazepine	1.54	1.52	1.57	<0.001	1.71	1.68	819.71
	Clonazepam	1.82	1.79	1.84	<0.001	1.95	1.93	1,468.43
	Clorazepate potassium	17.79	17.08	18.51	<0.001	10.42	10.04	113.01
	Fenfluramine	1.44	1.21	1.67	<0.001	1.48	1.27	9.52
	Fosphenytoin	5.06	4.95	5.17	<0.001	4.46	4.37	932.18
	Lamotrigine	1.63	1.61	1.66	<0.001	1.81	1.78	1,109.63
	Mephenytoin	7.09	6.51	7.68	<0.001	5.78	5.34	55.58
	Methylphenobarbital	3.60	3.41	3.78	<0.001	3.36	3.20	197.30
	Oxcarbazepine	1.13	1.07	1.18	<0.001	1.20	1.15	16.35
	Phenobarbital	1.60	1.54	1.65	<0.001	1.65	1.60	248.84

	Phenytoin	1.38	1.34	1.43	<0.001	1.47	1.44	210.99
	Tiagabine	1.85	1.66	2.04	<0.001	1.86	1.69	40.36
	Valproic acid and Sodium valproate	1.04	1.02	1.07	<0.001	1.25	1.23	8.99
	Zonisamide	1.59	1.50	1.68	<0.001	1.63	1.55	101.99
Other Medically Important Condition	Aminobutyric acid	2.89	2.35	3.44	<0.001	2.17	2.07	10.07
	Barbexaclone	3.43	2.97	3.88	<0.001	2.23	2.16	19.79
	Ethotoin	2.12	1.41	2.83	<0.001	2.03	1.86	2.80
	Felbamate	1.28	1.12	1.44	<0.001	1.76	1.70	5.90
	Fosphenytoin	1.15	1.05	1.24	<0.001	1.69	1.66	5.23
	Gabapentin	1.41	1.39	1.42	<0.001	1.92	1.91	1,323.27
	Oxcarbazepine	1.17	1.14	1.20	<0.001	1.73	1.72	86.63
	Phenytoin	1.36	1.34	1.38	<0.001	1.83	1.82	467.68
	Pregabalin	1.44	1.43	1.45	<0.001	2.14	2.14	2,908.30
	Retigabine	1.35	1.24	1.46	<0.001	1.79	1.75	17.31
	Topiramate	1.24	1.22	1.26	<0.001	1.79	1.78	292.72
Results in Death	Clonazepam	2.24	2.21	2.26	<0.001	2.36	2.34	3,721.90
	Clorazepate potassium	10.84	10.11	11.57	<0.001	7.31	6.87	60.80
	Ethotoin	3.83	3.06	4.60	<0.001	3.48	2.86	12.78
	Fenfluramine	1.26	1.04	1.48	<0.001	1.31	1.11	4.06
	Fosphenytoin	3.02	2.90	3.15	<0.001	2.87	2.76	318.25
	Gabapentin	1.66	1.64	1.68	<0.001	1.85	1.83	1,496.41
	Lamotrigine	1.05	1.02	1.08	<0.001	1.20	1.18	9.46
	Methylphenobarbital	5.42	5.27	5.57	<0.001	4.57	4.45	550.11
	Phenobarbital	2.13	2.08	2.18	<0.001	2.15	2.11	994.52
	Phenytoin	1.67	1.64	1.71	<0.001	1.76	1.73	738.64
	Primidone	1.18	1.04	1.32	<0.001	1.24	1.10	4.86
	Trimethadione	6.51	5.99	7.03	<0.001	5.22	4.85	62.91
	Vigabatrin	1.56	1.50	1.62	<0.001	1.62	1.56	179.06
	Zonisamide	1.10	1.00	1.19	<0.001	1.16	1.07	3.57

B Seriousness criterion with negative association of ASMs

Condition Seriousness negative	**ASM**	**ROR**	**Lower 95%CI**	**Upper 95%CI**	**p-value**	**PRR**	**Lower 95%CI**	**Upper 95%CI**	χ^2
Caused/Prolonged Hospitalisation	Brivaracetam	0.32	0.26	0.38	<0.001	0.57	0.52	0.62	1,179.66
	Cannabidiol	0.52	0.48	0.56	<0.001	0.86	0.83	0.89	696.84
	Cenobamate	0.76	0.65	0.87	<0.001	1.13	1.05	1.20	19.28
	Clobazam	0.94	0.91	0.98	<0.001	1.32	1.29	1.34	7.23
	Eslicarbazepine	0.59	0.53	0.65	<0.001	0.94	0.89	0.98	225.50
	Ethosuximide	0.74	0.64	0.85	<0.001	1.11	1.03	1.18	23.36
	Gabapentin	0.92	0.90	0.93	<0.001	1.37	1.36	1.38	103.58
	Lacosamide	0.86	0.83	0.88	<0.001	1.25	1.24	1.27	125.48
	Levetiracetam	0.87	0.85	0.88	<0.001	1.32	1.31	1.33	245.12
	Perampanel	0.90	0.85	0.95	<0.001	1.27	1.23	1.30	11.13
	Pregabalin	0.66	0.65	0.67	<0.001	1.25	1.25	1.26	3,988.17
	Retigabine	0.81	0.70	0.93	<0.001	1.18	1.10	1.26	9.20
	Stiripentol	0.74	0.64	0.85	<0.001	1.11	1.04	1.18	24.58
	Topiramate	0.72	0.70	0.74	<0.001	1.13	1.11	1.14	715.84
	Valproic acid and Sodium Valproate	0.84	0.83	0.85	<0.001	1.35	1.34	1.36	524.06

Congenital Anomaly	Carbamazepine	0.67	0.63	0.71	<0.001	0.77	0.73	0.81	332.00
	Clonazepam	0.29	0.22	0.36	<0.001	0.33	0.27	0.40	1,370.33
	Gabapentin	0.17	0.09	0.24	<0.001	0.20	0.13	0.27	2,612.47
	Lacosamide	0.20	0.09	0.31	<0.001	0.22	0.11	0.34	881.93
	Lamotrigine	0.80	0.77	0.84	<0.001	0.92	0.89	0.96	115.67
	Levetiracetam	0.56	0.52	0.61	<0.001	0.65	0.61	0.69	608.78
	Oxcarbazepine	0.40	0.31	0.50	<0.001	0.44	0.35	0.54	351.28
	Phenytoin	0.46	0.39	0.53	<0.001	0.51	0.44	0.58	431.08
	Zonisamide	0.65	0.51	0.79	<0.001	0.69	0.56	0.83	35.68
Disabling	Brivaracetam	0.35	0.17	0.54	<0.001	0.38	0.19	0.56	124.80
	Cannabidiol	0.32	0.15	0.48	<0.001	0.34	0.18	0.50	201.78
	Carbamazepine	0.57	0.52	0.62	<0.001	0.65	0.60	0.70	494.57
	Clobazam	0.66	0.54	0.77	<0.001	0.70	0.59	0.81	52.24
	Eslicarbazepine	0.36	0.13	0.59	0.002	0.38	0.16	0.61	82.02
	Lacosamide	0.59	0.51	0.66	<0.001	0.64	0.56	0.71	188.87
	Levetiracetam	0.58	0.53	0.62	<0.001	0.66	0.61	0.71	483.96
	Oxcarbazepine	0.58	0.50	0.67	<0.001	0.63	0.54	0.71	140.96
	Perampanel	0.67	0.51	0.84	<0.001	0.71	0.55	0.87	22.08
	Phenobarbital	0.69	0.60	0.79	<0.001	0.74	0.65	0.83	56.11
	Primidone	0.78	0.57	1.00	<0.001	0.82	0.61	1.03	4.81
	Stiripentol	0.39	0.00	0.78	0.048	0.41	0.03	0.79	23.63
	Vigabatrin	0.26	0.07	0.44	0.006	0.28	0.10	0.46	231.24
Life Threatening	Brivaracetam	0.34	0.18	0.50	<0.001	0.37	0.21	0.53	172.46
	Cannabidiol	0.18	0.00	0.37	0.048	0.20	0.02	0.39	385.96
	Cenobamate	0.44	0.10	0.77	0.01	0.47	0.14	0.80	23.88
	Clobazam	0.79	0.70	0.88	<0.001	0.85	0.76	0.93	24.55
	Eslicarbazepine	0.72	0.58	0.86	<0.001	0.77	0.63	0.90	20.00
	Gabapentin	0.79	0.76	0.83	<0.001	0.92	0.88	0.95	151.68
	Lacosamide	0.68	0.62	0.74	<0.001	0.75	0.69	0.81	142.08
	Levetiracetam	0.84	0.80	0.87	<0.001	0.96	0.93	1.00	85.65
	Pregabalin	0.52	0.49	0.54	<0.001	0.71	0.68	0.73	1,855.25
	Primidone	0.54	0.31	0.76	<0.001	0.58	0.36	0.79	29.26
	Stiripentol	0.60	0.32	0.87	<0.001	0.64	0.37	0.90	13.36
	Topiramate	0.83	0.78	0.87	<0.001	0.91	0.87	0.96	57.63
	Vigabatrin	0.36	0.22	0.49	<0.001	0.39	0.26	0.52	226.41
Other Medically Important Condition	Brivaracetam	0.35	0.30	0.39	<0.001	0.92	0.89	0.95	1,510.47
	Cannabidiol	0.25	0.21	0.29	<0.001	0.74	0.72	0.77	3,447.38
	Carbamazepine	0.77	0.75	0.78	<0.001	1.52	1.51	1.52	806.55
	Cenobamate	0.28	0.17	0.38	<0.001	0.79	0.72	0.87	402.45
	Ethosuximide	0.74	0.64	0.83	<0.001	1.41	1.36	1.45	24.67
	Fenfluramine	0.67	0.56	0.79	<0.001	1.34	1.29	1.40	29.92
	Lacosamide	0.71	0.69	0.73	<0.001	1.41	1.40	1.42	605.38
	Lamotrigine	0.94	0.92	0.95	<0.001	1.65	1.65	1.66	51.80
	Levetiracetam	0.98	0.96	0.99	<0.001	1.68	1.67	1.68	6.13
	Methylphenobarbital	0.72	0.59	0.86	<0.001	1.39	1.33	1.45	14.43
	Perampanel	0.34	0.29	0.40	<0.001	0.91	0.88	0.95	1,078.05
	Phenobarbital	0.85	0.82	0.88	<0.001	1.51	1.50	1.53	71.76
	Primidone	0.68	0.61	0.75	<0.001	1.35	1.31	1.38	73.52

	Stiripentol	0.28	0.18	0.38	<0.001	0.80	0.73	0.87	441.27
	Sultiame	0.43	0.26	0.61	<0.001	1.05	0.95	1.16	57.36
	Tiagabine	0.69	0.59	0.80	<0.001	1.36	1.31	1.41	30.20
	Trimethadione	0.53	0.05	1.00	0.028	1.18	0.92	1.44	4.61
	Valproic acid and Sodium Valproate	0.78	0.77	0.80	<0.001	1.59	1.59	1.60	1,001.82
	Vigabatrin	0.87	0.84	0.91	<0.001	1.53	1.51	1.54	34.25
	Zonisamide	0.84	0.80	0.89	<0.001	1.50	1.48	1.52	33.40
Results in Death	Brivaracetam	0.26	0.09	0.43	0.002	0.29	0.13	0.46	268.70
	Cannabidiol	0.74	0.66	0.83	<0.001	0.81	0.73	0.89	43.15
	Carbamazepine	0.89	0.86	0.92	<0.001	1.03	1.00	1.06	49.30
	Clobazam	0.75	0.67	0.84	<0.001	0.82	0.74	0.90	42.21
	Eslicarbazepine	0.25	0.03	0.46	0.02	0.27	0.06	0.48	186.14
	Felbamate	0.57	0.16	0.99	0.007	0.62	0.22	1.02	6.69
	Lacosamide	0.91	0.87	0.96	<0.001	1.00	0.96	1.05	12.07
	Levetiracetam	0.96	0.93	0.99	<0.001	1.10	1.08	1.13	6.90
	Oxcarbazepine	0.82	0.76	0.87	<0.001	0.89	0.84	0.95	43.31
	Perampanel	0.37	0.20	0.54	<0.001	0.41	0.24	0.57	135.38
	Pregabalin	0.54	0.52	0.57	<0.001	0.76	0.73	0.78	1,976.62
	Retigabine	0.47	0.15	0.79	0.004	0.52	0.21	0.83	21.09
	Stiripentol	0.52	0.26	0.79	<0.001	0.57	0.32	0.82	22.93
	Tiagabine	0.48	0.17	0.79	0.003	0.52	0.22	0.83	21.21
	Topiramate	0.76	0.72	0.80	<0.001	0.85	0.81	0.89	137.74
	Valproic acid and Sodium Valproate	0.77	0.74	0.79	<0.001	0.94	0.92	0.97	325.25

Table 7 Comparison old and new ASMs by seriousness of PTs

Seriousness		ROR	Lower 95%CI	Upper 95%CI	z statistic	p-value	PRR	Chi-square
Other Medically Important Condition	Old ASMs	0.77	0.76	0.78	185.50	<0.001	0.90	4,027.59
	Male	*0.77*	*0.75*	*0.78*	*140.72*	*<0.001*	*0.89*	*2,420.14*
	Female	*0.86*	*0.85*	*0.87*	*166.05*	*<0.001*	*0.94*	*921.86*
	New ASMs	1.30	1.29	1.31	313.77	<0.001	1.11	4,027.59
	Male	*0.99*	*0.98*	*1.00*	*205.92*	*<0.001*	*1.00*	*1.61*
	Female	*1.27*	*1.26*	*1.27*	*308.38*	*<0.001*	*1.10*	*3,304.22*
Caused/Prolonged Hospitalization	Old ASMs	1.32	1.31	1.32	310.84	<0.001	1.19	4,200.00
	Male	*1.28*	*1.27*	*1.29*	*231.20*	*<0.001*	*1.17*	*1,987.03*
	Female	*1.37*	*1.36*	*1.38*	*264.09*	*<0.001*	*1.22*	*3,739.14*
	New ASMs	0.76	0.75	0.77	179.74	<0.001	0.84	4,200.00
	Male	*1.07*	*1.06*	*1.08*	*218.25*	*<0.001*	*1.05*	*206.84*
	Female	*0.81*	*0.80*	*0.82*	*191.96*	*<0.001*	*0.87*	*2,565.15*
Congenital Anomaly	Old ASMs	6.05	6.03	6.07	536.30	<0.001	5.60	32,116.80
	Male	*3.05*	*3.03*	*3.07*	*291.97*	*<0.001*	*2.86*	*12,476.78*
	Female	*1.27*	*1.24*	*1.29*	*106.34*	*<0.001*	*1.25*	*392.83*
	New ASMs	0.17	0.14	0.19	14.66	<0.001	0.18	32,116.80
	Male	*0.40*	*0.37*	*0.43*	*25.26*	*<0.001*	*0.41*	*3,547.28*
	Female	*0.10*	*0.06*	*0.14*	*5.06*	*<0.001*	*0.11*	*21,053.38*
Disabling	Old ASMs	1.13	1.10	1.15	103.16	<0.001	1.12	118.26
	Male	*1.01*	*0.98*	*1.04*	*69.32*	*<0.001*	*1.01*	*0.70*
	Female	*1.09*	*1.06*	*1.11*	*80.73*	*<0.001*	*1.08*	*39.13*
	New ASMs	0.89	0.87	0.91	81.37	<0.001	0.89	118.26
	Male	*0.94*	*0.91*	*0.96*	*71.80*	*<0.001*	*0.94*	*24.25*
	Female	*1.03*	*1.00*	*1.05*	*94.89*	*<0.001*	*1.02*	*5.53*
Life Threatening	Old ASMs	1.54	1.52	1.56	165.77	<0.001	1.51	2,188.48
	Male	*1.29*	*1.26*	*1.31*	*108.67*	*<0.001*	*1.27*	*457.57*
	Female	*1.58*	*1.56*	*1.61*	*148.13*	*<0.001*	*1.55*	*1,881.26*
	New ASMs	0.65	0.63	0.67	69.92	<0.001	0.66	2,188.48
	Male	*0.95*	*0.92*	*0.97*	*83.42*	*<0.001*	*0.95*	*23.78*
	Female	*0.73*	*0.71*	*0.74*	*73.77*	*<0.001*	*0.74*	*1,074.02*
Results in Death	Old ASMs	1.34	1.32	1.36	158.10	<0.001	1.32	1,200.79
	Male	*1.39*	*1.37*	*1.41*	*132.45*	*<0.001*	*1.36*	*1,002.95*
	Female	*1.12*	*1.10*	*1.15*	*106.72*	*<0.001*	*1.12*	*124.53*
	New ASMs	0.75	0.73	0.76	88.02	<0.001	0.76	1,200.79
	Male	*1.30*	*1.28*	*1.32*	*136.64*	*<0.001*	*1.28*	*769.98*
	Female	*0.60*	*0.58*	*0.62*	*65.29*	*<0.001*	*0.62*	*3,153.48*

5.1.4. Outcomes

The age group of 18 to 64 years old had the highest number of PTs across all outcomes (Table 8).

The outcome of *'recovered/resolved'* had the highest frequency (214,442 PTs, 20.4%) followed by the outcome of *'not recovered/not resolved'* (135,970 PTs, 12.94%) and *'recovering/resolving'* (85,623 PTs, 8.15%). Similar patterns were observed in both males (88,494 PTs [22.62%], 46,223 PTs [11.82%] and 36,927 PTs [9.44%], respectively) and females (126,110 PTs [20.88%], 87689 PTs [14.52%] and 49,523 PTs [8.20%], respectively). Of all the reported PTs, 3.89% had *'fatal'* outcome (4.835% and 3.36% in males and females respectively). Overall, 482,597 PTs had a reported outcome, of which 364,319 (75.49%) were reported by healthcare professionals.

With respect to **barbiturates,** there was a significant positive association noticed with *'recovered/resolved'* and *'recovering/resolving'*, simultaneously, there was a significant negative association with *'not recovered/not resolved'* (Table 9). Besides, methylphenobarbital showed a significant positive association with *'fatal'* outcome with five-fold higher reported odds.

Regarding **benzodiazepines**, there was a significant positive association with *'fatal'* and *'not recovered/not resolved'* outcome, however a significant negative association was found with outcomes of *'recovered/resolved with sequelae'* (Table 9).

As regards to **carboxamides** and **fatty acid derivatives** the same pattern was observed, there was a significant negative association with *'fatal'* and *'not recovered/not resolved'* outcomes, while a significant positive association was found with *'recovered/resolved'*, *'recovered/resolved with sequelae'* and *'recovering/resolving'* demonstrating a favourable outcome (Table 9).

Looking at **hydantoins**, a significant positive association was observed with *'fatal'*, *'recovered/resolved'*, *'recovered/resolved with sequelae'* and *'recovering/resolving'* outcomes. On the other hand, a significant negative association was found with *'not recovered/not resolved'* outcomes (Table 9).

With respect to **other antiepileptics**, there was a significant positive association with *'not recovered/not resolved'* outcomes, though a significant negative association was found with the other four outcomes (Table 9).

Concerning **oxazolidines**, *'fatal'* outcomes had a significant positive association, which was the highest in trimethadione (Table 9).

As regards to **succinimides**, a significant positive association was exhibited with *'recovered/resolved'*, *'recovered/resolved with sequelae'* and *'recovering/resolving'* outcomes. In contrast, a significant negative association was observed with *'not recovered/not resolved'* outcome (Table 9).

Noteworthy, the most favourable negative association is observed with BRV and ESL. The poorest outcomes were observed in ethotion, trimethadione, methylphenobarbital, fosphenytion, CLZ and GBP (Table 10).

The *'Fatal'* outcome of PTs had the highest reporting frequency in the following ASMs: GBP (6,619, 16.21%), CLZ (5,994, 14.68%), PGB (5,671, 13.88%), VPA (4,221, 10.33%) and LEV (2,907, 7.12%). Among those PTs with *'not recovered/not resolved'* outcome, PGB (41,648, 30.63%), GBP (15,624, 11.49%), VPA (13,918, 10.24%), CLZ (11,186, 8.23%) and LEV (10,321, 7.59%) were among the most common reported (Table 10).

In old ASMs (Table 11), there was a significant negative association with outcome of *'not recovered/not resolved'* (ROR=0.71,95%CI: 0.70-0.72, p<0.001) demonstrating the effectiveness of them. Notably, there were variations between male and females. New ASMs had a significant positive association with '*not recovered/not resolved'* outcomes (ROR=1.41, 95%CI: 1.40-1.42, p<0.001). They showed a significant negative association (same in females) and a significant positive association in males with *'recovered/resolved'* (ROR=0.75, 95%CI: 0.75-0.76, p<0.001) and *'recovered/resolved with sequelae'* (ROR=0.85, 95%CI: 0.79-0.90, p<0.001) outcomes. A significant negative association (ROR=0.73, 95%CI: 0.71-0.75, p<0.001) and a significant positive association in males were found with *'fatal'* outcomes. With respect to 'recovering/resolving' outcomes, there was a significant negative association generally (ROR=0.66, 95%CI: 0.65-0.68, p<0.001), while no significant association was detected in males.

5.1.5. Sudden Unexpected Death in Epilepsy

Among all the reported PTs, 386 (0.04%) PTs were related to SUDEP, with healthcare professionals reporting 358 (91.56%). Where the field of sex was given, SUDEP was reported in 191 cases (0.05%) for males and 176 cases (0.03%) for females. The number of reported SUDEP across different age groups was as follows: 0 - 2 years: 11 (2.85%); 3 - 17 years: 50 (12.95%); 18 - 64 years: 249 (64.51%); 65 years or older: 2 (0.52%); not specified: 74 (19.17%). Age and sex

were dependent variables χ^2 (4, N = 276,694) = 97.6017, p < 0.0001 and χ^2 (1, N = 276,694) = 15.9611, p= 0.000065, respectively.

There was a significant increased association with SUDEP (Table 12) as a reported PT in subgroup of **barbiturates** (ROR=1.84, 95%CI: 1.32-2.35, p<0.001) (not significant in males) and **carboxamides** in males only (ROR=1.58, 95%CI: 1.20-1.97, p<0.001). Regarding **other antiepileptics**, generally there was no significant association, however males had a significant positive association (ROR=1.56, 95%CI: 1.34-1.78, p<0.001) and females had a significant negative association (ROR=0.67, 95%CI: 0.45-0.89, p<0.001).

The following ASMs had the most reported SUDEP PTs: LEV (65, 16.84%), LTG (58, 15.03%), LCM (43, 11.14%), VPA (36, 9.33%) and CBZ (24, 6.22%) (Table 12).

Interestingly, old type ASMs (Table 12) exhibited a significant negative association (ROR=0.72, 95%CI: 0.49-0.94, p<0.001) (not significant in females), however new type ASMs exhibited a significant positive association (ROR=1.40, 95%CI: 1.17-1.62, p<0.001) (same in males) and a significant negative association in females.

Detailed ASM can be found in Table 12B.

Table 8 Number of reported sADRs in different outcomes criteria by age group

Age Group	Outcome (Number of sADRs)						
	Fatal	Not Recovered/ Not Resolved	Recovered/ Resolved	Recovered/Resolved with Sequelae	Recovering/ Resolving	Not specified/Unknown	All
0 - 2 years	1,287	2,640	7,265	305	2,327	14,161	27,985
3 - 17 years	2,499	8,894	24,307	483	10,671	47,840	94,694
18 - 64 years	25,310	79,945	124,428	2,766	50,185	268,095	550,729
65 years or older	8,030	30,034	46,688	1,093	19,498	91,738	197,081
Not Specified	4,565	16,251	17,481	316	5,473	136,513	180,599
All	41,619	137,764	220,169	4,963	88,154	55,8347	1,051,088

Table 9 A and B Associations of outcome criteria by ASM chemical subgroups

A Outcome criterion with positive association of ASM chemical subgroups

Criterion	ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	χ^2
Not Recovered/Not Resolved	Benzodiazepines	1.23	1.21	1.25	<0.001	1.19	1.18	408.02
	Other Antiepileptics	1.50	1.49	1.52	<0.001	1.43	1.42	4385.91
Recovered/Resolved	Barbiturates	1.35	1.32	1.38	<0.001	1.26	1.24	371.55
	Carboxamides	1.57	1.56	1.58	<0.001	1.41	1.40	4214.37
	Fatty Acid derivatives	1.03	1.02	1.04	<0.001	1.02	1.01	20.84
	Hydantoins	1.38	1.36	1.41	<0.001	1.28	1.27	781.91
	Succinimides	1.32	1.21	1.42	<0.001	1.24	1.16	27.42
Recovered/Resolved with Sequelae	Carboxamides	1.20	1.12	1.28	<0.001	1.20	1.12	18.35
	Fatty Acid derivatives	1.11	1.04	1.19	<0.001	1.11	1.03	7.33
	Hydantoins	1.39	1.26	1.52	<0.001	1.39	1.26	26.02
	Succinimides	2.09	1.62	2.55	<0.001	2.08	1.61	10.04
Recovering/Resolving	Barbiturates	1.55	1.51	1.59	<0.001	1.49	1.45	416.16
	Carboxamides	2.17	2.15	2.18	<0.001	2.01	1.99	7023.83
	Fatty Acid derivatives	1.25	1.23	1.27	<0.001	1.23	1.21	535.99
	Hydantoins	1.21	1.17	1.24	<0.001	1.19	1.16	108.67
	Succinimides	1.98	1.85	2.11	<0.001	1.85	1.73	110.13
Fatal	Barbiturates	2.02	1.97	2.07	<0.001	1.95	1.90	762.76
	Benzodiazepines	2.28	2.25	2.30	<0.001	2.18	2.15	3591.52
	Hydantoins	1.55	1.51	1.59	<0.001	1.52	1.48	404.46
	Oxazolidines	4.66	4.07	5.25	<0.001	4.08	3.58	31.45

B Outcome criterion with negative association of ASM chemical subgroups

Criterion	ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	Chi-square value
Not Recovered/Not Resolved	Barbiturates	0.55	0.50	0.60	<0.001	0.59	0.54	565.69
	Carboxamides	0.60	0.58	0.62	<0.001	0.64	0.62	2,231.61
	Fatty Acid derivatives	0.69	0.67	0.70	<0.001	0.72	0.70	1,713.20
	Hydantoins	0.65	0.61	0.68	<0.001	0.68	0.65	612.78
	Succinimides	0.85	0.70	0.99	<0.001	0.86	0.74	5.24
Recovered/Resolved	Other Antiepileptics	0.74	0.73	0.75	<0.001	0.79	0.78	3,726.41
Recovered/Resolved with Sequelae	Benzodiazepines	0.78	0.66	0.89	<0.001	0.78	0.66	18.21
	Other Antiepileptics	0.86	0.81	0.92	<0.001	0.86	0.81	25.20
Recovering/Resolving	Other Antiepileptics	0.77	0.76	0.79	<0.001	0.79	0.78	1,199.55
Fatal	Carboxamides	0.77	0.74	0.81	<0.001	0.78	0.74	220.41
	Fatty Acid derivatives	0.82	0.79	0.85	<0.001	0.82	0.80	172.88
	Other Antiepileptics	0.74	0.72	0.76	<0.001	0.75	0.73	864.57

Table 10 A and B Associations of outcome criteria by ASMs

A Outcome criterion with positive association of ASMs

Criterion	ASM	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	Chi-square value
Not Recovered/Not Resolved	Brivaracetam	1.54	1.48	1.59	<0.001	1.44	1.39	246.64
	Cannabidiol	1.37	1.32	1.41	<0.001	1.31	1.27	171.77
	Cenobamate	3.15	3.04	3.25	<0.001	2.46	2.39	527.23
	Clonazepam	1.32	1.30	1.34	<0.001	1.27	1.25	659.73
	Eslicarbazepine	1.13	1.05	1.20	<0.001	1.11	1.05	10.17
	Fenfluramine	1.54	1.39	1.68	<0.001	1.44	1.32	34.30
	Gabapentin	1.38	1.36	1.40	<0.001	1.32	1.30	1,200.75
	Lacosamide	1.26	1.23	1.29	<0.001	1.22	1.19	227.27
	Pheneturide	6.73	5.34	8.12	<0.001	3.87	3.17	9.76
	Pregabalin	1.66	1.65	1.67	<0.001	1.54	1.53	6,323.04
Recovered/Resolved	Aminobutyric acid	1.79	1.33	2.24	<0.001	1.54	1.23	6.40
	Cannabidiol	1.21	1.17	1.26	<0.001	1.16	1.13	85.20
	Carbamazepine	1.62	1.61	1.64	<0.001	1.45	1.44	3,793.38
	Cenobamate	1.37	1.26	1.48	<0.001	1.28	1.20	32.64
	Clobazam	1.08	1.04	1.12	<0.001	1.06	1.03	12.58
	Clorazepate potassium	2.26	1.52	3.00	<0.001	1.80	1.33	4.89
	Eslicarbazepine	1.20	1.14	1.26	<0.001	1.15	1.11	35.29
	Ethosuximide	1.32	1.21	1.43	<0.001	1.24	1.16	25.18
	Fosphenytoin	1.96	1.87	2.06	<0.001	1.64	1.58	199.88
	Levetiracetam	1.05	1.03	1.07	<0.001	1.04	1.03	33.26
	Mesuximide	1.36	1.02	1.71	<0.001	1.27	1.01	3.10
	Methylphenobarbital	1.70	1.56	1.85	<0.001	1.49	1.39	53.04
	Oxcarbazepine	1.33	1.30	1.36	<0.001	1.24	1.22	370.47
	Perampanel	2.31	2.25	2.36	<0.001	1.82	1.79	1,049.20
	Pheneturide	3.90	2.52	5.29	<0.001	2.45	1.76	4.32
	Phenobarbital	1.33	1.30	1.36	<0.001	1.25	1.22	278.83
	Phenytoin	1.36	1.33	1.38	<0.001	1.27	1.25	647.67
	Primidone	1.36	1.27	1.44	<0.001	1.26	1.20	54.36
	Retigabine	1.65	1.54	1.77	<0.001	1.46	1.38	74.61
	Rufinamide	1.64	1.50	1.78	<0.001	1.45	1.35	48.47
	Stiripentol	1.32	1.21	1.42	<0.001	1.24	1.16	27.00
	Sultiame	1.81	1.63	2.00	<0.001	1.56	1.43	41.13
	Tiagabine	3.77	3.67	3.88	<0.001	2.41	2.36	725.83
	Topiramate	1.09	1.06	1.11	<0.001	1.07	1.05	52.13
	Valproic acid and Sodium Valproate	1.05	1.03	1.06	<0.001	1.04	1.03	43.65
	Zonisamide	1.47	1.42	1.52	<0.001	1.34	1.30	218.43
Recovered/Resolved with Sequelae	Aminobutyric acid	7.82	6.67	8.98	<0.001	7.59	6.47	17.22
	Carbamazepine	1.34	1.25	1.44	<0.001	1.34	1.25	40.77
	Ethosuximide	2.30	1.83	2.76	<0.001	2.28	1.82	13.00
	Fenfluramine	4.20	3.79	4.62	<0.001	4.14	3.74	54.83
	Lamotrigine	1.11	1.01	1.20	<0.001	1.10	1.01	4.09
	Perampanel	1.49	1.19	1.80	<0.001	1.49	1.19	6.71
	Phenytoin	1.39	1.26	1.52	<0.001	1.38	1.25	24.35
	Primidone	1.57	1.15	1.99	<0.001	1.56	1.14	4.44
	Topiramate	1.14	1.01	1.27	<0.001	1.14	1.01	4.08
	Valproic acid and Sodium Valproate	1.15	1.07	1.23	<0.001	1.15	1.07	12.59
Recovering/Resolving	Carbamazepine	2.35	2.33	2.37	<0.001	2.15	2.13	7,193.68
	Cenobamate	1.57	1.42	1.72	<0.001	1.50	1.37	34.33
	Clorazepate potassium	2.45	1.49	3.41	<0.001	2.21	1.41	3.57
	Ethosuximide	2.10	1.97	2.23	<0.001	1.94	1.82	123.14
	Ethotoin	9.19	8.58	9.80	<0.001	5.68	5.33	75.02
	Fosphenytoin	1.56	1.42	1.71	<0.001	1.50	1.37	38.59
	Lamotrigine	1.16	1.14	1.19	<0.001	1.15	1.13	141.97
	Oxcarbazepine	1.51	1.47	1.55	<0.001	1.45	1.42	398.64
	Perampanel	1.92	1.85	2.00	<0.001	1.80	1.73	315.32
	Phenobarbital	1.59	1.54	1.63	<0.001	1.52	1.48	389.37
	Phenytoin	1.18	1.15	1.22	<0.001	1.17	1.13	81.81
	Primidone	1.45	1.34	1.57	<0.001	1.41	1.30	40.92
	Retigabine	1.78	1.62	1.94	<0.001	1.68	1.54	51.99

	Rufinamide	2.56	2.39	2.73	<0.001	2.29	2.15	126.06
	Stiripentol	1.23	1.08	1.39	<0.001	1.21	1.07	6.87
	Sultiame	1.97	1.72	2.22	<0.001	1.83	1.62	29.55
	Valproic acid and Sodium Valproate	1.30	1.28	1.32	<0.001	1.27	1.25	678.52
	Zonisamide	1.70	1.63	1.77	<0.001	1.61	1.55	225.02
Fatal	Clonazepam	2.56	2.54	2.59	<0.001	2.43	2.40	4,474.94
	Ethotoin	5.82	5.05	6.59	<0.001	4.90	4.28	25.85
	Fosphenytoin	3.15	3.01	3.29	<0.001	2.91	2.78	277.10
	Gabapentin	2.03	2.00	2.06	<0.001	1.96	1.93	2,710.83
	Methylphenobarbital	5.03	4.85	5.21	<0.001	4.35	4.20	390.60
	Phenobarbital	1.99	1.93	2.05	<0.001	1.92	1.87	592.98
	Phenytoin	1.47	1.42	1.51	<0.001	1.44	1.40	278.49
	Primidone	1.38	1.22	1.54	<0.001	1.36	1.21	16.06
	Trimethadione	5.64	5.04	6.25	<0.001	4.78	4.29	40.43
	Vigabatrin	1.78	1.71	1.86	<0.001	1.73	1.66	257.57

B Outcome criterion with negative association of ASMs

Criterion	ASM	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	Chi-square value
Not Recovered/Not Resolved	Barbexaclone	0.54	0.48	0.59	<0.001	0.57	0.52	486.22
	Carbamazepine	0.53	0.51	0.56	<0.001	0.57	0.55	2,361.97
	Clobazam	0.79	0.74	0.85	<0.001	0.82	0.77	67.50
	Fosphenytoin	0.40	0.21	0.60	<0.001	0.44	0.26	88.99
	Lamotrigine	0.56	0.54	0.59	<0.001	0.60	0.57	2,112.44
	Levetiracetam	0.88	0.86	0.90	<0.001	0.89	0.87	144.26
	Methylphenobarbital	0.41	0.13	0.70	0.0047	0.45	0.18	39.47
	Oxcarbazepine	0.79	0.75	0.83	<0.001	0.81	0.78	128.72
	Phenobarbital	0.53	0.47	0.58	<0.001	0.56	0.51	519.12
	Phenytoin	0.66	0.62	0.69	<0.001	0.69	0.66	536.61
	Primidone	0.75	0.63	0.87	<0.001	0.77	0.67	23.38
	Retigabine	0.75	0.57	0.92	<0.001	0.77	0.61	10.63
	Rufinamide	0.77	0.56	0.98	<0.001	0.80	0.61	5.81
	Stiripentol	0.29	0.07	0.52	0.01	0.32	0.11	126.04
	Tiagabine	0.59	0.40	0.78	<0.001	0.62	0.45	30.45
	Valproic acid and Sodium Valproate	0.71	0.69	0.73	<0.001	0.74	0.72	1,319.08
	Vigabatrin	0.51	0.44	0.58	<0.001	0.55	0.48	376.07
	Zonisamide	0.91	0.84	0.98	<0.001	0.92	0.86	6.95
Recovered/Resolved	Brivaracetam	0.78	0.72	0.83	<0.001	0.81	0.77	76.66
	Clonazepam	0.96	0.94	0.98	<0.001	0.97	0.95	15.67
	Felbamate	0.75	0.54	0.95	<0.001	0.79	0.62	7.62
	Fenfluramine	0.79	0.64	0.95	<0.001	0.83	0.70	9.00
	Gabapentin	0.69	0.67	0.71	<0.001	0.74	0.72	1,616.15
	Lamotrigine	0.88	0.86	0.90	<0.001	0.90	0.89	207.50
	Pregabalin	0.72	0.71	0.74	<0.001	0.77	0.76	2,771.86
	Vigabatrin	0.68	0.63	0.73	<0.001	0.73	0.68	236.03
Recovered/Resolved with Sequelae	Cannabidiol	0.63	0.31	0.96	<0.001	0.63	0.31	7.83
	Clonazepam	0.72	0.59	0.85	<0.001	0.72	0.59	23.60
	Gabapentin	0.86	0.75	0.96	<0.001	0.86	0.75	8.09
	Lacosamide	0.78	0.60	0.96	<0.001	0.78	0.60	7.42
	Pregabalin	0.90	0.83	0.97	<0.001	0.90	0.83	9.61
	Vigabatrin	0.67	0.35	0.99	<0.001	0.67	0.35	6.07
Recovering/Resolving	Brivaracetam	0.71	0.62	0.80	<0.001	0.73	0.64	53.19
	Cannabidiol	0.78	0.71	0.86	<0.001	0.80	0.73	42.49
	Eslicarbazepine	0.86	0.75	0.96	<0.001	0.87	0.77	8.40
	Gabapentin	0.76	0.73	0.79	<0.001	0.77	0.75	374.50
	Lacosamide	0.84	0.79	0.88	<0.001	0.85	0.81	62.20
	Pregabalin	0.70	0.68	0.72	<0.001	0.72	0.70	1,335.30
	Tiagabine	0.57	0.32	0.82	<0.001	0.59	0.35	19.39
	Vigabatrin	0.84	0.76	0.91	<0.001	0.85	0.78	23.01
Fatal	Brivaracetam	0.25	0.04	0.46	0.02	0.26	0.05	194.94
	Carbamazepine	0.82	0.78	0.86	<0.001	0.83	0.79	96.87
	Cenobamate	0.42	0.05	0.80	0.03	0.43	0.06	21.76
	Clobazam	0.82	0.72	0.91	<0.001	0.82	0.73	16.77
	Eslicarbazepine	0.30	0.07	0.54	0.01	0.31	0.08	111.28
	Lacosamide	0.79	0.73	0.85	<0.001	0.80	0.74	54.26
	Lamotrigine	0.72	0.68	0.76	<0.001	0.73	0.69	252.69
	Levetiracetam	0.83	0.79	0.86	<0.001	0.83	0.79	95.57
	Oxcarbazepine	0.77	0.70	0.84	<0.001	0.78	0.71	49.08
	Perampanel	0.40	0.19	0.60	<0.001	0.40	0.21	88.23
	Pregabalin	0.55	0.52	0.58	<0.001	0.56	0.54	1,722.57
	Retigabine	0.42	0.01	0.83	0.046	0.43	0.02	18.25
	Stiripentol	0.50	0.18	0.83	0.003	0.51	0.19	17.85
	Tiagabine	0.57	0.22	0.92	0.002	0.58	0.23	10.41
	Topiramate	0.88	0.83	0.93	<0.001	0.89	0.84	23.84
	Valproic acid and Sodium Valproate	0.74	0.71	0.77	<0.001	0.75	0.72	336.71

Table 11 Comparison of outcomes of PTs by old ASMs and new ASMs

Outcome criterion		ROR	Lower 95%CI	Upper 95%CI	z statistic	p-value	PRR	Chi-square value
Fatal	Old ASMs	1.37	1.35	1.39	133.67	p<0.001	1.35	939.15
	Male	*0.94*	*0.92*	*0.97*	*66.35*	*p<0.001*	*0.95*	*16.36*
	Female	*1.15*	*1.12*	*1.17*	*90.92*	*p<0.001*	*1.14*	*121.88*
	New ASMs	0.73	0.71	0.75	71.60	p<0.001	0.74	939.15
	Male	*1.30*	*1.28*	*1.32*	*113.08*	*p<0.001*	*1.29*	*521.83*
	Female	*0.64*	*0.61*	*0.66*	*57.79*	*p<0.001*	*0.65*	*1,707.60*
Not recovered/Not resolved	Old ASMs	0.71	0.70	0.72	111.50	p<0.001	0.74	2,924.76
	Male	*0.36*	*0.33*	*0.38*	*31.63*	*p<0.001*	*0.39*	*9,213.21*
	Female	*0.88*	*0.86*	*0.89*	*112.05*	*p<0.001*	*0.89*	*281.13*
	New ASMs	1.41	1.40	1.42	221.41	p<0.001	1.35	2,924.76
	Male	*1.03*	*1.02*	*1.05*	*147.86*	*p<0.001*	*1.03*	*23.00*
	Female	*1.50*	*1.49*	*1.51*	*257.32*	*p<0.001*	*1.42*	*4,903.69*
Recovered/Resolved	Old ASMs	1.32	1.31	1.33	266.83	p<0.001	1.25	3,217.77
	Male	*0.67*	*0.66*	*0.69*	*91.33*	*p<0.001*	*0.72*	*2,971.72*
	Female	*1.30*	*1.29*	*1.31*	*215.22*	*p<0.001*	*1.23*	*1,883.17*
	New ASMs	0.75	0.75	0.76	152.08	p<0.001	0.80	3,217.77
	Male	*1.07*	*1.06*	*1.08*	*184.07*	*p<0.001*	*1.05*	*128.91*
	Female	*0.91*	*0.90*	*0.92*	*181.91*	*p<0.001*	*0.92*	*387.22*
Recovered/Resolved with sequelae	Old ASMs	1.18	1.12	1.24	40.07	p<0.001	1.18	32.26
	Male	*0.62*	*0.53*	*0.72*	*13.12*	*p<0.001*	*0.62*	*100.89*
	Female	*1.22*	*1.15*	*1.29*	*34.45*	*p<0.001*	*1.22*	*31.43*
	New ASMs	0.85	0.79	0.90	28.67	p<0.001	0.85	32.26
	Male	*1.14*	*1.07*	*1.20*	*33.70*	*p<0.001*	*1.14*	*14.53*
	Female	*0.93*	*0.87*	*0.99*	*31.30*	*p<0.001*	*0.93*	*5.95*
Recovering/Resolving	Old ASMs	1.51	1.49	1.52	209.29	p<0.001	1.46	3,282.49
	Male	*0.84*	*0.82*	*0.86*	*81.03*	*p<0.001*	*0.85*	*274.47*
	Female	*1.37*	*1.35*	*1.38*	*158.66*	*p<0.001*	*1.33*	*1,322.44*
	New ASMs	0.66	0.65	0.68	92.10	p<0.001	0.69	3,282.49
	Male	*1.01*	*1.00*	*1.03*	*117.49*	*p<0.001*	*1.01*	*2.01*
	Female	*0.82*	*0.81*	*0.84*	*110.60*	*p<0.001*	*0.84*	*683.07*

Table 12 Sudden unexplained death in epilepsy

A Sudden unexplained death by antiseizure medication chemical subgroups

ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	Chi-square value
Barbiturates	**1.84**	**1.32**	**2.35**	**<0.001**	**1.84**	**1.321706**	**5.51**
Benzodiazepines	0.66	0.22	1.10	0.003	0.66	0.222455	3.43
Carboxamides	1.05	0.74	1.36	<0.001	1.05	0.740172	0.09
Fatty Acid derivatives	0.93	0.64	1.22	<0.001	0.93	0.644622	0.23
Hydantoins	1.29	0.83	1.75	<0.001	1.29	0.82858	1.18
Other Antiepileptics	1.00	0.80	1.21	<0.001	1.00	0.801031	0.00
Oxazolidines	0.00	N/C	N/C	N/C	0.00	N/C	0.03
Succinimides	1.42	N/C	3.39	N/C	1.42	N/C	0.13

B Sudden unexplained death by antiseizure medications

ASM	ROR	Lower 95%CI	Upper 95%CI	p-value	PRR	Lower 95%CI	Chi-square value
Barbexaclone	40.31	38.91	41.71	<0.001	39.73	38.35	75.16
Brivaracetam	2.49	1.79	3.19	<0.001	2.48	1.78	6.95
Cenobamate	3.24	1.85	4.63	<0.001	3.24	1.85	3.08
Clobazam	2.02	1.40	2.65	<0.001	2.02	1.39	5.04
Eslicarbazepine	3.28	2.53	4.03	<0.001	3.28	2.53	10.87
Felbamate	8.01	6.62	9.40	<0.001	7.99	6.60	12.17
Fenfluramine	4.46	3.07	5.85	<0.001	4.46	3.07	5.34
Lacosamide	3.70	3.38	4.02	<0.001	3.70	3.38	75.30
Lamotrigine	1.88	1.60	2.16	<0.001	1.88	1.60	20.21
Levetiracetam	2.17	1.90	2.43	<0.001	2.16	1.90	33.96
Perampanel	5.85	5.30	6.41	<0.001	5.84	5.29	50.49
Phenobarbital	1.79	1.22	2.37	<0.001	1.79	1.22	4.06
Retigabine	15.96	15.26	16.67	<0.001	15.88	15.18	109.28
Stiripentol	2.91	1.52	4.30	<0.001	2.91	1.52	2.49
Sultiame	5.19	3.22	7.15	<0.001	5.18	3.22	3.37
Tiagabine	3.78	2.39	5.17	<0.001	3.77	2.39	4.06
Vigabatrin	3.62	3.12	4.12	<0.001	3.62	3.12	29.11

C Sudden unexplained death by comparing old and new antiseizure medications

	ROR	Lower 95%CI	Upper 95%CI	z statistic	p-value	PRR	Chi-square value
Old ASMs	0.72	0.49	0.94	6.33	p<0.001	0.72	8.78
Male	*0.51*	*0.15*	*0.87*	*2.81*	*p<0.001*	*0.51*	*14.05*
Female	*0.78*	*0.49*	*1.06*	*5.38*	*p<0.001*	*0.78*	*3.06*
New ASMs	1.40	1.17	1.62	12.34	p<0.001	1.40	8.78
Male	*2.07*	*1.86*	*2.28*	*19.56*	*p<0.001*	*2.07*	*49.38*
Female	*0.69*	*0.47*	*0.91*	*6.27*	*p<0.001*	*0.69*	*11.51*

5.1.6. Sex differences in ASMs outcomes, seriousness and SUDEP

In general, more sADRs were reported from females (603,936; 57.46%) than males (391,174; 37.21%).

In barbiturates, looking at outcomes, a significant increased association was noticed with *'recovered/resolved with sequalae'* in males only. Only females had a significant positive association with *'fatal'* outcome in phenobarbital, methylphenobarbital and primidone. As for seriousness criteria, *'congenital anomaly'* seriousness criterion had a significant positive association in males and a significant negative association in females. As regards *'hospitalisation'* and *'congenital anomaly'* seriousness criteria, there was a significant positive association with primidone in males. Only females had significant increased association with SUDEP. Only females taking barbexaclone had a significant positive association with SUDEP.

As regards benzodiazepines, a significant decreased association was found with outcomes of *'recovered/resolved with sequelae'* in females only. Regarding the outcomes of *'recovered/resolved'* and *'recovering/resolving'*, a significant positive association was found in males compared to significant negative association in females. PTs of *'not recovered/not resolved'* outcomes had a significant positive association in females, though a significant negative association was found in males. There was a significant positive association in clonazepam with *'not recovered/not resolved'* outcomes in females only compared to a significant negative association in males. Regarding seriousness, *'medically important condition'* seriousness criterion, males had negative significant association in comparison to positive significant association in females. As for *'disabling'* seriousness criterion, there was a significant positive association in females, though males had a significant negative association. There was a significant positive association in males taking clorazepate potassium with *'resulting in death'*, *'hospitalisation'* and *'life threatening'* seriousness criteria. As regards '*congenital anomaly'* seriousness, males had a significant positive association with clobazam compared to significant negative association in females. Only males taking clobazam had a significant positive association with SUDEP.

With respect to carboxamides, a significant positive association was found with *'recovered/resolved with sequelae'* in females only. There was a significant positive association in eslicarbazepine with *'not recovered/not resolved'* in males only. Focusing on seriousness, there was a significant positive association with *'hospitalisation'* in males taking rufinamide compared

to a significant negative association in females. Only females taking rufinamide had a significant positive association with *'disabling'* seriousness criterion. Only males had significant increased association with SUDEP. Only males taking eslicarbazepine and oxcarbazepine had a significant positive association with SUDEP. Only females taking rufinamide had a significant positive association with SUDEP.

With respect to fatty acid derivatives, males had a significant negative association with seriousness criterion of 'hospitalisation'. As for life threatening seriousness criterion, males had a significant negative association compared to a significant positive association observed in females. Only females had a significant positive association in Aminobutyric acid and valproate with 'life threatening' seriousness criterion. Only males taking Tiagabine had a significant positive association with SUDEP.

As regards hydantoins, there was a significant positive association in Ethotoin in females only with 'fatal' outcome. Only females had a significant positive association in Mephenytoin with 'not recovered/not resolved'. Looking at seriousness, as for 'disabling' seriousness criterion, a significant negative association was found in males in comparison to a significant positive association in females. Only females had a significant positive association in Ethotoin with 'resulting in death' seriousness criterion. As regards 'hospitalisation' seriousness criterion, there was a significant positive association with Mephenytoin in females only. There was a significant positive association in Mephenytoin in females with 'life threatening' seriousness criterion.

Regarding other antiepileptics, there was a significant negative association in females and a significant positive association in males with 'fatal', 'recovered/resolved' and 'recovered/resolved with sequelae'. There was a significant positive association in Cannabidiol and Lamotrigine in males only compared to a significant negative association in females with fatal outcome. There was a significant positive association in Pheneturide (females only), Fenfluramine (females only), Felbamate (females only) and Topiramate (females only) with 'not recovered/not resolved' outcome. Regarding Seriousness, with respect to seriousness criteria of 'hospitalisation' and 'death', females had a significant negative association in general, though males had a significant positive association. As regards seriousness criterion of 'disabling', there was a significant negative association in males, while there was a significant positive association in females. As for 'medically important condition' seriousness criterion, there was a significant positive association

in females, however there was a significant negative association in males. There was a significant positive association in Fenfluramine (females only), Lamotrigine (males only), Levetiracetam (males only) and Zonisamide (males only) with 'resulting in death' seriousness. As regards 'hospitalisation' seriousness, there was a significant positive association with Sultiame (males only), Felbamate (females only), Gabapentin (males only), Retigabine (males only) and Topiramate (males only). As for 'congenital anomaly' seriousness, males had a significant positive association with Topiramate. There was a significant positive association in Lamotrigine (males only) and Retigabine (females only) with 'disabling' seriousness. Regarding 'life threatening' seriousness, there was a significant positive association in Fenfluramine (females only), Levetiracetam (males only), Perampanel (males only) and Topiramate (males only). Males had a significant increased association with SUDEP in comparison to a significant negative association in females. Only males taking Stripentol and Topiramate had a significant positive association with SUDEP. Only females taking Sultiame, Brivaracetam and Cenobamate had a significant increased association with SUDEP.

With respect to oxazolidines, outcome of 'recovering/resolving', males only who had a significant positive association. Focusing on seriousness, only females had a significant positive association with 'medically important condition' seriousness criterion. With respect to 'congenital anomaly', there was a significant positive association in males. In females only, there was a significant positive association in Trimethadione with 'hospitalisation' seriousness. Regarding congenital anomaly seriousness, there was a significant positive association in Trimethadione in males only.

As for succinimides, there was a significant positive association in Mesuximide in males only with fatal outcome. With regards to seriousness, there was a significant positive association in Mesuximide in females only with 'hospitalisation' seriousness. Regarding life threatening seriousness, there was a significant positive association in Mesuximide in males only.

Table 13 Sex associations differences by ASM chemical subgroups

A Positive Associations in Males by ASM chemical subgroups

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	p-value	PRR	χ2
Seriousness	Other Medically Important Condition	Hydantoins	1.26	1.23	1.29	79.38	<0.001	1.09	210.11
	Caused/Prolonged Hospitalisation	Barbiturates	1.65	1.61	1.69	81.81	<0.001	1.34	630.62
		Benzodiazepines	1.21	1.19	1.23	104.03	<0.001	1.13	267.91
		Carboxamides	1.60	1.58	1.62	172.02	<0.001	1.32	2602.61
		Hydantoins	1.67	1.64	1.70	110.75	<0.001	1.35	1184.95
		Other Antiepileptics	1.03	1.02	1.04	202.67	<0.001	1.02	41.37
	Congenital Anomaly	Barbiturates	1.46	1.37	1.54	34.12	<0.001	1.43	78.40
		Fatty acid derivatives	6.63	6.61	6.65	588.39	<0.001	5.63	36344.31
		Oxazolidines	82.44	81.45	83.43	163.07	<0.001	18.70	314.70
	Disabling	Fatty acid derivatives	1.33	1.29	1.36	70.87	<0.001	1.31	228.59
	Life Threatening	Barbiturates	1.47	1.39	1.55	36.39	<0.001	1.44	91.80
		Benzodiazepines	1.30	1.25	1.34	53.72	<0.001	1.28	116.13
		Carboxamides	1.53	1.49	1.56	82.27	<0.001	1.49	527.16
		Hydantoins	1.61	1.55	1.66	55.08	<0.001	1.56	269.40
	Results in Death	Barbiturates	2.09	2.02	2.15	65.25	<0.001	1.96	553.09
		Benzodiazepines	2.37	2.34	2.41	135.05	<0.001	2.20	2566.15
		Hydantoins	1.64	1.59	1.69	62.28	<0.001	1.58	360.50
		Other Antiepileptics	1.32	1.30	1.33	134.45	<0.001	1.29	788.89
		Oxazolidines	3.42	2.35	4.50	6.22	<0.001	3.00	5.67
Outcome	Fatal	Barbiturates	1.99	1.91	2.07	51.43	<0.001	1.92	328.89
		Benzodiazepines	2.69	2.65	2.73	135.14	<0.001	2.53	2672.47
		Hydantoins	1.48	1.42	1.55	45.10	<0.001	1.46	145.34
		Other Antiepileptics	1.33	1.30	1.35	112.72	<0.001	1.31	579.71
		Oxazolidines	3.71	2.50	4.92	5.99	<0.001	3.36	5.16
	Not Recovered/Not Resolved	Other Antiepileptics	1.09	1.08	1.11	152.95	<0.001	1.08	153.61
	Recovered/Resolved	Barbiturates	1.51	1.47	1.55	67.07	<0.001	1.37	339.86
		Benzodiazepines	1.07	1.04	1.10	77.34	<0.001	1.06	24.14
		Carboxamides	1.57	1.55	1.59	151.37	<0.001	1.41	1914.18
		Fatty acid derivatives	1.11	1.09	1.13	119.03	<0.001	1.08	119.21
		Hydantoins	1.56	1.53	1.60	93.40	<0.001	1.40	724.78

		Other Antiepileptics	1.04	1.03	1.05	173.22	<0.001	1.03	48.36
		Succinimides	1.75	1.58	1.91	21.12	<0.001	1.52	46.63
	Recovered/Resolved With Sequelae	Barbiturates	1.45	1.21	1.70	11.68	<0.001	1.45	9.11
		Fatty acid derivatives	1.21	1.11	1.31	23.09	<0.001	1.21	13.29
		Hydantoins	1.51	1.33	1.69	16.47	<0.001	1.51	20.45
		Other Antiepileptics	1.15	1.08	1.22	33.24	<0.001	1.15	16.75
		Succinimides	2.56	1.86	3.25	7.18	<0.001	2.54	7.47
	Recovering/Resolving	Barbiturates	1.54	1.48	1.61	49.68	<0.001	1.48	198.41
		Benzodiazepines	1.12	1.08	1.16	56.12	<0.001	1.11	30.82
		Carboxamides	2.04	2.01	2.07	153.53	<0.001	1.89	2994.33
		Fatty acid derivatives	1.22	1.19	1.25	93.07	<0.001	1.20	230.28
		Hydantoins	1.24	1.19	1.29	49.22	<0.001	1.22	74.94
		Oxazolidines	4.93	4.05	5.82	10.89	<0.001	3.74	15.27
Event of special Interest	Sudden unexplained death in epilepsy	Carboxamides	1.58	1.20	1.97	8.06	<0.001	1.58	5.57
		Other Antiepileptics	1.56	1.34	1.78	13.81	<0.001	1.56	15.68

B Negative associations in Males by ASM chemical subgroups

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	Significance Level	PRR	χ2
Seriousness	Other Medically Important Condition	Barbiturates	0.80	0.76	0.84	39.31	<0.001	0.91	127.74
		Benzodiazepines	0.89	0.86	0.91	77.14	<0.001	0.95	110.13
		Carboxamides	0.80	0.78	0.82	85.96	<0.001	0.91	568.22
		Fatty acid derivatives	0.78	0.76	0.79	100.43	<0.001	0.90	1083.51
		Other antiepileptics	0.96	0.95	0.97	193.54	<0.001	0.99	53.78
		Succinimides	0.71	0.56	0.85	9.23	<0.001	0.86	21.13
	Caused/Prolonged Hospitalisation	Fatty acid derivatives	0.97	0.96	0.99	120.59	<0.001	0.98	11.58
		Succinimides	0.84	0.67	0.99	10.16	<0.001	0.89	4.74
	Congenital Anomaly	Benzodiazepines	0.55	0.47	0.62	14.76	<0.001	0.56	271.12
		Carboxamides	0.46	0.39	0.52	13.96	<0.001	0.47	608.70
		Hydantoins	0.41	0.30	0.52	7.28	<0.001	0.42	261.42
		Other antiepileptics	0.39	0.35	0.42	22.98	<0.001	0.40	3413.45
	Disabling	Barbiturates	0.58	0.44	0.72	8.26	<0.001	0.59	60.59
		Benzodiazepines	0.91	0.85	0.97	28.36	<0.001	0.91	8.33
		Carboxamides	0.69	0.63	0.75	23.41	<0.001	0.70	158.21
		Other antiepileptics	0.96	0.94	0.99	71.96	<0.001	0.97	7.13
		Hydantoins	0.86	0.78	0.95	19.79	<0.001	0.87	11.04
	Life Threatening	Fatty acid derivatives	0.92	0.88	0.96	49.11	<0.001	0.93	18.84
		Other antiepileptics	0.92	0.89	0.94	77.51	<0.001	0.92	52.51
	Results in Death	Carboxamides	0.93	0.89	0.97	45.71	<0.001	0.94	11.79
		Fatty acid derivatives	0.94	0.91	0.97	55.87	<0.001	0.94	13.18
		Succinimides	0.31	0.00	0.86	0.00	<0.001	0.33	19.11
Outcome	Fatal	Carboxamides	0.82	0.77	0.87	31.50	<0.001	0.83	57.37
		Fatty acid derivatives	0.89	0.85	0.93	42.63	<0.001	0.89	32.03
		Succinimides	0.37	0.00	0.99	0.00	<0.001	0.38	10.84
	Not Recovered/Not Resolved	Barbiturates	0.55	0.48	0.63	14.62	<0.001	0.59	250.25
		Benodiazepines	0.92	0.88	0.95	52.45	<0.001	0.93	25.30
		Carboxamides	0.59	0.55	0.62	34.97	<0.001	0.62	1033.29
		Fatty acid derivatives	0.75	0.72	0.77	59.05	<0.001	0.77	540.36
		Hydantoins	0.58	0.53	0.64	21.14	<0.001	0.62	387.60

C Positive associations in females by ASM chemical subgroups

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	p-value	PRR	χ^2
Seriousness	Other Medically Important Condition	Benzodiazepines	1.07	1.05	1.09	111.72	<0.001	1.03	51.14
		Hydantoins	1.38	1.35	1.41	90.93	<0.001	1.12	456.64
		Other Antiepileptics	1.21	1.21	1.22	292.40	<0.001	1.08	2182.82
		Oxazolidines	2.31	1.41	3.22	5.00	<0.001	1.29	3.49
	Caused/Prolonged Hospitalisation	Barbiturates	1.40	1.37	1.44	72.65	<0.001	1.23	310.69
		Benzodiazepines	1.28	1.26	1.30	135.11	<0.001	1.17	690.51
		Carboxamides	1.58	1.57	1.60	193.31	<0.001	1.32	3190.67
		Hydantoins	1.68	1.66	1.71	117.97	<0.001	1.36	1361.80
	Congenital Anomaly	Fatty acid derivatives	3.59	3.57	3.62	277.79	<0.001	3.28	11068.34
	Disabling	Benzodiazepines	1.30	1.26	1.35	57.27	<0.001	1.29	134.78
		Fatty acid derivatives	1.28	1.24	1.31	65.49	<0.001	1.26	156.76
		Hydantoins	1.10	1.03	1.18	29.82	<0.001	1.10	7.16
		Other Antiepileptics	1.08	1.06	1.10	99.33	<0.001	1.08	49.98
	Life Threatening	Barbiturates	1.62	1.54	1.69	43.85	<0.001	1.57	172.76
		Benzodiazepines	1.90	1.86	1.93	109.99	<0.001	1.82	1423.65
		Carboxamides	1.29	1.26	1.33	74.30	<0.001	1.28	220.03
		Fatty acid derivatives	1.20	1.17	1.24	69.24	<0.001	1.19	113.74
		Hydantoins	1.57	1.52	1.63	56.56	<0.001	1.53	270.41
	Results in Death	Barbiturates	2.08	2.02	2.14	68.50	<0.001	1.96	608.76
		Benzodiazepines	1.59	1.56	1.62	95.17	<0.001	1.54	784.87
		Hydantoins	1.76	1.71	1.80	72.29	<0.001	1.68	551.31
		Oxazolidines	13.01	12.25	13.77	33.59	<0.001	7.67	73.91
Outcome	Fatal	Barbiturates	1.99	1.92	2.07	54.29	<0.001	1.92	367.14
		Benzodiazepines	1.80	1.76	1.84	94.16	<0.001	1.75	972.04
		Hydantoins	1.52	1.46	1.58	49.30	<0.001	1.49	186.29
		Oxazolidines	7.07	6.16	7.98	15.27	<0.001	5.72	24.31
	Not Recovered/Not Resolved	Benzodiazepines	1.47	1.45	1.49	119.38	<0.001	1.39	990.77
		Other Antiepileptics	1.56	1.55	1.57	266.25	<0.001	1.47	5822.17
	Recovered/Resolved	Barbiturates	1.33	1.29	1.37	60.36	<0.001	1.25	167.90
		Carboxamides	1.59	1.57	1.61	174.46	<0.001	1.42	2622.65

		Fatty acid derivatives	1.12	1.10	1.14	117.58	<0.001	1.09	140.46
		Hydantoins	1.33	1.29	1.36	80.80	<0.001	1.24	298.29
		Succinimides	1.18	1.04	1.32	16.63	<0.001	1.14	5.31
	Recovered/Resolved With Sequelae	Carboxamides	1.40	1.30	1.50	26.83	<0.001	1.40	41.77
		Fatty acid derivatives	1.14	1.04	1.25	20.76	<0.001	1.14	5.93
		Hydantoins	1.40	1.22	1.57	15.55	<0.001	1.40	14.01
		Succinimides	1.95	1.32	2.57	6.13	<0.001	1.94	4.56
	Recovering/Resolving	Barbiturates	1.43	1.37	1.49	46.91	<0.001	1.38	137.89
		Carboxamides	1.85	1.82	1.87	152.40	<0.001	1.73	2638.62
		Fatty acid derivatives	1.22	1.19	1.24	90.30	<0.001	1.19	210.99
		Hydantoins	1.06	1.01	1.11	41.49	<0.001	1.05	4.71
		Succinimides	2.38	2.22	2.53	30.12	<0.001	2.14	128.00
Event of special Interest	Sudden unexplained death in epilepsy	Barbiturates	2.22	1.56	2.88	6.58	<0.001	2.22	5.89

D Negative associations in females by ASM chemical subgroups

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	p-value	PRR	χ2
Seriousness	Other Medically Important Condition	Barbiturates	0.88	0.84	0.92	45.65	<0.001	0.95	41.62
		Carboxamides	0.91	0.90	0.93	110.94	<0.001	0.96	116.10
		Fatty acid derivatives	0.80	0.78	0.81	100.14	<0.001	0.91	837.35
		Succinimides	0.76	0.65	0.88	12.73	<0.001	0.89	20.58
	Caused/Prolonged Hospitalisation	Other Antiepileptics	0.78	0.78	0.79	183.31	<0.001	0.85	3261.93
		Succinimides	0.84	0.71	0.97	13.07	<0.001	0.89	7.29
	Congenital Anomaly	Barbiturates	0.75	0.65	0.86	13.88	<0.001	0.76	27.17
		Benzodiazepines	0.21	0.12	0.31	4.56	<0.001	0.22	1311.04
		Carboxamides	0.21	0.13	0.29	5.21	<0.001	0.22	1776.59
		Hydantoins	0.14	0.00	0.32	0.00	<0.001	0.14	652.21
		Other Antiepileptics	0.10	0.06	0.14	4.63	<0.001	0.10	19464.93
	Disabling	Barbiturates	0.87	0.76	0.98	15.75	<0.001	0.88	6.18
		Carboxamides	0.51	0.46	0.57	17.48	<0.001	0.52	531.20
	Life Threatening	Other Antiepileptics	0.70	0.68	0.72	69.68	<0.001	0.71	1241.63
	Results in Death	Carboxamides	0.73	0.69	0.77	37.22	<0.001	0.75	249.02
		Fatty acid derivatives	0.76	0.72	0.80	40.26	<0.001	0.77	216.34
		Other Antiepileptics	0.59	0.57	0.61	62.85	<0.001	0.61	3159.60

		Succinimides	0.13	0.00	0.79	0.00	<0.001	0.14	51.27
Outcome	Fatal	Carboxamides	0.71	0.66	0.76	29.28	<0.001	0.72	200.29
		Fatty acid derivatives	0.79	0.74	0.83	34.87	<0.001	0.79	114.80
		Other Antiepileptics	0.63	0.61	0.65	55.64	<0.001	0.64	1728.73
	Not Recovered/Not Resolved	Barbiturates	0.62	0.55	0.69	18.11	<0.001	0.65	196.81
		Carboxamides	0.68	0.65	0.71	49.10	<0.001	0.71	782.41
		Fatty acid derivatives	0.73	0.71	0.76	56.11	<0.001	0.76	568.01
		Hydantoins	0.76	0.72	0.81	32.48	<0.001	0.79	134.31
	Recovered/Resolved	Benzodiazepines	0.94	0.92	0.97	80.31	<0.001	0.95	24.39
		Other Antiepileptics	0.89	0.88	0.90	176.39	<0.001	0.91	509.43
	Recovered/Resolved With Sequelae	Benzodiazepines	0.78	0.63	0.93	10.19	<0.001	0.78	10.04
		Other Antiepileptics	0.94	0.88	0.99	31.07	<0.001	0.94	4.92
	Recovering/Resolving	Benzodiazepines	0.81	0.78	0.85	44.15	<0.001	0.83	123.76
		Other Antiepileptics	0.80	0.78	0.81	105.23	<0.001	0.81	872.42
Event of special Interest	Sudden unexplained death in epilepsy	Other Antiepileptics	0.67	0.45	0.89	5.98	<0.001	0.67	12.79

Table 14 Sex associations differences by ASMs

A Positive Associations in Males by ASMs

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	p-value	PRR	χ2
Seriousness	Other Medically Important Condition	Clorazepate Potassium	3.31	2.07	4.55	5.23	<0.001	1.38	4.02
		Aminobutyric acid	2.78	1.80	3.75	5.58	<0.001	1.34	4.60
		Phenytoin	1.27	1.24	1.31	78.12	<0.001	1.09	221.05
		Gabapentin	1.39	1.36	1.41	114.92	<0.001	1.13	739.34
		Pregabalin	1.20	1.18	1.21	145.13	<0.001	1.07	470.32
		Retigabine	1.20	1.04	1.36	14.76	<0.001	1.07	5.18
		Topiramate	1.19	1.16	1.23	63.42	<0.001	1.07	87.90
	Caused/Prolonged Hospitalisation	Phenobarbital	1.65	1.61	1.69	74.14	<0.001	1.34	517.50
		Methylphenobarbital	2.42	2.22	2.63	23.43	<0.001	1.61	78.16
		Primidone	1.51	1.40	1.62	27.67	<0.001	1.28	57.84
		Clonazepam	1.21	1.18	1.23	93.22	<0.001	1.13	212.69
		Clorazepate Potassium	31.14	29.13	33.16	30.27	<0.001	2.67	27.55
		Clobazam	1.20	1.15	1.25	46.53	<0.001	1.12	48.73
		Carbamazepine	1.87	1.85	1.89	174.74	<0.001	1.44	3528.27
		Oxcarbazepine	1.07	1.03	1.11	51.51	<0.001	1.04	9.60
		Rufinamide	1.36	1.17	1.55	14.14	<0.001	1.21	10.34
		Tiagabine	4.74	4.53	4.95	44.62	<0.001	2.04	261.50
		Vigabatrin	1.57	1.51	1.62	59.19	<0.001	1.31	291.86
		Phenytoin	1.70	1.67	1.73	109.60	<0.001	1.36	1196.25
		Fosphenytoin	1.22	1.09	1.35	18.02	<0.001	1.13	8.61
		Fenfluramine	1.29	1.06	1.53	10.76	<0.001	1.17	4.63
		Sultiame	1.49	1.26	1.72	12.60	<0.001	1.27	11.50
		Gabapentin	1.08	1.05	1.10	91.93	<0.001	1.05	40.81
		Lamotrigine	1.84	1.81	1.86	153.14	<0.001	1.42	2646.14
		Levetiracetam	1.10	1.08	1.12	97.94	<0.001	1.06	69.15
		Retigabine	11.50	11.34	11.66	138.69	<0.001	8.00	1392.69
		Topiramate	1.08	1.05	1.12	58.11	<0.001	1.05	18.66
		Zonisamide	1.33	1.25	1.40	34.47	<0.001	1.19	54.03
	Congenital Anomaly	Phenobarbital	1.42	1.32	1.51	29.77	<0.001	1.39	54.11
		Primidone	1.92	1.72	2.12	18.90	<0.001	1.85	42.75
		Clobazam	1.24	1.12	1.35	21.66	<0.001	1.22	13.82

		Valproic acid and Sodium Valproate	7.43	7.41	7.46	654.21	<0.001	6.18	41427.01
		Mephenytoin	64.88	63.95	65.81	136.63	<0.001	17.67	278.84
		Topiramate	2.85	2.79	2.90	97.50	<0.001	2.65	1403.48
		Trimethadione	82.44	81.45	83.43	163.07	<0.001	18.70	314.70
	Disabling	Aminobutyric acid	3.58	2.38	4.79	5.84	<0.001	3.28	4.94
		Valproic acid and Sodium Valproate	1.42	1.38	1.46	74.99	<0.001	1.40	348.05
		Tiagabine	2.59	2.26	2.92	15.26	<0.001	2.45	33.90
		Fenfluramine	2.19	1.74	2.63	9.64	<0.001	2.10	12.50
		Gabapentin	1.15	1.09	1.21	39.73	<0.001	1.14	23.28
		Lamotrigine	1.15	1.09	1.21	37.61	<0.001	1.15	21.27
		Pregabalin	1.16	1.12	1.20	56.97	<0.001	1.15	50.96
	Life Threatening	Phenobarbital	1.57	1.49	1.66	36.45	<0.001	1.53	112.27
		Methylphenobarbital	2.45	2.13	2.78	14.83	<0.001	2.30	31.45
		Clonazepam	1.41	1.36	1.46	54.22	<0.001	1.38	174.98
		Clorazepate Potassium	71.17	70.06	72.28	125.53	<0.001	16.59	215.19
		Carbamazepine	1.70	1.66	1.74	83.04	<0.001	1.65	686.08
		Oxcarbazepine	1.12	1.03	1.21	24.96	<0.001	1.11	6.44
		Tiagabine	1.48	1.11	1.85	7.85	<0.001	1.45	4.41
		Phenytoin	1.43	1.37	1.50	45.71	<0.001	1.41	133.60
		Fosphenytoin	5.34	5.18	5.50	65.23	<0.001	4.44	526.15
		Lamotrigine	1.52	1.47	1.56	63.63	<0.001	1.48	310.38
		Levetiracetam	1.06	1.01	1.11	42.18	<0.001	1.05	4.84
		Perampanel	1.23	1.07	1.39	15.19	<0.001	1.22	6.60
		Topiramate	1.22	1.15	1.30	31.30	<0.001	1.21	26.53
		Zonisamide	1.45	1.30	1.60	18.99	<0.001	1.42	23.82
		Mesuximide	7.82	7.09	8.55	21.01	<0.001	5.93	42.95
	Results in Death	Phenobarbital	2.23	2.17	2.30	65.07	<0.001	2.09	578.19
		Methylphenobarbital	4.82	4.58	5.06	39.45	<0.001	3.95	202.82
		Clonazepam	2.83	2.80	2.87	154.34	<0.001	2.57	3508.39
		Clorazepate Potassium	32.53	31.55	33.51	65.06	<0.001	11.51	122.22
		Vigabatrin	1.72	1.64	1.81	38.37	<0.001	1.65	150.43
		Phenytoin	1.58	1.52	1.63	57.44	<0.001	1.53	280.26
		Fosphenytoin	2.91	2.73	3.09	31.43	<0.001	2.62	146.22

		Gabapentin	2.40	2.37	2.44	137.83	<0.001	2.23	2687.44
		Lamotrigine	1.32	1.27	1.36	57.46	<0.001	1.29	145.55
		Levetiracetam	1.11	1.06	1.15	49.80	<0.001	1.10	21.26
		Zonisamide	1.29	1.15	1.44	17.78	<0.001	1.27	12.54
		Trimethadione	3.42	2.35	4.50	6.22	<0.001	3.00	5.67
Outcome	Fatal	Phenobarbital	2.13	2.05	2.21	51.30	<0.001	2.04	347.26
		Metharbital	74.21	71.95	76.48	64.27	<0.001	19.30	54.17
		Methylphenobarbital	3.57	3.27	3.87	23.10	<0.001	3.24	77.47
		Clonazepam	3.21	3.17	3.25	155.08	<0.001	2.96	3539.86
		Vigabatrin	1.84	1.74	1.95	35.40	<0.001	1.79	142.27
		Phenytoin	1.40	1.34	1.47	40.68	<0.001	1.38	97.74
		Fosphenytoin	3.02	2.81	3.23	28.34	<0.001	2.80	119.00
		Cannabidiol	1.39	1.28	1.50	24.21	<0.001	1.37	33.34
		Gabapentin	2.82	2.78	2.85	144.51	<0.001	2.64	3075.06
		Lamotrigine	1.14	1.08	1.20	38.84	<0.001	1.13	19.69
		Trimethadione	3.71	2.50	4.92	5.99	<0.001	3.36	5.16
		Mesuximide	2.25	1.07	3.43	3.73	<0.001	2.14	1.91
	Not Recovered/Not Resolved	Barbexaclone	1.95	1.21	2.70	5.16	<0.001	1.74	3.25
		Eslicarbazepine	1.32	1.20	1.43	22.24	<0.001	1.27	21.87
		Cannabidiol	1.38	1.32	1.45	40.38	<0.001	1.32	90.94
		Brivaracetam	1.62	1.53	1.70	36.56	<0.001	1.50	120.43
		Cenobamate	2.95	2.79	3.11	37.21	<0.001	2.36	205.03
		Gabapentin	1.12	1.08	1.15	68.67	<0.001	1.10	45.24
		Lacosamide	1.35	1.30	1.39	59.03	<0.001	1.29	171.63
		Pregabalin	1.28	1.25	1.30	116.55	<0.001	1.23	496.04
	Recovered/Resolved	Phenobarbital	1.46	1.41	1.51	58.42	<0.001	1.34	232.39
		Methylphenobarbital	2.14	1.93	2.35	19.99	<0.001	1.74	53.04
		Primidone	1.67	1.55	1.78	28.10	<0.001	1.47	75.80
		Clobazam	1.22	1.17	1.28	41.53	<0.001	1.17	47.42
		Carbamazepine	1.60	1.58	1.62	134.80	<0.001	1.43	1596.68
		Oxcarbazepine	1.52	1.48	1.56	68.27	<0.001	1.37	358.94
		Rufinamide	1.78	1.58	1.98	17.30	<0.001	1.53	32.23
		Valproic acid and Sodium Valproate	1.14	1.12	1.15	117.84	<0.001	1.10	173.52

		Tiagabine	3.49	3.30	3.67	36.53	<0.001	2.31	194.62
		Ethotoin	3.25	2.06	4.44	5.37	<0.001	2.23	4.25
		Phenytoin	1.52	1.49	1.55	87.88	<0.001	1.38	594.35
		Fosphenytoin	2.47	2.34	2.60	36.31	<0.001	1.90	189.02
		Cannabidiol	1.18	1.12	1.24	38.48	<0.001	1.14	28.21
		Fenfluramine	1.60	1.35	1.86	12.30	<0.001	1.43	13.35
		Phenacemide	7.80	6.11	9.50	9.01	<0.001	3.27	7.91
		Sultiame	2.15	1.91	2.39	17.52	<0.001	1.74	40.82
		Cenobamate	1.52	1.36	1.68	18.75	<0.001	1.38	27.17
		Lamotrigine	1.43	1.41	1.46	105.47	<0.001	1.32	709.67
		Levetiracetam	1.19	1.17	1.22	93.03	<0.001	1.15	191.94
		Perampanel	2.57	2.50	2.65	66.93	<0.001	1.95	650.34
		Retigabine	1.73	1.57	1.90	20.49	<0.001	1.51	43.32
		Stiripentol	1.45	1.30	1.60	18.99	<0.001	1.33	24.02
		Topiramate	1.16	1.12	1.20	53.90	<0.001	1.12	46.54
		Zonisamide	1.50	1.42	1.58	35.39	<0.001	1.36	92.80
		Ethosuximide	1.72	1.56	1.89	20.23	<0.001	1.50	41.79
		Mesuximide	2.21	1.53	2.89	6.36	<0.001	1.77	5.47
	Recovered/Resolved With Sequelae	Phenobarbital	1.31	1.03	1.59	9.10	<0.001	1.31	3.55
		Primidone	2.75	2.27	3.23	11.25	<0.001	2.73	18.64
		Aminobutyric acid	28.24	27.03	29.44	45.99	<0.001	25.09	69.68
		Valproic acid and Sodium Valproate	1.22	1.12	1.33	22.54	<0.001	1.22	13.91
		Phenytoin	1.50	1.32	1.69	15.92	<0.001	1.50	18.85
		Fenfluramine	2.30	1.16	3.44	3.97	<0.001	2.29	2.19
		Lamotrigine	2.00	1.87	2.12	30.92	<0.001	1.99	119.35
		Perampanel	1.54	1.10	1.98	6.84	<0.001	1.53	3.71
		Retigabine	3.01	2.35	3.67	8.96	<0.001	2.98	11.88
		Ethosuximide	2.70	2.00	3.40	7.58	<0.001	2.68	8.44
	Recovering/Resolving	Phenobarbital	1.62	1.55	1.69	48.16	<0.001	1.54	209.81
		Primidone	1.21	1.02	1.39	13.10	<0.001	1.19	4.13
		Clonazepam	1.14	1.10	1.19	52.10	<0.001	1.13	37.60
		Carbamazepine	2.27	2.24	2.30	154.12	<0.001	2.06	3264.81
		Oxcarbazepine	1.43	1.37	1.49	45.21	<0.001	1.38	129.82
		Rufinamide	2.42	2.18	2.67	19.42	<0.001	2.17	53.68

		Valproic acid and Sodium Valproate	1.26	1.23	1.28	93.09	<0.001	1.23	288.71
		Phenytoin	1.23	1.18	1.28	47.23	<0.001	1.21	63.75
		Fosphenytoin	1.53	1.33	1.73	15.01	<0.001	1.47	17.77
		Sultiame	1.96	1.64	2.29	11.88	<0.001	1.82	17.31
		Cenobamate	1.51	1.29	1.74	13.41	<0.001	1.45	13.69
		Lamotrigine	1.54	1.51	1.58	82.82	<0.001	1.48	549.71
		Levetiracetam	1.11	1.07	1.15	58.21	<0.001	1.10	29.30
		Perampanel	1.66	1.55	1.77	29.41	<0.001	1.57	81.93
		Retigabine	1.48	1.24	1.71	12.09	<0.001	1.42	10.29
		Topiramate	1.25	1.19	1.31	41.62	<0.001	1.23	56.45
		Zonisamide	1.94	1.83	2.04	36.11	<0.001	1.80	157.68
		Trimethadione	4.93	4.05	5.82	10.89	<0.001	3.74	15.27
Event of spcial Interest	Sudden unexplained death in epilepsy	Phenobarbital	1.99	1.19	2.80	4.84	<0.001	1.99	2.92
		Clobazam	2.99	2.24	3.74	7.84	<0.001	2.99	9.10
		Eslicarbazepine	6.54	5.65	7.42	14.51	<0.001	6.52	23.09
		Oxcarbazepine	2.97	2.38	3.57	9.72	<0.001	2.97	14.00
		Tiagabine	6.12	4.16	8.09	6.11	<0.001	6.11	4.26
		Vigabatrin	5.23	4.63	5.83	17.09	<0.001	5.22	36.53
		Fenfluramine	9.48	7.52	11.45	9.46	<0.001	9.45	7.54
		Felbamate	11.18	9.21	13.14	11.14	<0.001	11.13	9.20
		Lacosamide	4.60	4.18	5.03	21.40	<0.001	4.60	60.97
		Lamotrigine	1.62	1.14	2.11	6.55	<0.001	1.62	3.90
		Levetiracetam	2.40	2.03	2.77	12.62	<0.001	2.40	22.56
		Perampanel	7.73	7.03	8.43	21.61	<0.001	7.71	45.80
		Retigabine	25.14	24.33	25.95	60.83	<0.001	24.92	135.69
		Stiripentol	6.24	4.85	7.63	8.79	<0.001	6.23	8.74
		Topiramate	2.19	1.56	2.82	6.83	<0.001	2.19	6.29
		Zonisamide	2.91	1.77	4.05	5.02	<0.001	2.91	3.73

B Negative Associations in Males by ASMs

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	Significance Level	PRR	χ2
Seriousness	Other Medically Important Condition	Phenobarbital	0.80	0.76	0.85	35.90	<0.001	0.91	98.17
		Primidone	0.74	0.63	0.85	13.57	<0.001	0.88	31.28
		Clonazepam	0.87	0.85	0.90	68.05	<0.001	0.94	117.90
		Carbamazepine	0.74	0.72	0.76	69.26	<0.001	0.88	773.81
		Oxcarbazepine	0.87	0.83	0.91	43.18	<0.001	0.94	47.64
		Rufinamide	0.55	0.36	0.74	5.74	<0.001	0.75	40.54
		Valproic acid and Sodium Valproate	0.78	0.76	0.79	96.27	<0.001	0.90	1003.28
		Tiagabine	0.52	0.34	0.71	5.47	<0.001	0.73	46.98
		Vigabatrin	0.83	0.78	0.88	31.35	<0.001	0.93	48.32
		Cannabidiol	0.26	0.21	0.32	9.16	<0.001	0.47	2557.91
		Fenfluramine	0.31	0.06	0.55	2.39	0.02	0.52	97.40
		Sultiame	0.33	0.08	0.57	2.62	0.01	0.55	88.83
		Brivaracetam	0.37	0.30	0.44	10.14	<0.001	0.60	812.02
		Cenobamate	0.27	0.11	0.43	3.38	<0.001	0.48	303.15
		Lacosamide	0.65	0.61	0.68	38.19	<0.001	0.82	664.49
		Lamotrigine	0.93	0.90	0.95	76.23	<0.001	0.97	38.57
		Levetiracetam	0.91	0.89	0.94	83.16	<0.001	0.96	67.43
		Perampanel	0.36	0.29	0.44	9.23	<0.001	0.59	726.01
		Stiripentol	0.31	0.17	0.45	4.28	<0.001	0.53	286.48
		Zonisamide	0.69	0.62	0.77	18.28	<0.001	0.85	93.81
		Ethosuximide	0.71	0.56	0.87	9.07	<0.001	0.86	18.90
	Caused/Prolonged Hospitalisation	Eslicarbazepine	0.58	0.48	0.68	11.22	<0.001	0.68	117.84
		Valproic acid and Sodium Valproate	0.92	0.90	0.93	108.29	<0.001	0.95	101.03
		Cannabidiol	0.60	0.54	0.66	20.11	<0.001	0.70	298.86
		Brivaracetam	0.38	0.29	0.47	8.20	<0.001	0.49	474.13
		Pregabalin	0.79	0.77	0.81	92.29	<0.001	0.85	748.64
		Stiripentol	0.80	0.66	0.95	10.86	<0.001	0.86	8.98
	Congenital Anomaly	Clonazepam	0.39	0.29	0.48	7.92	<0.001	0.40	408.11
		Carbamazepine	0.48	0.41	0.55	12.95	<0.001	0.49	410.44

		Eslicarbazepine	0.08	0.00	0.82	0.00	<0.001	0.08	77.12
		Oxcarbazepine	0.49	0.36	0.63	7.14	<0.001	0.50	108.80
		Vigabatrin	0.07	0.00	0.54	0.00	<0.001	0.07	219.99
		Phenytoin	0.41	0.29	0.52	6.95	<0.001	0.42	252.43
		Cannabidiol	0.02	0.00	0.90	0.00	<0.001	0.02	255.78
		Gabapentin	0.14	0.01	0.28	2.04	<0.001	0.15	1042.41
		Lacosamide	0.24	0.08	0.40	2.90	<0.001	0.25	350.34
		Levetiracetam	0.56	0.49	0.63	15.90	<0.001	0.57	285.36
		Pregabalin	0.03	0.00	0.23	0.00	<0.001	0.03	2973.52
	Disabling	Phenobarbital	0.64	0.49	0.78	8.52	<0.001	0.64	37.62
		Primidone	0.45	0.03	0.87	2.10	0.04	0.46	14.35
		Clobazam	0.84	0.69	0.98	11.33	<0.001	0.84	5.67
		Carbamazepine	0.71	0.64	0.78	21.06	<0.001	0.72	102.84
		Eslicarbazepine	0.31	0.00	0.72	0.00	<0.001	0.31	35.73
		Oxcarbazepine	0.66	0.53	0.78	9.94	<0.001	0.66	41.70
		Vigabatrin	0.22	0.00	0.51	0.00	<0.001	0.23	127.02
		Phenytoin	0.89	0.80	0.98	20.12	<0.001	0.89	6.79
		Fosphenytoin	0.43	0.00	0.96	0.00	<0.001	0.44	10.51
		Cannabidiol	0.18	0.00	0.49	0.00	<0.001	0.18	147.99
		Brivaracetam	0.10	0.00	0.67	0.00	<0.001	0.10	96.40
		Lacosamide	0.58	0.46	0.69	9.73	<0.001	0.59	87.62
		Levetiracetam	0.77	0.71	0.84	23.35	<0.001	0.78	62.38
		Stiripentol	0.48	0.00	0.99	0.00	<0.001	0.49	8.14
	Life Threatening	Primidone	0.63	0.32	0.94	3.99	<0.001	0.64	8.45
		Clobazam	0.81	0.68	0.94	12.43	<0.001	0.82	10.22
		Eslicarbazepine	0.69	0.44	0.93	5.56	<0.001	0.70	9.47
		Vigabatrin	0.34	0.14	0.55	3.37	<0.001	0.36	118.37
		Cannabidiol	0.13	0.00	0.45	0.00	<0.001	0.13	224.89
		Brivaracetam	0.39	0.14	0.64	3.04	<0.001	0.40	57.94
		Gabapentin	0.90	0.84	0.95	31.92	<0.001	0.90	15.42
		Lacosamide	0.77	0.69	0.86	17.23	<0.001	0.78	32.41
		Pregabalin	0.70	0.66	0.74	32.31	<0.001	0.71	274.89

	Results in Death	Primidone	0.65	0.37	0.92	4.58	<0.001	0.66	9.58
		Clobazam	0.68	0.55	0.80	10.62	<0.001	0.69	37.06
		Eslicarbazepine	0.42	0.14	0.69	2.96	<0.001	0.43	41.56
		Oxcarbazepine	0.86	0.77	0.95	18.97	<0.001	0.87	10.33
		Valproic acid and Sodium Valproate	0.88	0.84	0.91	48.47	<0.001	0.88	54.16
		Brivaracetam	0.42	0.20	0.63	3.71	<0.001	0.43	65.73
		Cenobamate	0.22	0.00	0.84	0.00	<0.001	0.23	27.47
		Perampanel	0.43	0.20	0.67	3.69	<0.001	0.45	52.97
		Stiripentol	0.50	0.11	0.89	2.52	0.01	0.52	12.41
		Ethosuximide	0.23	0.00	0.89	0.00	<0.001	0.24	23.16
Outcome	Fatal	Clobazam	0.76	0.61	0.90	10.28	<0.001	0.77	14.04
		Carbamazepine	0.87	0.81	0.92	29.39	<0.001	0.87	23.99
		Eslicarbazepine	0.52	0.22	0.82	3.38	<0.001	0.53	18.54
		Oxcarbazepine	0.77	0.66	0.88	13.25	<0.001	0.78	20.14
		Valproic acid and Sodium Valproate	0.81	0.76	0.85	35.62	<0.001	0.81	90.32
		Brivaracetam	0.33	0.03	0.63	2.13	0.03	0.34	58.65
		Cenobamate	0.33	0.00	0.96	0.00	<0.001	0.34	13.16
		Lacosamide	0.87	0.78	0.96	18.69	<0.001	0.88	8.58
		Perampanel	0.52	0.25	0.78	3.88	<0.001	0.53	25.88
		Stiripentol	0.52	0.06	0.99	2.20	<0.001	0.53	7.61
	Not Recovered/Not Resolved	Phenobarbital	0.52	0.43	0.60	12.07	<0.001	0.55	241.56
		Methylphenobarbital	0.37	0.00	0.82	0.00	<0.001	0.41	19.99
		Primidone	0.80	0.63	0.97	9.06	<0.001	0.82	6.52
		Clonazepam	0.95	0.91	0.98	49.12	<0.001	0.95	8.49
		Clobazam	0.81	0.73	0.89	19.92	<0.001	0.83	27.62
		Carbamazepine	0.51	0.47	0.55	24.97	<0.001	0.55	1095.51
		Oxcarbazepine	0.74	0.67	0.80	22.01	<0.001	0.76	85.14
		Valproic acid and Sodium Valproate	0.76	0.74	0.79	58.41	<0.001	0.79	425.37
		Vigabatrin	0.56	0.46	0.65	11.23	<0.001	0.59	144.55
		Phenytoin	0.60	0.55	0.66	21.53	<0.001	0.64	332.34
		Fosphenytoin	0.27	0.00	0.61	0.00	<0.001	0.30	66.95
		Lamotrigine	0.67	0.63	0.71	32.57	<0.001	0.70	369.03

		Levetiracetam	0.96	0.93	0.99	58.63	<0.001	0.97	6.09
		Stiripentol	0.23	0.00	0.60	0.00	<0.001	0.26	70.87
		Topiramate	0.77	0.72	0.83	26.14	<0.001	0.80	76.06
	Recovered/Resolved	Vigabatrin	0.70	0.63	0.77	19.09	<0.001	0.75	95.97
		Brivaracetam	0.84	0.75	0.93	18.29	<0.001	0.87	15.08
		Gabapentin	0.73	0.70	0.77	47.70	<0.001	0.78	402.92
		Pregabalin	0.85	0.83	0.87	82.50	<0.001	0.87	261.86
	Recovered/Resolved With Sequelae	Clonazepam	0.79	0.58	0.99	7.49	<0.001	0.79	5.30
		Gabapentin	0.78	0.59	0.96	8.25	<0.001	0.78	7.27
	Recovering/Resolving	Eslicarbazepine	0.71	0.53	0.89	7.70	<0.001	0.73	13.41
		Vigabatrin	0.81	0.71	0.91	15.41	<0.001	0.82	15.91
		Cannabidiol	0.69	0.59	0.80	12.62	<0.001	0.71	44.41
		Brivaracetam	0.76	0.62	0.90	10.61	<0.001	0.78	14.56
		Gabapentin	0.74	0.69	0.78	31.38	<0.001	0.75	173.47
		Lacosamide	0.82	0.75	0.88	24.17	<0.001	0.83	36.65
		Pregabalin	0.77	0.74	0.80	48.33	<0.001	0.79	267.35

C Positive Associations in Females by ASMs

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	Significance Level	PRR	χ2
Seriousness	Other Medically Important Condition	Barbexaclone	5.81	5.12	6.50	16.50	<0.001	1.49	32.14
		Clonazepam	1.07	1.05	1.09	104.35	<0.001	1.03	44.14
		Clobazam	1.07	1.02	1.12	41.38	<0.001	1.03	6.89
		Oxcarbazepine	1.29	1.26	1.33	72.18	<0.001	1.10	207.71
		Rufinamide	1.38	1.19	1.58	14.07	<0.001	1.12	11.00
		Aminobutyric acid	2.95	2.29	3.60	8.83	<0.001	1.36	11.55
		Ethotoin	2.31	1.41	3.22	5.00	<0.001	1.29	3.49
		Phenytoin	1.39	1.36	1.43	89.46	<0.001	1.13	459.26
		Fosphenytoin	1.16	1.03	1.30	16.85	<0.001	1.06	4.85
		Felbamate	1.56	1.35	1.78	14.28	<0.001	1.17	16.90
		Gabapentin	1.38	1.36	1.40	152.22	<0.001	1.12	1262.35
		Levetiracetam	1.07	1.05	1.09	107.79	<0.001	1.03	44.02
		Pregabalin	1.45	1.44	1.46	250.94	<0.001	1.15	4190.09
		Retigabine	1.30	1.13	1.46	15.49	<0.001	1.10	9.76
		Topiramate	1.27	1.25	1.30	108.14	<0.001	1.09	420.63
	Caused/Prolonged Hospitalisation	Phenobarbital	1.50	1.46	1.54	70.06	<0.001	1.28	363.48
		Methylphenobarbital	2.41	2.22	2.60	25.08	<0.001	1.61	89.27
		Clonazepam	1.37	1.35	1.39	135.50	<0.001	1.21	973.97
		Carbamazepine	1.89	1.87	1.91	198.47	<0.001	1.44	4590.66
		Oxcarbazepine	1.06	1.03	1.10	60.39	<0.001	1.04	12.29
		Tiagabine	2.52	2.38	2.66	36.52	<0.001	1.64	192.49
		Vigabatrin	1.56	1.51	1.61	59.05	<0.001	1.30	288.66
		Mephenytoin	17.40	15.95	18.86	23.41	<0.001	2.56	27.98

		Phenytoin	1.68	1.65	1.71	115.09	<0.001	1.36	1294.04
		Fosphenytoin	1.68	1.55	1.81	25.25	<0.001	1.35	62.01
		Fenfluramine	1.80	1.67	1.94	27.07	<0.001	1.41	80.72
		Felbamate	1.34	1.14	1.54	13.24	<0.001	1.20	8.43
		Lamotrigine	1.74	1.72	1.75	199.68	<0.001	1.38	4112.78
		Zonisamide	1.23	1.17	1.29	39.59	<0.001	1.14	45.53
		Trimethadione	3.66	2.59	4.74	6.69	<0.001	1.89	6.46
		Mesuximide	2.58	2.21	2.95	13.81	<0.001	1.66	27.72
	Congenital Anomaly	Valproic acid and Sodium Valproate	4.05	4.03	4.08	311.38	<0.001	3.65	13399.05
		Clonazepam	1.42	1.38	1.47	60.80	<0.001	1.40	229.18
		Rufinamide	2.33	2.00	2.67	13.61	<0.001	2.23	25.92
		Valproic acid and Sodium Valproate	1.39	1.36	1.43	70.77	<0.001	1.38	287.50
		Phenytoin	1.14	1.07	1.22	30.63	<0.001	1.14	12.93
		Fenfluramine	3.20	2.99	3.42	29.37	<0.001	2.97	127.38
		Gabapentin	1.18	1.14	1.23	54.82	<0.001	1.18	61.32
		Pregabalin	1.33	1.30	1.35	97.57	<0.001	1.31	435.09
	Disabling	Retigabine	2.96	2.70	3.23	22.16	<0.001	2.77	72.75
		Rufinamide	2.33	2.00	2.67	13.61	<0.001	2.23	25.92
	Life Threatening	Phenobarbital	1.69	1.62	1.77	42.21	<0.001	1.64	176.55
		Methylphenobarbital	5.06	4.83	5.29	42.45	<0.001	4.25	229.26
		Clonazepam	2.08	2.04	2.11	116.64	<0.001	1.98	1756.98
		Carbamazepine	1.39	1.36	1.43	71.04	<0.001	1.37	289.84
		Oxcarbazepine	1.14	1.07	1.22	30.16	<0.001	1.14	12.41
		Aminobutyric acid	4.07	3.39	4.75	11.74	<0.001	3.56	19.27
		Valproic acid and Sodium Valproate	1.26	1.23	1.30	70.70	<0.001	1.25	172.25
		Tiagabine	2.34	2.12	2.56	20.91	<0.001	2.20	61.33
		Mephenytoin	50.84	49.89	51.78	105.24	<0.001	15.24	209.33
		Phenytoin	1.41	1.35	1.47	47.25	<0.001	1.38	133.53
		Fosphenytoin	5.15	4.98	5.31	62.12	<0.001	4.31	486.44
		Fenfluramine	1.77	1.53	2.01	14.37	<0.001	1.71	22.01
		Lamotrigine	1.70	1.66	1.73	101.22	<0.001	1.64	1016.27
		Zonisamide	1.81	1.70	1.91	32.26	<0.001	1.74	114.68
	Results in Death	Phenobarbital	2.00	1.93	2.07	58.23	<0.001	1.89	423.42
		Methylphenobarbital	6.57	6.36	6.77	62.44	<0.001	4.97	426.38
		Primidone	1.56	1.39	1.73	17.68	<0.001	1.51	25.81
		Clonazepam	1.73	1.70	1.77	100.10	<0.001	1.66	1032.41
		Vigabatrin	1.52	1.43	1.62	32.29	<0.001	1.48	80.82
		Ethotoin	2.83	1.77	3.89	5.22	<0.001	2.56	4.03
		Phenytoin	1.68	1.63	1.73	66.33	<0.001	1.62	427.97
		Fosphenytoin	3.41	3.23	3.58	38.77	<0.001	2.99	220.13
		Fenfluramine	1.31	1.06	1.56	10.29	<0.001	1.28	4.46
		Gabapentin	1.21	1.18	1.24	71.52	<0.001	1.20	128.48
		Trimethadione	65.06	63.79	66.33	100.79	<0.001	13.81	151.35
Outcome	Fatal	Phenobarbital	1.83	1.74	1.91	43.16	<0.001	1.77	208.73
		Methylphenobarbital	6.88	6.65	7.10	59.56	<0.001	5.60	376.56
		Primidone	1.76	1.56	1.96	17.57	<0.001	1.71	32.74
		Clonazepam	1.96	1.93	2.00	99.64	<0.001	1.90	1217.07
		Vigabatrin	1.86	1.76	1.96	35.94	<0.001	1.80	148.76
		Ethotoin	4.30	3.24	5.36	7.94	<0.001	3.81	8.64
		Phenytoin	1.42	1.36	1.48	43.83	<0.001	1.40	118.57
		Fosphenytoin	3.56	3.36	3.76	35.49	<0.001	3.24	182.89
		Gabapentin	1.46	1.43	1.50	77.18	<0.001	1.44	408.48

		Trimethadione	16.49	15.46	17.53	31.29	<0.001	10.30	52.38
	Not Recovered/Not Resolved	Clonazepam	1.57	1.54	1.59	121.49	<0.001	1.46	1235.50
		Mephenytoin	4.14	3.26	5.02	9.22	<0.001	2.95	11.80
		Cannabidiol	1.25	1.18	1.32	35.96	<0.001	1.21	41.35
		Fenfluramine	1.67	1.51	1.83	19.98	<0.001	1.54	38.47
		Pheneturide	6.73	5.34	8.12	9.52	<0.001	3.87	9.76
		Brivaracetam	1.86	1.79	1.94	51.14	<0.001	1.68	301.27
		Cenobamate	3.48	3.34	3.62	48.45	<0.001	2.64	342.46
		Felbamate	1.31	1.04	1.57	9.63	<0.001	1.26	3.90
		Gabapentin	1.53	1.51	1.55	137.11	<0.001	1.43	1473.87
		Lacosamide	1.35	1.31	1.39	65.68	<0.001	1.29	213.69
		Pregabalin	1.73	1.71	1.74	239.50	<0.001	1.59	5854.49
		Topiramate	1.12	1.09	1.15	69.78	<0.001	1.10	49.38
	Recovered/Resolved	Phenobarbital	1.35	1.30	1.39	55.15	<0.001	1.26	149.45
		Methylphenobarbital	1.57	1.37	1.78	14.97	<0.001	1.41	18.90
		Primidone	1.17	1.06	1.29	19.88	<0.001	1.13	7.45
		Clorazepate Potassium	7.80	6.60	9.00	12.74	<0.001	3.27	15.82
		Carbamazepine	1.69	1.67	1.71	162.12	<0.001	1.49	2596.26
		Eslicarbazepine	1.40	1.32	1.48	35.63	<0.001	1.29	73.72
		Oxcarbazepine	1.24	1.20	1.27	62.12	<0.001	1.18	113.75
		Rufinamide	1.56	1.36	1.76	15.31	<0.001	1.40	19.31
		Aminobutyric acid	1.95	1.41	2.49	7.12	<0.001	1.63	6.18
		Valproic acid and Sodium Valproate	1.13	1.11	1.15	113.51	<0.001	1.10	152.04
		Tiagabine	5.25	5.11	5.38	76.16	<0.001	2.81	723.67
		Mephenytoin	2.93	2.06	3.79	6.64	<0.001	2.10	6.52
		Phenytoin	1.31	1.28	1.35	77.90	<0.001	1.23	262.61
		Fosphenytoin	1.63	1.48	1.77	22.31	<0.001	1.44	45.37
		Cannabidiol	1.26	1.21	1.32	43.04	<0.001	1.20	64.02
		Pheneturide	3.90	2.52	5.29	5.52	<0.001	2.45	4.32
		Sultiame	1.69	1.39	1.99	11.12	<0.001	1.48	12.23
		Cenobamate	1.26	1.10	1.41	15.81	<0.001	1.19	8.23
		Lacosamide	1.07	1.03	1.10	57.43	<0.001	1.05	12.31
		Lamotrigine	1.31	1.29	1.33	129.97	<0.001	1.23	717.79
		Levetiracetam	1.09	1.07	1.11	93.47	<0.001	1.07	56.65
		Perampanel	2.23	2.15	2.30	59.38	<0.001	1.78	480.52
		Retigabine	1.85	1.69	2.02	21.83	<0.001	1.58	54.48
		Stiripentol	1.30	1.15	1.45	16.96	<0.001	1.22	11.63
		Topiramate	1.12	1.09	1.15	83.09	<0.001	1.09	69.74
		Zonisamide	1.54	1.47	1.60	45.23	<0.001	1.38	162.14
		Ethosuximide	1.18	1.03	1.32	15.65	<0.001	1.13	4.64
	Recovered/Resolved With Sequelae	Carbamazepine	1.61	1.49	1.72	28.22	<0.001	1.60	70.56
		Valproic acid and Sodium Valproate	1.23	1.12	1.34	21.89	<0.001	1.23	13.32
		Phenytoin	1.41	1.23	1.59	15.39	<0.001	1.41	14.21
		Fenfluramine	4.93	4.48	5.37	21.75	<0.001	4.84	60.97
		Lamotrigine	1.21	1.10	1.33	20.57	<0.001	1.21	10.62
		Perampanel	1.56	1.14	1.98	7.26	<0.001	1.55	4.33
		Topiramate	1.22	1.07	1.37	16.20	<0.001	1.22	7.06
		Zonisamide	1.47	1.10	1.84	7.87	<0.001	1.47	4.31
		Ethosuximide	2.19	1.57	2.82	6.89	<0.001	2.18	6.41
	Recovering/Resolving	Phenobarbital	1.43	1.37	1.50	42.51	<0.001	1.39	115.56
		Primidone	1.53	1.38	1.69	19.99	<0.001	1.47	31.60
		Clorazepate Potassium	5.64	4.44	6.84	9.21	<0.001	4.09	10.17
		Carbamazepine	2.02	2.00	2.05	148.76	<0.001	1.87	2791.50
		Oxcarbazepine	1.39	1.34	1.45	51.11	<0.001	1.35	149.20
		Rufinamide	2.40	2.16	2.64	19.86	<0.001	2.16	55.91

		Valproic acid and Sodium Valproate	1.27	1.24	1.30	91.24	<0.001	1.24	293.99
		Ethotoin	22.56	21.76	23.36	55.25	<0.001	8.19	123.59
		Fosphenytoin	1.43	1.22	1.63	13.58	<0.001	1.38	11.58
		Sultiame	1.86	1.47	2.25	9.27	<0.001	1.74	9.87
		Cenobamate	1.41	1.20	1.62	13.03	<0.001	1.37	10.24
		Lamotrigine	1.52	1.49	1.54	110.73	<0.001	1.46	934.88
		Perampanel	1.98	1.88	2.08	39.11	<0.001	1.84	189.47
		Retigabine	2.03	1.81	2.24	18.37	<0.001	1.87	42.72
		Stiripentol	1.31	1.10	1.52	12.06	<0.001	1.28	6.18
		Zonisamide	1.39	1.29	1.48	28.35	<0.001	1.35	45.21
		Ethosuximide	2.55	2.39	2.71	31.24	<0.001	2.27	141.40
Event of spcial Interest	Sudden unexplained death in epilepsy	Phenobarbital	1.83	1.02	2.63	4.44	<0.001	1.83	2.21
		Barbexaclone	62.81	61.41	64.22	87.60	<0.001	61.41	118.28
		Rufinamide	5.71	3.74	7.67	5.69	<0.001	5.70	3.86
		Vigabatrin	2.34	1.46	3.22	5.19	<0.001	2.34	3.78
		Fenfluramine	2.99	1.03	4.95	2.99	<0.001	2.99	1.32
		Sultiame	13.20	11.24	15.17	13.16	<0.001	13.14	11.20
		Brivaracetam	3.03	2.15	3.92	6.74	<0.001	3.03	6.73
		Cenobamate	6.27	4.88	7.66	8.83	<0.001	6.26	8.79
		Felbamate	6.75	4.78	8.71	6.73	<0.001	6.74	4.87
		Lacosamide	2.36	1.84	2.88	8.96	<0.001	2.36	11.30
		Lamotrigine	2.01	1.69	2.34	12.06	<0.001	2.01	18.32
		Levetiracetam	1.72	1.34	2.11	8.79	<0.001	1.72	7.91
		Perampanel	3.52	2.53	4.50	6.99	<0.001	3.51	7.12
		Retigabine	8.50	7.11	9.89	11.97	<0.001	8.48	13.13

D Negative Associations in Females by ASMs

Seriousness/Outcome/ SUDEP		ASM chemical subgroup	ROR	Lower 95%CI	Upper 95%CI	Z statistic	Significance Level	PRR	χ^2
Seriousness	Other Medically Important Condition	Phenbarbital	0.93	0.89	0.97	43.06	<0.001	0.97	11.19
		Methylphenobarbital	0.73	0.54	0.92	7.67	<0.001	0.87	10.95
		Primidone	0.65	0.56	0.75	13.09	<0.001	0.83	74.30
		Carbamazepine	0.82	0.80	0.84	85.81	<0.001	0.92	436.47
		Valproic acid and Sodium Valproate	0.80	0.78	0.81	95.55	<0.001	0.91	754.56
		Tiagabine	0.63	0.50	0.77	9.30	<0.001	0.81	45.45
		Vigabatrin	0.83	0.78	0.88	31.37	<0.001	0.93	48.17
		Cannabidiol	0.24	0.18	0.30	8.42	<0.001	0.44	2961.39
		Sultiame	0.62	0.34	0.89	4.42	<0.001	0.80	12.11
		Brivaracetam	0.37	0.31	0.44	12.03	<0.001	0.60	1071.51
		Cenobamate	0.25	0.10	0.40	3.30	<0.001	0.46	383.38
		Lacosamide	0.77	0.74	0.80	50.47	<0.001	0.90	285.40
		Lamotrigine	0.92	0.90	0.94	104.52	<0.001	0.97	93.69
		Perampanel	0.32	0.25	0.40	8.38	<0.001	0.54	967.44
		Stiripentol	0.26	0.11	0.40	3.49	<0.001	0.47	395.40

		Zonisamide	0.92	0.86	0.98	29.73	<0.001	0.97	7.14
		Ethosuximide	0.72	0.60	0.85	11.39	<0.001	0.87	26.59
	Caused/Prolonged Hospitalisation	Clobazam	0.81	0.76	0.86	29.71	<0.001	0.87	60.47
		Eslicarbazepine	0.60	0.53	0.68	15.09	<0.001	0.70	162.50
		Rufinamide	0.71	0.51	0.91	6.92	<0.001	0.79	11.36
		Valproic acid and Sodium Valproate	0.96	0.94	0.97	109.84	<0.001	0.97	25.57
		Cannabidiol	0.47	0.41	0.54	15.22	<0.001	0.58	599.66
		Sultiame	0.59	0.27	0.91	3.63	<0.001	0.69	10.71
		Brivaracetam	0.34	0.26	0.42	8.37	<0.001	0.45	745.69
		Cenobamate	0.51	0.34	0.67	6.13	<0.001	0.61	70.39
		Gabapentin	0.83	0.81	0.85	90.52	<0.001	0.88	417.86
		Lacosamide	0.88	0.85	0.91	54.14	<0.001	0.92	60.39
		Levetiracetam	0.86	0.84	0.88	83.69	<0.001	0.91	206.39
		Perampanel	0.84	0.76	0.91	21.52	<0.001	0.89	21.20
		Pregabalin	0.67	0.66	0.68	111.23	<0.001	0.76	4457.97
		Stiripentol	0.74	0.59	0.88	10.06	<0.001	0.81	17.70
		Topiramate	0.65	0.63	0.68	51.44	<0.001	0.74	1170.72
		Ethosuximide	0.73	0.59	0.87	10.38	<0.001	0.81	20.55
	Congenital Anomaly	Phenobarbital	0.76	0.64	0.88	12.65	<0.001	0.77	20.63
		Clonazepam	0.13	0.01	0.26	2.11	<0.001	0.14	1396.74
		Clobazam	0.79	0.65	0.92	11.24	<0.001	0.79	11.77
		Carbamazepine	0.25	0.16	0.33	5.50	<0.001	0.25	1155.99
		Eslicarbazepine	0.08	0.00	0.67	0.00	<0.001	0.08	124.99
		Oxcarbazepine	0.16	0.00	0.36	0.00	<0.001	0.16	432.55
		Vigabatrin	0.08	0.00	0.51	0.00	<0.001	0.09	212.30
		Phenytoin	0.15	0.00	0.32	0.00	<0.001	0.15	610.03
		Brivaracetam	0.08	0.00	0.57	0.00	<0.001	0.09	164.04
		Gabapentin	0.07	0.00	0.21	0.00	<0.001	0.07	2312.41
		Lacosamide	0.12	0.00	0.32	0.00	<0.001	0.12	593.43
		Lamotrigine	0.31	0.24	0.38	8.61	<0.001	0.32	1153.35
		Levetiracetam	0.28	0.19	0.36	6.40	<0.001	0.28	1025.26
		Pregabalin	0.01	0.00	0.21	0.00	<0.001	0.01	7876.54

		Topiramate	0.50	0.43	0.58	13.25	<0.001	0.51	340.24
		Zonisamide	0.15	0.00	0.52	0.00	<0.001	0.15	134.67
	Disabling	Phenobarbital	0.83	0.71	0.95	13.14	<0.001	0.83	8.90
		Clobazam	0.54	0.37	0.72	5.98	<0.001	0.55	46.42
		Carbamazepine	0.51	0.44	0.58	14.77	<0.001	0.52	388.16
		Eslocarbazepine	0.43	0.16	0.71	3.08	<0.001	0.44	38.33
		Oxcarbazepine	0.52	0.39	0.64	8.23	<0.001	0.52	115.46
		Vigabatrin	0.31	0.07	0.56	2.49	0.01	0.32	98.25
		Fosphenytoin	0.37	0.00	0.94	0.00	<0.001	0.38	12.88
		Cannabidiol	0.36	0.14	0.58	3.23	<0.001	0.37	91.96
		Brivaracetam	0.63	0.43	0.83	6.19	<0.001	0.64	21.58
		Lacosamide	0.68	0.58	0.77	13.68	<0.001	0.69	62.63
		Lamotrigine	0.95	0.90	0.99	39.37	<0.001	0.95	5.04
		Levetiracetam	0.54	0.47	0.61	15.65	<0.001	0.55	333.86
		Perampanel	0.60	0.36	0.84	4.82	<0.001	0.61	17.20
		Stiripentol	0.33	0.00	0.93	0.00	<0.001	0.34	14.40
	Life Threatening	Primidone	0.49	0.17	0.81	2.99	<0.001	0.50	19.63
		Clobazam	0.77	0.64	0.90	11.59	<0.001	0.78	14.79
		Eslicarbazepine	0.63	0.43	0.83	6.23	<0.001	0.64	21.27
		Vigabatrin	0.42	0.23	0.60	4.47	<0.001	0.43	92.84
		Cannabidiol	0.23	0.00	0.46	0.00	<0.001	0.24	180.65
		Brivaracetam	0.38	0.17	0.60	3.46	<0.001	0.39	80.59
		Cenobamate	0.19	0.00	0.89	0.00	<0.001	0.20	27.35
		Gabapentin	0.77	0.72	0.81	34.21	<0.001	0.78	138.21
		Lacosamide	0.71	0.62	0.79	16.77	<0.001	0.72	68.54
		Levetiracetam	0.79	0.74	0.84	31.45	<0.001	0.80	87.00
		Perampanel	0.79	0.61	0.98	8.38	<0.001	0.80	5.95
		Pregabalin	0.49	0.46	0.52	29.54	<0.001	0.50	1888.46
		Stiripentol	0.43	0.00	0.89	0.00	<0.001	0.44	13.94
		Topiramate	0.73	0.67	0.79	24.17	<0.001	0.74	106.70
	Results in Death	Clobazam	0.72	0.59	0.84	11.46	<0.001	0.73	28.98
		Carbamazepine	0.78	0.73	0.82	34.45	<0.001	0.79	126.95

		Eslicarbazepine	0.15	0.00	0.51	0.00	<0.001	0.15	148.13
		Oxcarbazepine	0.79	0.71	0.86	19.46	<0.001	0.80	35.80
		Valproic acid and Sodium Valproate	0.70	0.66	0.74	34.09	<0.001	0.71	310.15
		Tiagabine	0.31	0.00	0.80	0.00	<0.001	0.32	24.50
		Cannabidiol	0.60	0.47	0.74	8.87	<0.001	0.62	57.12
		Brivaracetam	0.18	0.00	0.46	0.00	<0.001	0.19	179.80
		Cenobamate	0.27	0.00	0.80	0.00	<0.001	0.28	27.53
		Lacosamide	0.83	0.76	0.90	23.32	<0.001	0.84	28.86
		Lamotrigine	0.89	0.86	0.93	46.07	<0.001	0.90	33.76
		Levetiracetam	0.86	0.82	0.90	39.26	<0.001	0.87	46.73
		Perampanel	0.27	0.00	0.55	0.00	<0.001	0.28	97.11
		Pregabalin	0.38	0.35	0.41	22.89	<0.001	0.40	3641.08
		Retigabine	0.29	0.00	0.88	0.00	<0.001	0.30	19.31
		Stiripentol	0.53	0.16	0.90	2.82	<0.001	0.55	11.51
		Topiramate	0.69	0.63	0.74	24.45	<0.001	0.70	180.40
		Ethosuximide	0.13	0.00	0.83	0.00	<0.001	0.14	45.61
Outcome	Fatal	Clobazam	0.76	0.61	0.90	10.20	<0.001	0.76	14.50
		Carbamazepine	0.75	0.69	0.80	26.97	<0.001	0.76	108.94
		Eslicarbazepine	0.18	0.00	0.58	0.00	<0.001	0.18	90.66
		Oxcarbazepine	0.76	0.66	0.85	15.19	<0.001	0.76	31.33
		Valproic acid and Sodium Valproate	0.70	0.65	0.75	27.99	<0.001	0.71	211.46
		Tiagabine	0.29	0.00	0.91	0.00	<0.001	0.30	17.16
		Cannabidiol	0.82	0.68	0.96	11.47	<0.001	0.83	7.67
		Brivaracetam	0.25	0.00	0.54	0.00	<0.001	0.25	101.22
		Cenobamate	0.41	0.00	0.94	0.00	<0.001	0.42	11.85
		Lacosamide	0.72	0.63	0.81	15.59	<0.001	0.72	53.40
		Lamotrigine	0.89	0.85	0.94	37.97	<0.001	0.90	23.48
		Levetiracetam	0.71	0.65	0.77	24.55	<0.001	0.72	141.97
		Perampanel	0.24	0.00	0.60	0.00	<0.001	0.25	70.27
		Pregabalin	0.39	0.35	0.43	19.08	<0.001	0.40	2395.91
		Stiripentol	0.47	0.00	0.95	0.00	<0.001	0.48	10.05
		Topiramate	0.85	0.79	0.91	27.26	<0.001	0.85	28.19

		Zonisamide	0.70	0.51	0.88	7.45	<0.001	0.70	15.15
	Not Recovered/Not Resolved	Phenobarbital	0.61	0.53	0.68	15.74	<0.001	0.64	171.66
		Methylphenobarbital	0.51	0.14	0.87	2.72	0.01	0.54	13.77
		Primidone	0.75	0.59	0.91	9.07	<0.001	0.78	11.94
		Clobazam	0.87	0.79	0.94	21.92	<0.001	0.88	13.23
		Carbamazepine	0.60	0.57	0.64	35.63	<0.001	0.64	893.95
		Oxcarbazepine	0.87	0.82	0.92	32.57	<0.001	0.88	28.22
		Valproic acid and Sodium Valproate	0.76	0.74	0.79	56.35	<0.001	0.79	402.53
		Tiagabine	0.44	0.16	0.72	3.11	<0.001	0.48	35.29
		Vigabatrin	0.51	0.41	0.61	9.85	<0.001	0.54	180.64
		Phenytoin	0.77	0.72	0.82	32.16	<0.001	0.79	119.26
		Fosphenytoin	0.58	0.34	0.82	4.72	<0.001	0.61	20.22
		Lamotrigine	0.79	0.76	0.81	56.03	<0.001	0.81	296.24
		Levetiracetam	0.96	0.93	0.99	66.25	<0.001	0.97	6.62
		Stiripentol	0.37	0.08	0.66	2.51	0.01	0.41	47.96
	Recovered/Resolved	Clonazepam	0.94	0.91	0.96	74.44	<0.001	0.95	25.98
		Vigabatrin	0.68	0.61	0.76	18.54	<0.001	0.73	106.62
		Fenfluramine	0.59	0.39	0.78	5.95	<0.001	0.64	29.63
		Brivaracetam	0.90	0.83	0.98	23.52	<0.001	0.92	7.19
		Gabapentin	0.68	0.66	0.71	57.89	<0.001	0.73	1049.67
		Pregabalin	0.73	0.71	0.74	99.96	<0.001	0.77	1906.74
	Recovered/Resolved With Sequelae	Clonazepam	0.73	0.56	0.90	8.53	<0.001	0.73	13.94
		Vigabatrin	0.34	0.00	0.99	0.00	<0.001	0.34	11.81
		Cannabidiol	0.41	0.00	0.98	0.00	<0.001	0.41	10.12
		Gabapentin	0.85	0.72	0.98	12.54	<0.001	0.85	5.88
		Pregabalin	0.86	0.77	0.94	20.12	<0.001	0.86	13.09
	Recovering/Resolving	Clonazepam	0.79	0.75	0.82	39.13	<0.001	0.80	146.12
		Tiagabine	0.35	0.00	0.74	0.00	<0.001	0.37	30.34
		Vigabatrin	0.81	0.71	0.92	15.47	<0.001	0.83	15.55
		Cannabidiol	0.76	0.66	0.86	14.76	<0.001	0.78	27.42
		Fenfluramine	0.20	0.00	0.70	0.00	<0.001	0.22	48.90
		Brivaracetam	0.72	0.60	0.84	11.45	<0.001	0.74	27.20

		Gabapentin	0.71	0.67	0.74	39.73	<0.001	0.73	380.89
		Lacosamide	0.80	0.74	0.86	26.07	<0.001	0.81	54.49
		Levetiracetam	0.91	0.88	0.95	49.95	<0.001	0.92	25.62
		Pregabalin	0.64	0.62	0.66	55.55	<0.001	0.66	1525.72
		Topiramate	0.85	0.80	0.89	38.76	<0.001	0.86	58.01

5.2. Questionnaire based study on the use of CAM

5.2.1. Overview

Two hundred and twenty-seven patients filled the questionnaire (127 patients with epilepsy and 100 patients with diabetes mellitus). Among them, 114 (50.2%) were male and 112 (49.3%) were female, with one participant not specifying sex preference. Mean age was 54.54±17.33years, with PWE being significantly younger.

5.2.2. Listed CAMs

PWE listed the following CAM, used simultaneously with the ASMs: lemon balm (Melissa officinalis) (three patients), pomegranate (*Punica granatum*), rose hip (*Rosa canina*), aloe vera, valerian (*Valeriana officinalis*), Sedacur (contains: lemon balm, valerian, hop (*Humulus lupulus*)), linden (Tilia), thymus, mint (Mentha) and senna.

Patients with DM reported the following CAM, used simultaneously with the antidiabetic therapy: cinnamon (*Cinnamomum cassia*), European blueberry (*Vaccinium myrtillus*), nettle (*Urtica dioica*), dill (*Anethum graveolens*), gurmar (*Gymnema sylvestre*), Tea 'György' (fantasy name; contains: dandelion-*Taraxacum officinale*, nettle-*Urtica dioica*, perforate St John's-wort-*Hypericum perforatum*, European blueberry-*Vaccinium myrtillus*, chicory-*Cichorium intybus*) by three patients.

Patients did not report homeopathic remedies use.

Reported CAM therapies, together with their ADRs and potential drug-herb interactions are listed in Table 15. Among ADRs are GI (gastrointestinal) and CNS (central nervous system) symptoms, and dermatological conditions. In drug-herb interactions, a wide range of medicines are affected due to the modulation of cytochrome P450 enzymes such as CYP3A4 and CYP2C9, which are involved with the metabolism of many medicines.

5.2.3. patients' characteristics

Table 16 presents basic patients' characteristics. If PWE are compared to DM patients, statistically significant differences were revealed in body weight, smoking status and alcohol consumption.

5.2.4. Disease and treatment characteristics

Better disease control was observed in PWE (73.2% *vs.* 28%), but CAM was not significant among the groups despite that 7% of the patients with epilepsy had controlled disease using CAM versus 1% of patients with diabetes mellitus. Adherence rate was higher among patients with epilepsy (Table 17).

Table 15 Reported complementary and alternative therapies (CAM) and their possible consequences

Name of CAM	Is it used to treat epilepsy or diabetes mellitus?	Adverse drug reaction	Drug-herbal interaction
Lemon balm (*Melissa officinalis*)	Yes (both hypoglycaemic and anticonvulsant effects) (52) (53)	Sleep disturbances and tiredness may happen (54).	It may interact with: • Thyroid medications • Barbiturates • Sedatives • Nicotine and scopolamine • SSRIs (55, 56)
Pomegranate (*Punica granatum*)	Yes (both hypoglycaemic and anticonvulsant effects) (57, 58)	No ADR in case of moderate consumption (59)	Inhibits CYP3A4 and CYP2C9, so increases levels of drugs that are substrates of them (60)
Valerian (*Valeriana officinalis*)	Yes (hypoglycaemic effects and traditionally used in epilepsy) (61, 62)	Rare adverse events -Dizziness -Migraine -GIT effects (63)	In vitro evidence demonstrates CYP3A4 inhibition by valerian, and thus the potential to interact with CYP3A4 substrates (e.g. atorvastatin and warfarin) (64)
Rose hip (*Rosa canina*)	Traditional folk remedy for diabetes (65)	Gastrointestinal discomfort (66)	Marginal effect on CYP3A4 activity (67)
Aloe vera	Yes (both hypoglycaemic and anticonvulsant effects) (68, 69)	-Carcinogenic activity in rats (Group 2B human carcinogen) -Skin irritation -Hives -Cramping and diarrhoea -Hepatotoxicity (70)	-Reduction in prostaglandins synthesis, which may inhibit secondary aggregation of platelets. -The increased loss of potassium may potentiate the actions of conventional drugs, such as cardiac glycosides and corticosteroids. (71)
Sedacur (contains: -Lemon balm, -Valerian, -Hop (*Humulus lupulus*)	-Look above for Lemon balm and Valerian - Hop (*Humulus lupulus*) has shown both hypoglycaemic and anticonvulsant properties (72, 73).	- Look above for Lemon balm and Valerian -No significant adverse effects were reported from hop (74).	- Look above for Lemon balm and Valerian -Hop interacts with both serotonin (5-HT6) and melatonin (ML1) receptor subtypes in the CNS. -Hop can inhibit CYP enzymes (75)
Linden (*Tilia*)	Anticonvulsant effect (76)	No reported adverse effects in literature apart from rare reports about allergic reactions (77).	No documented drug interactions have been reported (78).
Mint (*Mentha*)	Yes (both hypoglycaemic and anticonvulsant effects) (79, 80).	It can be an irritant and may cause, although rarely, hypersensitivity reactions and provoke contact dermatitis (81).	-Increases topical absorption of 5-fluorouracil. -Synergy effect with some antibacterials -Calcium channel blocking activity, so it can have additive effect with antihypertensives. -It may inhibit CYP3A4 (82).
Thymus	Yes (both hypoglycaemic and anticonvulsant effects) (83, 84).	-Dermatologic or allergic reactions. -Conjunctivitis - Pulmonary adverse effects like occupational asthma, alveolitis and rhinitis. -Gastrointestinal adverse effects like heartburn, vomiting, diarrhoea and nausea. - Musculoskeletal adverse effects (85).	-Decreased levels of thyroid hormones. -In-vivo oestrogen and progesterone activity. -Enhanced percutaneous absorption of 5-Fluorouracil (85).
Senna	Yes (both hypoglycaemic and anticonvulsant effects) (86)	-Mild abdominal complaints like cramps or abdominal pain. -Discolouration of urine.	-It can decrease absorption of other drugs (88).

		-Haemorrhoid congestion. -Diarrhoea and loss of electrolytes in case of prolonged use or overdosing (87)	
Cinnamon (*Cinnamomum cassia*)	Yes (both hypoglycaemic and anticonvulsant effects) (89, 90)	Despite being safe as spice or flavouring agent, significant adverse effects occurred at larger doses or longer use duration. -The most frequent adverse events were gastrointestinal disorders and allergic reactions (91)	Interaction with CYP2A6 (92).
Dill (*Anethum graveolens*)	Yes (both hypoglycaemic and anticonvulsant effects) (93, 94)	-Skin irritation -It can reduce the duration of labour (95)	Interaction with antidiabetic drugs because of cardiovascular effects (96)
European blueberry (*Vaccinium myrtillus*)	Yes (both hypoglycaemic and anticonvulsant effects) (97, 98)	-Gastrointestinal discomfort. -Drop in blood pressure -Bleeding risk (99)	Mild modulation of CYP enzymes (100).
Nettle (*Urtica dioica*)	Yes (both hypoglycaemic and anticonvulsant effects) (101, 102)	-Urticarial rash -Upset stomach (103)	-Increased sensitivity of breast cancer cells to paclitaxel - Nettle seed extract may have the potential to inhibit and/or induce the metabolism of certain co-administered drugs due to effects on enzymes like CYP2C6 and CYP2E1 (104, 105)
Gurmar (*Gymnema sylvestre*)	Yes (both hypoglycaemic and anticonvulsant effects) (106, 107).	No clinically significant adverse effect (108)	-Potentiating the effect of hypoglycaemic drugs -Reduction of serum triglycerides, total cholesterol, VLDL and LDL which can potentiate the effects of antihyperlipidemic medications (108)
Tea 'György' (contains: - dandelion (*Taraxacum officinale*), - Nettle (*Urtica dioica*), -perforate St John's-wort (*Hypericum perforatum*), -European blueberry (*Vaccinium myrtillus*), -Chicory (*Cichorium intybus*).	-Look above for Nettle and European blueberry. -Dandelion has hypoglycaemic effect (109). -Chicory has hypoglycaemic effect (110). - St John's-wort has both anticonvulsant effects and hypoglycaemic effects (111, 112)	-Look above for Nettle and European blueberry - Adverse effects of Dandelion include stomach discomfort, diarrhoea and heartburn (113). -Chicory is generally regarded as safe (114). -Adverse effects of St John's wort includes gastrointestinal symptoms, dizziness, confusion, tiredness, sedation and dry mouth (115).	- Look above for Nettle and European blueberry - Dandelion can potentiate the effects of other antihyperlipidemics (113). - Chicory may induce CYP enzymes (116). - St John's wort induces cytochrome P450 isoenzymes such as CYP3A4, CYP2C9, CYP1A2 and the transport protein P-glycoprotein causing clinically significant interactions with prescribed medicines including warfarin, phenprocoumon, cyclosporin, HIV protease inhibitors, theophylline, digoxin and oral contraceptives resulting in a decrease in concentration or effect of the medicines (115).

Table 16 Basic characteristics of overall study population, PWE and patients living with DM. Significant difference between the epilepsy and diabetes group was considered if $p<0.05$.

	All patients (N=227)	Patients with epilepsy (N=127)	Patients with diabetes mellitus (N=100)	p-value
Mean body weight (kg±SD)	80.3±17.3	76.1±17.8	85.7±15	**0.0089**
Mean age (year±SD)	54.54±17.33	45.1±16.1	65.51±8.66	**<0.00001**
Education				0.65
Primary school	64	28	36	
High school	111	66	45	
University	44	28	16	
Doctoral School	1	1	0	
Smoking status				**<0.00001**
Smoker	30	22	8	
Never smoked	121	80	41	
Stopped smoking	71	23	48	
Physical activity	yes: 190	103	87	0.28
	no: 31	20	11	
Alcohol consumption	no: 179	113	66	**0.000048**
	yes: 42	12	30	

5.2.5. Related issues to use of CAM and factors impacting it

The percentage of CAM users was 9.7% in the overall study population. It was less in PWE than among diabetic patients; 7.9% and 12%, respectively. PWE, that were also CAM users, were mainly younger, while the CAM-using DM patients were members of the elderly population. Only two patients (9.1% of CAM users – prevalence of CAM ADR) reported ADR from the used CAM (Table 18).

Nonetheless, we failed to find significant association between CAM use and age, sex, adherence to prescribed medicine (although it should be noted that at 90% CI it is significant), ADR due to prescribed medicine, control of disease, smoking, satisfaction with prescribed medicines and education. A patient reporting alcohol consumption and physical activity had 4.56- and 9.1-times odds of using CAM, respectively, in contrast to a person who did not (Table 19).

Table 17 Disease and treatment characteristics. Significant difference between the epilepsy and diabetes groups was if p <0.05.

	All patients (N=227)	Patients with epilepsy (N=127)	Patients with diabetes mellitus (N=100)	p-value
Monotherapy	112	73	39	0.14
Bitherapy	52	27	25	
Polytherapy	32	12	20	
Not stated	31	15	16	
Controlled disease	121	93	28	**<0.00001**
no CAM use	*111*	*84*	*27*	0.45
CAM use	*10*	*9*	*1*	
Adverse drug reactions from prescribed medicines	no: 177 yes: 26	no: 101 yes: 18	no: 76 yes: 8	0.24
Adherence to prescribed medicines	always: 197 less often: 5 poor: 6	always: 114 less often: 3 poor: 0	always: 83 less often: 2 poor: 6	**0.047**
Satisfaction with prescribed medicines	yes: 197 no: 11	yes: 118 no: 4	yes: 79 no: 7	0.12
Quality of life assessment (Likert scale)				0.74
1	106	77	29	
2	79	31	48	
3	4	2	2	
4	1	0	1	
5	0	0	0	

Table 18 Complementary and alternative medicines (CAM) usage related issues. Significant difference between the epilepsy and diabetes group was if p <0.05.

	All patients (N=227)	Patients with epilepsy (N=127)	Patients with diabetes mellitus (N=100)	p-value
CAM users	22	10	12	0.3
by age group				0.2
≤65-year-old	*11*	*7*	*4*	
>65-year old	*11*	*3*	*8*	
CAM ADR	2	0	2	

Table 19 Factors possibly affecting the use of complementary and alternative medicines (CAM)

	CAM user (N=22)	**Non-CAM user (N=205)**	**Odds ratio (95% CI; p-value)**
Age >65years	10	51	2.02 (0.83-5.02;0.12)
Sex male	12	90	1.17 (0.48-2.85;0.72)
Obesity	6	16	0.7 (0.26-1.88;0.49)
Epilepsy	10	108	0.54 (0.22-1.31,0.18)
Adherence to prescribed medicine	22	159	13.12 (0.78-220.41;0.0096)
ADR	4	20	0.56 (0.17-1.85;0.35)
Control of the disease	10	97	0.93 (0.38-2.24;1.0)
Epilepsy	*9*	*84*	*3.54 (0.43-29.01;0.29)*
Diabetes mellitus	*1*	*13*	*0.71 (0.08-6.9;1.0)*
Smoking			
yes	2	23	0.79 (0.17-3.61;1.0)
never	10	95	0.96 (0.4-2.33;1.0)
stopped	10	56	2.22 (0.91-5.42;0.86)
Alcohol consumption	9	27	**4.56 (1.78-11.7;0.0026)**
Physical activity	21	143	**9.1 (1.2-69.19;0.01)**
Satisfaction	19	160	0.28 (0.07-1.16;0.58)
Education			
Primary school	4	49	0.56 (0.18-1.75;0.32)
High school	13	88	1.41 (0.57-3.47;0.45)
University	5	36	1.13 (0.39-3.26;0.82)
Doctoral School	0	1	N/A

6. Discussion

6.1. Pharmacovigilance study of ASMs

Selecting the suitable ASM for each patient has become very challenging due to the complexity of epilepsy treatment, besides the availability of many ASMs to choose from. In addition to that, ADRs caused by ASMs can play a crucial role in ASM selection (117). It is essential in understanding the outcomes and seriousness of ASMs to study the potential ADRs regardless of whether old or new ASMs are used.

Despite the unique value of EV in sADRs reporting, only some studies have utilized it analysing a smaller region within a shorter time. To our knowledge, this study spans one of the longest time periods, 10 years, resulting in a substantial amount of data (276,694 reports including 1,051,142 sADRs reported in PTs) thereby enhancing the power of the findings. Moreover, during this period many new ASMs were marketed, allowing ample time to gather reports on their ADRs.

In our study, more reports belonged to females than males. In a population-based analysis covering an earlier time period similarly there was a female dominance bit higher (67%) (118).

According to our findings, the majority of PTs were observed in adults aged 18 to 64 years old, accounting for 52.40% of all PTs and having the highest number of PTs across all outcomes and seriousness criteria. This may be attributed to the fact that ASMs are primarily prescribed for adults after being marketed and are only administered to children if they are safe. Even though ADR was reported as a consequence of an adult ASM treatment, the seriousness criterion of *'congenital anomaly'* had the highest percentage of PTs in the age group of 2 to 17 years old (27.05%). Similarly, in the literature, variation in pattern was detected (119, 120). However, it's important to note that among adults, comorbidities and polytherapy are common, which could influence prescriptions.

Chronologically, the year of 2021 witnessed the highest number of reported PTs (150,689), followed by 2017, 2019 and 2020 (120695, 120163 and 118564 respectively). Noteworthy, the Annual Report on EudraVigilance for the European Parliament emphasized that the year 2021 had the remarkably increased number of reports in comparison to previous years (51). The enhanced awareness on COVID-19 vaccines could have played a role in this increase reporting on one hand, on the other hand, increased number of potential interactions could be responsible it as least

partially. The use of new online interactions search engines over these years highlights the importance of the knowledge of interactions causing ADRs (121).

The most frequently reported PTs were '*seizure', 'drug ineffective', 'somnolence'* and *'dizziness'*. Noteworthy, withdrawal of ASMs or non-adherence to ASM may cause seizure. Also, it is crucial to state that interaction decreases the effectiveness of an ASM, potentially causing ineffectiveness, seizure or may lead to intoxication resulting in seizure, somnolence or dizziness. The large number of reported PTs may indicate that the patients were more likely to experience no seizure control rather than seizure exacerbation with an ASM or paradoxical drug reaction (122, 123). In NorPD database, the most frequently reported PT was rash, followed by dizziness, SUDEP , cross-sensitivity reaction and pyrexia (118).

The most frequently reported sADRs belonged to four SOCs: *'nervous system disorders', 'general disorders and administration site conditions', 'psychiatric disorders'*, these shows a similar pattern in a previous publication where *'injury, poisoning and procedural complications'* was 3.6-times higher (118). Still, the pattern of prescribed ASMs within above mentioned SOC groups varied. For instance, a significant positive association with *'nervous system disorders'* was detected in fatty acid derivatives, hydantoins and succinimides pharmacological ASMs groups in our study, however, in their research, pregabalin was the most common ASM.

Although the SOC of *'congenital, familial and genetic disorders'* accounted for only 1.58% of all the reported PTs, it is noteworthy that significant positive associations were observed in oxazolidines and fatty acid derivates. The notable association in fatty acid derivatives may be explained by VPA, a member of this group, which contributed to 91.08% of its reported PTs and is well recognized for its high risk of teratogenicity (124).

The new ASMs had two-thirds of reported PTs (678,482 PTs, 64.55%), when compared to old ASMs (372,660 PTs, 35.45%). This can be justified by the increased awareness given to the newly marketed ASMs and their being stricter Pharmacovigilance monitoring than old ones. This highlights the reason why in the group of other ASMs, *'not recovered / not resolved'* reports were overreported and those reports came mostly from studies. Overall, 75.49% of PTs had an outcome and 70.42% of PTs had seriousness criteria. With respect to seriousness, it is noteworthy to mention that 35.31% of PTs had seriousness of *'caused/prolonged hospitalisation'* while 5.79% had seriousness criterion of *'results in death'*. Old ASMs had a significant positive association

with *'caused/prolonged hospitalisation'*, *'congenital anomaly'*, *'disabling'*, *'life threatening'* and *'results in death'*. As regards outcomes, only 20.4% of PTs had outcome of *'recovered/resolved'* while 12.94% had the outcome of *'not recovered/not resolved'* which ranked second. All in all, 3.89% of all the reported PTs had *'fatal'* outcome out of all outcomes. The seemingly high percentage can be also due to the fact that severe cases were more likely reported. We had more beneficial outcomes in comparison to the study of Baftiu which showed more reported ADRs (118). Old ASMs had a significant negative association with outcome of *'not recovered/not resolved'*, though an increased significant association was found with *'fatal'* outcome. It could be elucidated from our analysis that although more ADRs were reported for new ASMs, old ASMs had more serious ADRs. Also, an increased significant association in old ASMs with *'fatal'* outcomes association and with *'hospitalization'*, *'congenital anomaly'*, *'disabling'*, *'life threatening'* and *'death'* seriousness criteria was detected; nevertheless, higher number of sADRs was found in new ASMs.

The majority of reported sADRs belonged to females and regarding old *vs.* new ASMs, correlation was significant. Nonetheless, association was found among males in many findings.

SUDEP is a rare, but fatal event among PWE, so even a smaller ratio of reported PTs - 386 (0.04%) - has high impact. A higher ratio was detected in a Norwegian analysis (2.13%), which mirrors regional patterns. Healthcare professionals reported SUDEP mainly (91.56% of cases) which also underlines it.

It is worth mentioning, regarding *'fatal'* outcome and *'results in death'* seriousness, our study found a significant positive association with old ASMs in general.

A limited number of studies is published on correlation of ASMs and SUDEP (37). These highlight the importance of adherence, polytherapy (≥3 ASMs), alongside non-pharmacological risk factors (seizure type) (125). Even less examine specific ASMs with contradictory findings. LEV, LTG and VPA were showing reduced risk for SUDEP in one study (126). Whilst in another analysis by LTG, VPA and CBZ higher occurrence of SUDEP was shown (118). In these studies, the control was the PWE not having SUDEP. In our study, old ASMs had a significant negative association, while new ASMs had a significant positive association. But we used different controls than previously mentioned studies RORs were calculated and compared with all ASMs as

control/background in the EV. Currently, there is a need for more detailed evaluation of specific ASMs within both the old and new groups.

To compare old and new ASMs in general is complex so these studies are rare. To have an insight, a review from 2011 presented that old ASMs (namely VPA, CBZ) caused ADRs like somnolence, rash, and fatigue than new ASMs (127). According to this study old ASMs (PHT, VPA and CBZ) did, new ones did not a significant effect on the risk of mortality. Examining specific ASMs, we found that PHT had a significant positive association, however CBZ showed a significant negative association with SOC of *'nervous system disorders'*.

This study has limitations of course reporting is mandatory in case of serious sADRs. Different factor can influence reporting e.g. media, public awareness. Nevertheless, EV contains huge number of reports, mainly reported by healthcare professionals.

The strength of the study is it contains real-world data guiding the epileptologist by ASM choice. It can be valuable for healthcare professionals working with PWE to study the ADRs attributed to ASMs, especially the serious ones, because this could limit the use of ASMs. Our work may highlight the contribution of clinical pharmacists to assistance epileptologists with regards to that can be helpful. Prior to prescribing an ASM, it is crucial to consider ADRs, as they are among the most influential factors affecting tolerability and may also contribute to reduced adherence. Adherence is crucial to achieve seizure control or seizure freedom, especially that a life-threatening outcome of status epilepticus may occur among non-adherent patients (128). Likewise, our findings indicated that improper ASM selection or inadequate dosage resulted in a higher incidence of *'seizure'* and *'drug ineffective'* PTs, which may emphasize the role of the clinical pharmacist in the team treating PWE, who may help the epileptologist with tailoring the treatment.

It is important to note that new ASMs are not devoid of ADRs, but they were found to result in less serious ones and more favourable outcome in comparison to old ASMs. SOCs along with their ROR by old and new ASMs can provide valuable insights for prescription decision making.

To summarize our PV findings, the majority of PTs were serious in the EV. Undesired outcomes and seriousness among reported ICSR were more common by old ASMs. Safety profile of the different ASMs, considering their expected seriousness and outcomes, can contribute crucially to ASMs selection.

6.2. Questionnaire based study on the use of CAM

In our study of CAM use in PWE, we have chosen DM which is similar to epilepsy in some aspects, it needs a life-long treatment and it might have severe consequences as well. It is common in two disease that they have an impact on the relatives lives as well. Special attention should be given to these chronic diseases. Epileptic seizure is unpredictable and can be dramatic. Using CAM therapy chosen by the PWE may create a perception that they can manage their condition alone, ruling it. DM is a typical disease, where patients with health-conscious behaviour can do much for their well-being for example diet and changes in life-style. Healthcare professionals have to be aware that CAM use is increasing and may cause ADRs as a consequence of interactions. So being informed about them is essential to customize the best-tailored therapy for each patient.

In a population-based study examining the incidence of epilepsy in association with T2DM and severe hypoglycaemia, based on Taiwan's National Health insurance claims, 751,792 people with T2DM and 824,253 matched controls identified in 2002–2003. The study followed them until the occurrence of epilepsy was observed up to 2011(129), The study found that type 2 diabetes mellitus (T2DM) may increase the risk of epilepsy independently of severe hypoglycaemia. That study demonstrated a 50% higher hazard of epilepsy in T2DM patients, which was consistently observed across all gender and age groups. Additionally, both epilepsy and T2DM patients are commonly prescribed many medicines concurrently over long periods and they may also use complementary and alternative medicine (CAM) therapies.

A systematic review indicated that the prevalence of any CAM use ranged from 9.8 to 76% in the general population and emphasized the importance of periodic surveys in monitoring CAM usage at population level (130). Compared with our findings' prevalence was a bit lower (7.9%) among PWE. We tried to decrease bias by choosing a disease with similar characteristics like epilepsy within the same cultural background (131). In comparison to the population with DM, treatment characteristics differed in some aspects like adherence, which could be attributed to the unpredictable and dramatic nature of epilepsy; conversely, in DM, high blood sugar level can be 'just' a laboratory finding. A seizure is distressing experience, that may impact the quality of life (e.g. job, driving license, relationships), and the majority patients try to avoid it. Epileptologists believe that continuous care and a good physician-patient relationship enhance trust and sincerity.

Differently than the article by Nahin et al (132), smoking and obesity were not confirmed as risk factors related to CAM use in our study population. Physical activity was associated with CAM use, which may indicate that health-conscious people may seek to manage their disease through additional treatments and exert every effort for promoting their well-being. This hypothesis is further supported by other findings in this study, such as the independence of CAM use from disease control, satisfaction with prescribed medications and quality of life assessment.

Among those, who reported regular alcohol consumption, the likelihood of CAM use was four-times higher. However, it must be noted that this did not mean heavy drinking. Similar to our findings, a Norwegian study among women also detected more frequent use of natural medicine among frequent alcohol drinkers (133).

CAM users in the "epileptic" group tended to be less, although this trend can be attributed to their younger mean age compared to DM patients.

As shown in Table 15, most CAMs are used for both of epilepsy and DM among patients. Regardless of the small size of the study population, ADR was reported by 9.1% of CAM users. Very important to note that the use of CAM mainly altered CYP enzyme activity as a source for ADRs arising from interactions in case of concomitant ASM therapy. Besides these, other unfavourable mechanism could occur like absorption disturbance. This finding highlights the importance of history taking which should include the CAM use. Besides patients' education, the knowledge of different CAM effects by the treating team including clinical pharmacists is very important.

In conclusion, while CAM users were only a minority in the studied population, it warranted attention required to reliance on CAM during the follow-up. Our finding that health-conscious patients tend to favour CAM use more frequently than the general population may emphasizes the importance of honest open discussion about CAM usage. CAMs capable of modulating CYPs enzymes were the most prevalent among users, leading to potential interactions with medications and resulting in ADR. This underscores the necessity for patient's education and treating them by a team including a clinical pharmacist.

New scientific results

A- Based on the pharmacovigilance study of ASMs using EV database

1. The highest number of PTs was reported in 2021, which coincided with the remarkable increase in pharmacovigilance reporting during the COVID-19 pandemic era.
2. Most PTs were observed in adults (18 to 64 years old - 52.40%).
3. More PTs was reported in females taking ASMs and there were sex differences regarding seriousness and outcomes.
4. The most frequently reported PTs were 'seizure', 'drug ineffective', 'somnolence' and 'dizziness'.
5. The most frequently reported sADRs belonged to four SOCs: *'nervous system disorders'*, *'general disorders and administration site conditions'*, *'psychiatric disorders'*
6. Significant notable positive associations were found in oxazolidines and fatty acid derivates with the SOC of *'congenital, familial and genetic disorders'*.
7. The new ASMs had more ADRs, and two-thirds of reported PTs belonged to new ones, in comparison to old ASMs, however the old ASMs had more serious ADRs and showed positive associations with fatal outcomes, hospitalization, congenital anomaly, disabling, life threatening and death seriousness criteria.
8. As regards seriousness, 35.31% of PTs had seriousness of *'caused/prolonged hospitalisation'* while 5.79% had seriousness criterion of *'results in death'*.
9. Old ASMs had a significant positive association with *'caused/prolonged hospitalisation'*, *'congenital anomaly'*, *'disabling'*, *'life threatening'* and *'results in death'*.
10. As for outcomes, only 20.4% of PTs had outcome of *'recovered/resolved'* and 12.94% had the outcome of *'not recovered/not resolved'*. Only 3.89% of all the reported PTs had *'fatal'* outcome.
11. SUDEP is a rare, fatal event among PWE, especially, among adults, in males and higher odds if taken new ASMs.

B- Related to the CAM use

1. We mapped CAM use firstly in our region among PWE. The percentage of CAM users was 9.7% in the overall study population. It was less in PWE than among diabetic patients; 7.9% and 12% respectively. ADR was reported by 9.1% of CAM users.

2. By comparing PWE and DM better disease control was observed in PWE than in DM. CAM use was not significant among PWE. Adherence rate was higher among PWE than DM patients.
3. Physical activity was associated with more CAM use. This may mean the patients show more health conscious behaviour, they want participate actively in therapy to do more for their well-being.
4. The CYPs enzymes modulators were the most prevalent among the reported CAMs, which could cause potential interactions with medications and lead to ADR.

7. Summary

Epilepsy is a disease needing life-long treatment affecting millions of people. We have focused on two important aspects of treatment in order to achieve better tailored therapy.

Firstly, we conducted a pharmacovigilance study of ASMs covering a ten-year-period using EV database with focus on their seriousness and outcomes of reported sADRs. A total of 276,694 reports were retrieved, including1,051,142 individual sADRs reported as PTs. ROR, 95% CI, p-value and chi-square statistics were calculated. The most frequent SOCs were the following: nervous system disorders (19.26%), general disorders and administration site conditions (14.39%), psychiatric disorders (11.29%) and injury, poisoning and procedural complications (9.79%). Old ASMs had a significant positive association with *'caused/prolonged hospitalisation'*, *'congenital anomaly'*, *'disabling'*, *'life threatening'* and *'results in death'*, while new ASMS with *'other medically important condition'*. SUDEP was reported in 0.04% of PTs. Concluding, Old ASMs were generally more commonly associated with undesired outcomes and seriousness. Considering their expected seriousness and outcomes, the safety profile of the different ASMs, can play a major role in the selection of ASMs. Summarizing our PV studies, most of the PTs felt in the serious condition. Undesired outcomes and seriousness among reported ICSR were more common by old ASMs. Only with the precise knowledge of the safety profile of prescribed ASMs can fulfil patients' preference and lead to adequate adherence increasing the probability of better seizure control.

Secondly, CAM use was examined with a self-developed questionnaire focusing on the outcomes of treatment among PWE. Filled questionnaires were used in compiling database that was eventually analysed. Number of PWE was 127. Mean age was 45.1±16.1 years. From PWE group, ten patients (7.9%) used CAM because they believed in CAM. Comparing to patients with diabetes mellitus, the prevalence was 12%. Two of them reported ADR. The CAM users among PWE were younger, while patients with DM were elderly who tended to use CAM. The major findings were that health-conscious patients tended to use more CAM which highlights the necessity to discuss CAM use openly. The most commonly reported CAMs were CYPs enzymes modulating that can lead to many interactions and lead to ADR. Accordingly, role of treating team including clinical pharmacists and patient's education may be essential.

Both studies may show, how a clinical pharmacist could contribute to the treatment of PWE.

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9. List of own publications

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Registry number: DEENK/404/2024.PL
Subject: PhD Publication List

Candidate: Michael Magdy Fahmy Girgis
Doctoral School: Doctoral School of Pharmacy

List of publications related to the dissertation

1. **Girgis, M. M. F.**, Farkasinszky, G., Fekete, K., Fekete, I., Vecsernyés, M., Bácskay, I., Horváth, L.: Seriousness and outcomes of reported adverse drug reactions in old and new antiseizure medications: a pharmacovigilance study using EudraVigilance database.
Front. Pharmacol. [Epub ahead of print], 2024.
DOI: http://dx.doi.org/10.3389/fphar.2024.1411134
IF: 4.4 (2023)

2. **Girgis, M. M. F.**, Fekete, K., Homoródi, N., Márton, S., Fekete, I., Horváth, L.: Use of complementary and alternative medicine among patients with epilepsy and diabetes mellitus, focusing on the outcome of treatment.
Front. Neurosci. 15, 1-12, 2022.
DOI: http://dx.doi.org/10.3389/fnins.2021.787512
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List of other publications

3. Horváth, L., Mirani, S., **Girgis, M. M. F.**, Rácz, S., Bácskay, I., Bhattoa, H. P., Tóth, E. B.: Six years' experience and trends of serum 25-hydroxy vitamin D concentration and the effect of vitamin D3 consumption on these trends.
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DEBRECENI EGYETEM
Egyetemi és Nemzeti Könyvtár

10. Keywords

Epilepsy, Seizure, treatment, Antiseizure medications (ASMs), Adverse events, Adverse drug reactions, Pharmacovigilance, EudraVigilance (EV), System Organ Classifications (SOCs), Outcomes, Seriousness, Sudden Unexpected Death in Epilepsy (SUDEP), Complementary and alternative medicines, epilepsy, diabetes mellitus, seriousness, outcome, adherence

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12. Appendices

12.1. Survey used for people with epilepsy (Hungarian)

Az ön neme: (Kérjük aláhúzással jelezze válaszát)

férfi nő

Hány éves ön?.....

Milyen típusú epilepsziája van Önnek? a. kis roham

b. nagy roham

c. egyéb:……

Az utóbbi időben volt-e rohama?

a. nem, rohammentes vagyok……éve/ hónapja

b. van

Ha igen, milyen gyakran?.....

Fogyaszt-e alkoholt?

a. Nem

b. Igen, Milyen gyakran:_____ mennyit?_____

Ön dohányzik?

a. Igen, Milyen gyakran:_____mit?_____mennyit?_____

b. Nem, sohasem dohányoztam

c. Nem, már abbahagytam. Mikor?_____

Az Ön legmagasabb iskolai végzettsége?

a. Általános iskola

b. Középiskola

c. Főiskolai / egyetemi

d. Doktori iskola

Naponta legalább 30 percet tölt-e fizikai aktivitással?

a. Igen

b. Nem

Az Ön testsúlya jelenleg: kg
Csak hölgyeknek:

Szed-e fogamzásgátló tablettát, vagy használ-e hormonális hüvelygyűrűt?

a. nem

b. igen
Jelenleg terhes-e? (Kérjük aláhúzással jelezze válaszát) Igen Nem

Gyógyszerszedéssel kapcsolatos kérdések
Írt-e fel Önnek az orvosa az epilepszia kezelésére gyógyszert?

a. Nem

b. Igen, mit és milyen dózisban:

1. ……

2. ……

3. ……

4. ……

A felírt epilepszia elleni gyógyszeréből az utóbbi időben (pl. az elmúlt 1 hónapban vagy félévben) mennyi vett be?

a. Mindig beszedem, az orvos által felírt epilepszia ellni gyógyszeremet.(Minimum az előírt mennyiség 90%-át, ez azt jelenti, hogy egy hónapban maximum 2-3 napot hagyok ki).

b. Az orvos által javallottnál kevesebbszer szedem be, de a felírt mennyiség több mint felét beszedem.

c. Ritkán szedem be, időszakosan (egy hónapban a tabletták kevesebb mint felét szedem be, esetleg hosszabb szüneteket tartok).

d. Soha nem szedem be.

Elégedett-e az epilepszia ellen felírt gyógyszereivel?

a. Igen
b. Nem

Szed-e <u>rendszeresen</u> vény nélkül kapható gyógyszert?

a. Nem

b. Igen, mit és milyen dózisban:

1. ……

2. ……

3. ……

4. ……

A vény nélkül kapható gyógyszeréből az utóbbi időben (pl. az elmúlt 1 hónapban vagy félévben) mennyi vett be?

a. Mindig beszedem, a vény nélkül kapható gyógyszeremet.(Minimum az előírt mennyiség 90%-át, ez azt jelenti, hogy egy hónapban maximum 2-3 napot hagyok ki).

b. A javallottnál kevesebbszer szedem be, de a felírt mennyiség több mint felét beszedem.

c. Ritkán szedem be, időszakosan (egy hónapban a tabletták kevesebb mint felét szedem be, esetleg hosszabb szüneteket tartok).

d. Soha nem szedem be.

Szed-e <u>időnként, átmenetileg</u> vény nélkül kapható gyógyszert? (pl.
görcsoldó, fájdalomcsillapító, köptető, hasfogó, lázcsillapító), ha igen mit és milyen dózisban:

a. Nem

b. Igen, mit és milyen dózisban:

1. ……

2. ……

3. ……

4. ……..……

Az időnként vagy átmenetileg alkalmazott vény nélküli gyógyszereiből mennyi vett be?

a. Mindig beszedem, a kúrát végig csinálom. (Minimum az előírt mennyiség 90%-át, ez azt jelenti, hogy egy kúrából maximum 1-2 napot hagyok ki).

b. A javallottnál kevesebbszer szedem be, de a felírt mennyiség több mint felét beszedem.

c. Egy kúrán belül a tabletták kevesebb mint felét szedem be.

Szed-e rendszeresen étrendkiegészítőt? (pl. C-vitamin, multivitamin, magnézium-B6, fehérjepor, szépségvitamin), ha igen mit és milyen dózisban:

a. Nem

b. Igen, mit és milyen dózisban:

1. ……

2. ……

3. ……

4. ……

Az étrendkiegészítőből az utóbbi időben (pl. az elmúlt 1 hónapban vagy félévben) mennyi vett be?

a. Mindig beszedem a teljes mennyiséget. (Minimum az előírt mennyiség 90%-át, ez azt jelenti, hogy egy hónapban maximum 2-3 napot hagyok ki).

b. A javallottnál kevesebbszer szedem be, de a felírt mennyiség több mint felét beszedem.

c. Ritkán szedem be, időszakosan (egy hónapban a tabletták kevesebb mint felét szedem be, esetleg hosszabb szüneteket tartok).

d. Soha nem szedem be.

Szed-e rendszeresen gyógynövény-tartalmú étrendkiegészítőt, ha igen, mit és milyen gyakorisággal:

a. Nem

b. Igen, mit és milyen dózisban:

1. ……

2. ……

3. ……

4. ……

A gyógynövény tartalmú készítményből az utóbbi időben (pl. az elmúlt 1 hónapban vagy félévben) mennyi vett be?

a. Mindig beszedem a teljes mennyiséget.(Minimum az előírt mennyiség 90%-át, ez azt jelenti, hogy egy hónapban maximum 2-3 napot hagyok ki).

b. A javallottnál kevesebbszer szedem be, de a felírt mennyiség több mint felét beszedem.

c. Ritkán szedem be, időszakosan (egy hónapban a tabletták kevesebb mint felét szedem be, esetleg hosszabb szüneteket tartok).

d. Soha nem szedem be.

Esetleges mellékhatásokkal kapcsolatos kérdések

Tapasztalt-e mellékhatást az epilepszia elleni gyógyszeré(ei)től?

a. nem

b. igen (ha igen, kérem, töltse ki az alábbi táblázatot)

Mellékhatás	Okozó gyógyszer neve	Dózisa (pl. 2x 200 mg)	Mennyi ideje szedte az epilepszia ellni gyógyszerét, amikor a mellékhatás jelentkezett? (pl. 10 napja)

Jelentette-e ezt valakinek?

a. Nem
b. Igen, Házi orvosnak
c. Igen a gyártónak vagy képviselőjének
d. Igen, a hatóságnak
e. Igen a gyógyszerésznek, az eladónak
f. Igen on-line jelentettem

A mellékhatás megjelenése után mi történt?

a. az orvosom leállította.
b. az orvosom módisította a dózist
c. az orvosom javaslatára változatlanul szedtem tovább
d. saját döntésem alapján nem szedtem tovább
e. saját döntésem alapján csökkentettem a dózist
f. saját döntésem alapján változatlanul szedtem tovább

Tapasztalt-e mellékhatást az ön által szedett vény nélkül kapható gyógyszerektől (pl. görcsoldó, fájdalomcsillapító, köptető, hasfogó, lázcsillapító)?

a. nem
b. igen (ha igen, kérem, töltse ki az alábbi táblázatot)

Mellékhatás	Okozó gyógyszer neve	Dózisa (pl. 2x 200 mg)	Mennyi ideje szedte azt, amikor a mellékhatás jelentkezett? (pl. 10 napja)

Jelentette-e ezt valakinek?

a. Nem
b. Igen, Házi orvosnak
c. Igen a gyártónak vagy képviselőjének
d. Igen, a hatóságnak
e. Igen a gyógyszerésznek, az eladónak
f. Igen on-line jelentettem

A mellékhatás megjelenése után mi történt?

a. az orvosom leállította.
b. az orvosom módisította a dózist
c. az orvosom javaslatára változatlanul szedtem tovább
d. saját döntésem alapján nem szedtem tovább
e. saját döntésem alapján csökkentettem a dózist
f. saját döntésem alapján változatlanul szedtem tovább

Tapasztalt-e mellékhatást bármilyen ön által szedett étrend-kiegészítőtől (akár gyógynövénytartalmú), ha igen, mit tapasztalt melyik szertől?

a. nem
b. igen (ha igen, kérem, töltse ki az alábbi táblázatot)

Mellékhatás	Okozó gyógyszer neve	Dózisa (pl. reggel 50 ml)	Mennyi ideje szedte azt, amikor a mellékhatás jelentkezett? (pl. 10 napja)

Jelentette-e ezt valakinek?

a. Nem
b. Igen, Házi orvosnak
c. Igen a gyártónak vagy képviselőjének
d. Igen, a hatóságnak
e. Igen a gyógyszerésznek, az eladónak
f. Igen on-line jelentettem

A mellékhatás megjelenése után mi történt?

a. az orvosom leállította.
b. az orvosom módisította a dózist
c. az orvosom javaslatára változatlanul szedtem tovább
d. saját döntésem alapján nem szedtem tovább
e. saját döntésem alapján csökkentettem a dózist
f. saját döntésem alapján változatlanul szedtem tovább

Az epilepszia betegségével, kezelésével kapcsolatos kérdések

Ön úgy érzi-e, hogy az ön által szedett antiepileptikum javított az életminőségén?

a. igen

b. nem

Az orvos által felírt antiepileptikumon kívül szed-e más gyógyszert, étrendkiegészítőt, homeopátiás szert epilepsziájának kezelésére?

a. nem
b. régebben szedtem, de már nem szedem Miért hagyta abba?
c. igen,
   mit……
   …….

Ezt a felírt antiepileptikum mellett szedi vagy helyette? (Kérem, húzza alá azt, amelyik igaz Önre.)

Igénybe vett-e egyéb természetgyógyászati, alternatív kezelést epilepsziájának kezelése érdekében?

a. nem
b. igen,
   mit……
   ……

Ezt a kezelést az antiepileptikum mellett alkalmazza/alkalmazta vagy helyette? (Kérem, húzza alá azt, amelyik igaz Önre.)

Miért használ gyógynövényeket/természetgyógyászati módszereket?

……..

……..

Az Ön véleménye szerint összességében, jelen terápia mellett, milyennek érzi életminőségét? Kérem, jelölje be a skálán!



12.2. Survey used for patients with diabetes (Hungarian)

1. Neme:

☐ Férfi
☐ Nő

2. Életkora: éves

3. Az Ön testsúlya jelenleg: kg

4. Az Ön legmagasabb iskolai végzettsége?

☐ Általános iskola ☐ Középiskola
☐ Főiskolai / egyetemi
☐ Doktori iskola

5. Naponta legalább 30 percet tölt-e fizikai aktivitással?

☐ Igen
☐ Nem

6. Dohányzik-e?

☐ Igen, Milyen gyakran:_____mit?_____mennyit?_____ ☐ Nem, sohasem dohányoztam

☐ Nem, már abbahagytam. Mikor?_____

7. Fogyaszt-e alkoholt?
☐ Nem

☐ Igen, Milyen gyakran:_____ mennyit?_____

8. Milyen gyakran eszik zöldséget/gyümölcsöt?
☐ Minden nap többször
☐ Naponta egyszer
☐ Nem minden nap

9. Ön jelenleg tartja-e a cukorbetegek diétáját annak érdekében, hogy jobban ellenőrizzék a vércukorszintjét?
☐ Igen, tartom a diétát.
☐ Nem, nem követem a diétás tanácsokat.

10. Szokott-e a normálistól eltérő, magasabb vércukorértéke lenni?

☐ Igen, milyen gyakran:

☐ Nem

11. Mióta ismert cukorbetegsége?

☐ Kevesebb, mint 1éve

☐ 1-5 éve

☐ Több mint 5 éve

12. Van-e az Ön családjában 2. típusú cukorbeteg?

☐ Van

☐ Nincs

13. Van-e saját vércukor mérője?

☐ Van

☐ Nincs

14. Milyen gyakran méri a vércukor értékét?

☐ alkalmanként, szükség esetén

☐ Havonta 1 vagy 2 alkalommal

☐ Hetente 1 vagy 2 alkalommal

☐ egyszer egy naponta

☐ naponta többször

15. Mennyi volt az utolsó éhgyomri vércukor értéke és HbA1c értéke?

vércukor:_____HbA1c: _____

16. Van-e valamilyen szövődménye a cukorbetegségének? (pl. érzészavar, veseelégtelenség)

17. Influenza elleni védőoltást beadatja-e évente?

☐ Igen

☐ Nem

18. Milyen gyógyszereket szed a cukorbetegségére és milyen dózisban?

1. ……

2. ……

3. ……

4. ……

19. A felírt cukorbetegség elleni gyógyszeréből az utóbbi időben (pl. az elmúlt 1 hónapban vagy félévben) mennyi vett be?

☐ Mindig beszedem, az orvos által felírt cukorelleni gyógyszeremet.(Minimum az előírt mennyiség 90%-át, ez azt jelenti, hogy egy hónapban maximum 2-3 napot hagyok ki).

☐ Az orvos által javallottnál kevesebbszer szedem be, de a felírt mennyiség több mint felét beszedem.

☐ Ritkán szedem be, időszakosan (egy hónapban a tabletták kevesebb mint felét szedem be, esetleg hosszabb szüneteket tartok).

☐ Soha nem szedem be.

20. Elégedett-e a gyógyszereivel?

☐ Igen
☐ Nem

21. Ennek mennyi a körülbelüli havi költsége?

körülbelül _____ Ft.

22. Tapasztalt-e mellékhatást a cukorbetegségére szedett gyógyszerektől?

☐ Nem

☐ Igen, (ha igen, kérem, töltse ki az alábbi táblázatot)

Mellékhatás	Okozó gyógyszer neve	Dózisa (pl. 3x 850 mg)	Mennyi ideje szedte az cukorbetegségére gyógyszerét, amikor a mellékhatás jelentkezett? (pl. 10 napja)

23. Jelentette-e ezt valakinek?

☐ Nem
☐ Igen, Házi orvosnak
☐ Igen a gyártónak vagy képviselőjének
☐ Igen, a hatóságnak
☐ Igen a gyógyszerésznek
☐ Igen on-line jelentettem

24. Mi történt a mellékhatás megjelenése után?

☐ saját döntésem alapján változatlanul szedtem tovább ☐ az orvosom leállította.
☐ az orvosom módisította a dózist
☐ az orvosom javaslatára változatlanul szedtem tovább
☐ saját döntésem alapján nem szedtem tovább ☐ saját döntésem alapján csökkentettem a dózist

25. Használ-e és ha igen, milyen gyógynövényeket vagy gyógynövény tartalmú készítményeket a cukorbetegsége gyógyítására?
☐ Nem

☐ Igen, _____

26. Mennyibe kerül a havi költsége a gyógynövény készítményeknek?

_____ Ft.

27. Elégedett-e a hatásukkal?

☐ Igen
☐ Nem

28. Tapasztalt-e mellékhatást a cukorbetegségére szedett gyógynövény készítményektől?
☐ Nem

☐ Igen, részletezze:

Mellékhatás	Okozó gyógynövény neve	Dózisa	Mennyi ideje szedte azt, amikor a mellékhatás jelentkezett? (pl. 10 napja)

29. Jelentette-e ezt valakinek?

☐ Nem
☐ Igen, Házi orvosnak
☐ Igen a gyártónak vagy képviselőjének
☐ Igen, a hatóságnak
☐ Igen a gyógyszerésznek, az eladónak
☐ Igen on-line jelentettem

30. Mi történt a mellékhatás megjelenése után?

☐ saját döntésem alapján változatlanul szedtem tovább ☐ az orvosom leállította.
☐ az orvosom módisította a dózist
☐ az orvosom javaslatára változatlanul szedtem tovább
☐ saját döntésem alapján nem szedtem tovább ☐ saját döntésem alapján csökkentettem a dózist

31. Alkalmaz-e és ha igen milyen egyéb természetgyógyászati módszereket a cukorbetegségével kapcsolatban?
☐ Nem

☐ Igen, _____

32. Miért használ gyógynövényeket/természetgyógyászati módszereket?

……
……..

33. Az Ön véleménye szerint összességében, jelen terápia mellett, milyennek érzi életminőségét? Kérem, jelölje be a skálán!

  

12.3. The two publications on which the thesis is based