SHORT THESIS 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

EDC = Endocrine-Disrupting Chemicals

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

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. 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).

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).

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 forgotten that the morbidity and mortality of this age group improved enormously thanks to better perinatal care and better control of infectious diseases. 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. Epilepsy usually needs life-long treatment, even after epilepsy surgery. ASMs are important for most people with epilepsy (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. Still multiple traditional ones continued to be employed widely. However, this provided more therapeutic options, but still adverse drug reactions (ADRs), interactions and hypersensitivity reactions were not eliminated.

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”. Adverse drug reactions (ADRs) contribute outstandingly to debilitation of health quality and treatment failure in PWE. 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”. We have to face the increase the ADRs, therefore PV supports proper and safe use of drugs, through increasing reporting rates. 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. 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). 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.

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 healthcare approaches with a history of use or origins outside of

mainstream medicine. 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. 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. 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. 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.

CAM therapies can alter the drug metabolism and drug disposition leading to ADRs ineffectiveness and may have toxic consequence. Complementary and alternative medicines 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.

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.

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. The most frequently taken products include ginseng, *Ginkgo biloba*, St. John's wort, echinacea, garlic and soy. Interestingly, the aforementioned products have not been reported to have either beneficial or detrimental effects on seizures, though their presumed activity on the P450 system could potentially lead to interactions with ASMs metabolised by the liver. Melatonin, kava kava and valerian were reported to have sleep inducing and anticonvulsant effects, however 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. The interactions between the herbal remedies and active pharmaceutical ingredients can be additive/synergistic or antagonistic altering the efficacy and clinical safety.

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. Methods

3.1. PV study of ASMs

EV system was mined to obtain information about sADRs which is based on ICSRs. 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.

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*

The Anatomical Therapeutic Chemical (ATC) classification system N03A subgroups was used to obtain list of ASMs (also known as antiepileptics)

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).

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 $p<0.05$.

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

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)..

3.2. Questionnaire based study on the use of CAM

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 DM. 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).

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 and participated in regular check-ups prior to being involved in the survey.

In the DM 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. Additionally, both epilepsy and T2DM patients are commonly prescribed many medicines concurrently over long periods and they may also use CAM therapies. Therefore, comparing

patients' adherence to their prescribed medications, CAM use and the impact on patients' satisfaction is valuable.

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.

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.

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 $\chi 2$ test and Fisher's exact test. As per standard pharmacovigilance practices, the values of the Odds ratio (OR) were computed using 2x2 contingency table. Significant differences were considered if $p<0.05$.

4. Results

4.1. Pharmacovigilance study of ASMs

4.1.1. 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. 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. 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%). There were more reports of new ASMs than old ones 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.

4.1.2. 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%).

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%), 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. 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'*.

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'*

4.1.3. 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, 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. 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.

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'*, 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 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.

4.1.4. Outcomes

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

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'.* 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'*.

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.

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.

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.

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

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.

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.

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.

In old ASMs, 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.

4.1.5. Sudden Unexpected Death in Epilepsy (SUDEP)

Among all the reported PTs, 386 (0.04%) PTs were related to SUDEP, with healthcare professionals reporting 358 (91.56%). In terms of sex, 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 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%).

Interestingly, old type ASMs 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.

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.

4.2. Questionnaire based study on the use of CAM

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.

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.

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.

If PWE are compared to DM patients, statistically significant differences were revealed in body weight, smoking status and alcohol consumption.

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.

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.

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 one person who did not.

5. Discussion

5.1. 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. 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%) .

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. 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. 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.

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. In NorPD database, the most frequently reported PT was rash, followed by dizziness, SUDEP, cross-sensitivity reaction and pyrexia.

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. 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.

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. We had more beneficial outcomes in comparison to the study of Baftiu which showed more reported ADRs. 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 mirrores 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. These highlight the importance of adherence, polytherapy (≥3 ASMs), alongside non-pharmacological risk factors (seizure type). Even less examine specific ASMs with contradictory findings. LEV, LTG and VPA were showing reduced risk for SUDEP in one study. Whilst in another analysis

by LTG, VPA and CBZ higher occurrence of SUDEP was shown. 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. 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. 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.

5.2. 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.

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. 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. 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, 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.

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

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.

6. 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. 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.
2. ADR was reported by 9.1% of CAM users.
3. Better disease control was observed in PWE, but CAM was not significant among this group.
4. Adherence rate was higher among PWE than DM patients.
5. Physical activity was associated with more CAM use.
6. The CYPs enzymes modulators were the most prevalent among the reported CAMs, which could cause potential interactions with medications and lead to ADR.

7. List of Scientific 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.
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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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IF: 4.4

Total IF of journals (all publications): 13,1
Total IF of journals (publications related to the dissertation): 8,7

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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