Preprints.org

Article

Not peer-reviewed version

A Real-World Safety Profile in Neurological, Skin, and Sexual disorders of Antiepileptic Drugs Using Pharmacovigilance Database of the Korea Adverse Event Reporting System (KAERS)

DaJeong Kim * and Sukhyang Lee *

Posted Date: 12 June 2024

doi: 10.20944/preprints202406.0844.v1

Keywords: Adverse event reporting system; Anti-epileptic drugs; Adverse reproductive outcome; Sodium channel blockers; Epilepsy; Pharmacovigilance

Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Article

A Real-World Safety Profile in Neurological, Skin, and Sexual disorders of Antiepileptic Drugs Using Pharmacovigilance Database of the Korea Adverse Event Reporting System (KAERS)

DaJeong Kim [1,*] and Sukhyang Lee [2,*]

[1] Department of Biohealth Regulatory Science, College of Pharmacy, Ajou University, Suwon, Republic of Korea
[2] Division of Clinical Pharmacy, College of Pharmacy, Ajou University, Suwon, Republic of Korea
* Correspondence: kdajg1234@ajou.ac.kr, suklee@ajou.ac.kr

Abstract: This study aims to examine the safety profile of antiepileptic drugs (AEDs) using real-world data, with a focus on neurological, skin, and sexual/reproductive disorders. Data were collected from AED-caused reports in the Korea Adverse Event Reporting System Database (KAERS-DB) from 2012 to 2022. Totally, 46,963 adverse drug reaction (ADR)-drug pairs were analyzed. At the system organ class level, the most frequently reported classes for sodium channel blockers (SCBs) were skin (37.9%), neurological (16.7%), and psychiatric disorders (9.7%). However, for non-SCBs, these were neurological (31.2%), gastrointestinal (22.0%), and psychiatric disorders (18.2%). The most common ADRs induced by SCBs were rash (17.8%), pruritus (8.2%), and dizziness (6.7%). In contrast, non-SCBs induced dizziness (23.7%), somnolence (13.0%), and nausea (6.3%). Among the most commonly reported ADRs, rash, pruritus, and urticaria occurred on average two days later with SCBs compared to non-SCBs. Sexual/reproductive disorders were reported at a frequency of 0.23%. SCBs were reported as the cause more frequently than non-SCBs (59.8% vs. 40.2%, Fisher's exact test, $p<0.0001$). Based on real-world data, we identified the safety profiles of AEDs. AED-induced ADRs exhibited different patterns depending on the mechanism. Therefore, it is important to establish different pharmacovigilance strategies to ensure proper monitoring.

Keywords: Adverse event reporting system; Anti-epileptic drugs; Adverse reproductive outcome; Sodium channel blockers; Epilepsy; Pharmacovigilance

1. Introduction

Epilepsy is the third most common neurological disorder, following stroke and dementia [1,2]. Epilepsy affects approximately 50 million people worldwide, with a lifetime prevalence of 7.6 per 1,000 persons. In Korea, the incidence and prevalence of epilepsy were 35.4 per 100,000 persons and 4.8 per 1,000 persons, respectively, in 2017 [3,4]. It affects individuals across all age groups, with a higher incidence observed in children compared to youth and middle-aged individuals, and an even more pronounced prevalence in the elderly. Consequently, the incidence curve exhibits a U-shape, which significantly increases and transitions to a J-shape after the age of 60[2,4,5].

The pharmacotherapy of epilepsy typically begins with monotherapy. It is expected that 70% of all patients with epilepsy will achieve remission through the use of the appropriate antiepileptic drugs (AEDs) [6]. The mechanisms of AEDs are divided to modulation of voltage-dependent ion channels, potentiation of γ-amino butyric acid, multiple mechanisms of action and another mechanism of action [7]. The choice of an AED is primarily based on the type of epilepsy. Other important considerations include pharmacokinetic properties, drug interactions, patient age and sex, comorbidities, and adverse events [8]. Adverse events lead to the discontinuation of AEDs in 1.35% of patients[9]. The long-term safety of AEDs is associated with chronic and cumulative effects, as well as rare but potentially serious idiopathic reactions, delayed onset of adverse effects, and other related concerns[10]. AEDs have the potential to cause central nervous system-related disorders by

© 2024 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

pathologically suppressing the overactivation of neurons. It has been reported that most AEDs may cause dose-dependent side effects such as sedation, somnolence, incoordination, nausea, and fatigue [11,12]. Other important safety issues of AEDs include sexual and reproductive disorders such as sexual dysfunction [13,14] and teratogenicity [15,16]. The use of AEDs during pregnancy may affect fetal cognitive and behavioral development, both in the early and full-term stages [15]. The impact of paternal exposure to AEDs on offspring is controversial topic. Specially, paternal valproate exposure led behavioral alterations in mice [17]. However, other studies found no correlation between paternal exposure to valproate and cognitive disorders in offspring [18,19]. Epilepsy is a chronic neurological disorder that requires long-term pharmacotherapy. Therefore, it is necessary to develop individual clinical strategies that take into account the safety profile of AEDs, as the possibility of adverse events inevitably increases [20]. This study aims to analyze the patterns of ADRs based on the mechanisms of action of AEDs, with a focus on major ADRs including neurological, dermatological, and sexual/reproductive disorders, using real-world data.

2. Materials and Methods

2.1. Study Design and Data Source

This retrospective study analyzed ADRs caused by AEDs using nationwide spontaneous reporting data from the Korea Adverse Reporting System database (KAERS-DB) between 2012 and 2022. We excluded incomplete data (n=900), AEDs that were not considered doubtful drugs (n=1,034), data with logical errors (n=1,034), and missed adverse event information (n=1,101), from a total of 167,072 ADR-AED pairs. We included only ADR cases with causality assessment results of certain (n=817), probable (n=11,868), or possible (n=34,278) according to the World Health Organization-Uppsala Monitoring Centre (WHO-UMC). The study design is summarized in Figure S1 in the Supplementary Appendix.

2.2. Identification of Anti-Epileptic Drugs

Study drugs were screened according to their label indications approved by the Ministry of Food and Drug Safety (MFDS). Thirteen AEDs were chosen based on the standard for providing KAERS database. The selected AEDs were carbamazepine, clonazepam, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and valproic acid. The drugs were classified as either sodium channel blockers (SCBs) or non-SCBs based on their mechanism of action. SCBs comprised carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenytoin, topiramate, and valproate, while non-SCBs included clonazepam, gabapentin, levetiracetam, phenobarbital, and pregabalin (Table S1).

2.3. Definition of Adverse Drug Reactions

ADRs were coded according to the Preferred Term (PT) and System Organ Class (SOC) of the World Health Organization-Adverse Reaction Terminology (WHO-ART). ADRs were considered serious if they resulted in death, life-threatening situation, initial or prolonged hospitalization, disability or permanent damage, or other significant medical events. To compare the sexual and reproductive disorders caused by different drugs, we defined sexual/reproductive disorder as any of the following conditions within the SOCs of WHO-ART: Male reproductive disorders (WHO-ART code: 1410), female reproductive disorders (WHO-ART code: 1420), foetal disorders (WHO-ART code: 1500), and neonatal and infancy disorders (WHO-ART code: 1600).

2.4. Onset Times of ADR

The median onset time of ADRs was calculated using the date of ADR occurrence and the start date of ADR use. For the sensitivity analysis, the onset time was divided into two groups: if the date of ADR occurrence was limited to 8 weeks due to the development time of type 2 allergic reactions (onset time 1) [21], or not limited (onset time 2).

2.5. Statistical Analysis

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

To identify ADR reporting properties, we conducted a descriptive analysis of sex, age, ADRs, drugs, and seriousness. We compared categorical variables using the Chi-square test or Fisher's exact test and identified statistical significance if the P-value was less than 0.05.

We evaluated the association between AEDs and frequently reported ADRs by estimating reporting odds ratios (RORs), proportional reporting ratios (PRRs), and information components (ICs) based on disproportionality analysis [22]. We considered a signal if the report met all of the following criteria: the number of cases ≥ 3, ROR and PRR ≥ 2, and $\chi 2 \geq 4$, The tower limit of the 95% confidence interval for IC ≥ 0 [23]. All analyses were performed using SAS software, version 9.4 (SAS Institute), or Excel 2019 (Microsoft).

3. Results

3.1. Baseline Characteristics of Adverse Drug Reactions (ADR) Reports (2012~2021)

Data was extracted from the KAERS DB between 2012 and 2021, following the exclusion criteria. Out of a total of 46,963 ADR-AED pairs, 14,847 were SCBs (31.6%) and 32,116 were non-SCBs (68.4%). In terms of sex, 16,349 were male (34.8%), 29,454 were female (62.7%), and 1,160 were unknown (2.5%). In both SCBs and non-SCBs, ADRs occurred more frequently in females than in males. Specifically, for SCBs, 8,403 cases (56.6%) were reported in females compared to 5,891 cases (39.7%) in males. For non-SCBs, 21,051 cases (65.6%) were reported in females compared to 10,458 cases (32.6%) in males. ADRs were more frequently reported in order individuals, particularly those aged 60 years or older (45.8%) and those in their 50s (19.8%). In non-SCBs, individuals aged 60 years or older accounted for 55.03% of the total, indicating a more pronounced trend. The primary reporters were distributed as follows: pharmacists (39.2%), nurses (31.9%), clinicians (20.9%), customers (5.6%), and others. Out of a total of 2,888 serious ADRs, 1,903 cases were reported in SCBs and 985 cases were reported in non-SCBs. Specifically, 3.5% of the total reports resulted in initial or prolonged hospitalization (n=1,633), 2.6% were other important medical events (n=1,240), and 0.3% were life-threatening (n=130). The incidence of ADRs varied depending on the age group of the patients. Importantly, it should be noted that the incidence of rash, pruritus, and urticaria was elevated within the younger age group. Among patients under 10 years old, rash (28.6%), pruritus (9.7%), and urticaria (6.5%) were frequently reported. In patients in their 10s, rash (13.0%), dizziness (10.8%), and somnolence (10.8%) were commonly reported. Meanwhile, the older age group experienced dizziness and somnolence more frequently. Among patients in their 50s, dizziness was the most commonly reported symptom (19.1%), followed by somnolence (11.5%) and rash (6.4%). In patients over 60 years, dizziness was also the most frequently reported symptom (22.7%), followed by somnolence (10.9%) and nausea (5.4%) (Table S2). The most common ADRs reported in male patients were dizziness (14.2%), somnolence (9.8%), and rash (9.8%). Similarly, female patients reported higher incidence of dizziness (12.4%), somnolence (10.5%), and rash (6.8%) (Table S3).

Table 1. Characteristics of reporting from the Korea Adverse Event Reporting System database (2012 to 2021).

Characteristics	Total		SCBs		Non-SCBs		p-value
	N	%	N	%	N	%	
Reports	46,963	100.0	14,847	31.6	32,116	68.4	-
Sex							<.0001
Male	16,349	34.8	5,891	39.7	10,458	32.6	
Female	29,454	62.7	8,403	56.6	21,051	65.5	
Unknown	1,160	2.5	553	3.7	607	1.9	
Age group							<.0001
00-09	1,494	3.2	1,093	7.4	401	1.3	
10-19	1,580	3.4	1,177	7.9	403	1.3	
20-29	2,717	5.8	1,775	12.0	942	2.9	
30-39	3,577	7.6	1,815	12.2	1,762	5.5	
40-49	5,319	11.3	1,907	12.8	3,412	10.6	

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

50-59	9,300	19.8	2,409	16.2	6,891	21.5	
>60	21,509	45.8	3,837	25.8	17,672	55.0	
Unknown	1,467	3.1	834	5.6	633	2.0	
Original reporter							<.0001
Clinician	9,805	20.9	4,495	36.0	5,310	15.4	
Pharmacist	18,396	39.2	2,167	17.4	16,229	47.1	
Nurse	14,974	31.9	4,484	35.9	10,493	30.4	
Other medical specialists	251	0.5	167	1.3	167	0.5	
Consumer	2,629	5.6	999	8.0	1,630	4.7	
Unknown	908	1.9	260	2.1	648	1.9	
Assessment							<.0001
Certain	817	1.7	399	2.7	418	1.3	
Probable/likely	11,868	25.3	5,247	35.3	6,621	20.6	
Possible	34,278	73.0	9,201	62.0	25,077	78.1	
Seriousness							<.0001
Yes	2,888	6.1	1,903	12.8	985	3.1	
No	44,075	93.9	12,944	87.2	31,131	96.9	
Seriousness category							<.0001
Death	65	0.1	26	0.2	39	0.1	
Life-threatening	130	0.3	76	0.5	54	0.2	
Hospitalization	1,633	3.5	1,144	7.7	489	1.5	
Disability	31	0.1	22	0.2	9	0.0	
Congenial anomaly	2	0.0	2	0.0	-	-	
Other significant medical events	1,240	2.6	818	5.5	422	1.3	

3.2. Analysis of Reporting Odds Ratio based on System Organ Classes

At the level of system organ class (SOC), central and peripheral nervous system disorders accounted for 26.6% of cases, followed by skin and appendages disorders at 18.0%, gastro-intestinal system disorder at 17.9%, psychiatric disorders at 15.5%, and body as a whole-general disorders at 8.1%. In SCBs, skin and appendages disorders were the most prevalent (5,631, 37.9%), while central and peripheral nervous system disorders were dominant in non-SCBs (10,007, 31.2%) (Table 2). The major drugs associated with skin and appendage disorders in SCBs were carbamazepine, lamotrigine, oxcarbazepine, phenytoin, and valproate (carbamazepine ROR 4.22 (3.91-4.54); oxcarbazepine ROR 6.44 (5.79-7.16); phenytoin ROR 3.41 (2.97-3.91); valproate ROR 1.74 (1.61-1.87); lacosamide ROR 0.89 (0.7-1.13); topiramate ROR 0.52 (0.45-0.59)). In non-SCBs, gabapentin and pregabalin were reported frequently for central and peripheral nervous system disorders, while clonazepam, levetiracetam, and phenobarbital were reported less frequently (gabapentin ROR 1.24 (1.18-1.29); pregabalin ROR 2.37 (2.27-2.48); clonazepam ROR 0.77 (0.7-0.85); levetiracetam ROR 0.37 (0.33-0.41); phenobarbital ROR 0.15 (0.08-0.26)) (Table 3).

Table 2. Distribution of adverse drug reaction(ADR)-antiepileptic drug(AED) pairs according to relevant System Organ Classes.

SOC	Total		SCBs		Non-SCBs	
	N	%	N	%	N	%
Total	46,963	100	*14,847*	*100.0*	*32,116*	*100.0*
Central & peripheral nervous system disorders	12,484	26.6	2,477	16.7	10,007	31.2
Skin and appendages disorders	8,438	18.0	5,631	37.9	2,807	8.7
Gastro-intestinal system disorders	8,413	17.9	1,351	9.1	7,062	22.0
Psychiatric disorders	7,290	15.5	1,436	9.7	5,854	18.2
Body as a whole - general disorders	3,810	8.1	1,078	7.3	2,732	8.5
Liver and biliary system disorders	1,197	2.5	662	4.5	535	1.7
Metabolic and nutritional disorders	1,092	2.3	495	3.3	597	1.9

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

White cell and RES* disorders	577	1.2	380	2.6	197	0.6
Platelet, bleeding & clotting disorders	416	0.9	308	2.1	108	0.3
Vision disorders	519	1.1	193	1.3	326	1.0
Urinary system disorders	936	2.0	146	0.98	790	2.46
Respiratory system disorders	381	0.8	130	0.9	251	0.8
Heart rate and rhythm disorders	257	0.5	101	0.7	156	0.5
Secondary terms - events	159	0.3	89	0.6	70	0.2
Musculo-skeletal system disorders	338	0.7	81	0.5	257	0.8
Cardiovascular disorders, general	212	0.5	67	0.5	145	0.5
Red blood cell disorders	87	0.2	51	0.3	36	0.1
Reproductive disorders, female	72	0.2	44	0.30	28	0.087
Hearing and vestibular disorders	69	0.1	33	0.2	36	0.1
Vascular (extracardiac) disorders	60	0.1	30	0.2	30	0.1
Special senses other, disorders	65	0.1	15	0.1	50	0.2
Neonatal and infancy disorders	11	0.0	11	0.1	-	0.0
Resistance mechanism disorders	14	0.0	8	0.1	6	0.019
Reproductive disorders, male	22	0.0	7	0.0	15	0.047
Endocrine disorders	15	0.0	6	0.0	9	0.0
Neoplasms	10	0.0	6	0.0	4	0.0
Application site disorders	8	0.0	6	0.0	2	0.0
Collagen disorders	7	0.0	3	0.0	4	0.0
Foetal disorders	2	0.0	2	0.01	-	0.000
Poison specific terms	2	0.0	-	0.00	2	0.01

SOC: system organ class; SCB: sodium channel blocker; RES: reticuloendothelial system.

Table 3. Signal strength of reports with antiepileptic drugs at the System Organ Class level.

Group	SOC ROR (95% CI)				
Drug	**Skin and appendages disorders**	**CNS & PNS system disorders**	**Psychiatric disorders**	**Gastro-intestinal system disorders**	**Body as a whole - general disorders**
SCBs					
Carbamazepine	4.22 (3.91-4.54)	0.51 (0.46-0.56)	0.36 (0.31-0.41)	0.41 (0.36-0.47)	1.4 (1.24-1.57)
Lacosamide	0.89 (0.7-1.13)	1.41 (1.16-1.7)	1.09 (0.86-1.39)	0.47 (0.35-0.64)	0.34 (0.2-0.58)
Lamotrigine	10.96 (10.04-11.97)	0.16 (0.13-0.19)	0.29 (0.24-0.34)	0.21 (0.17-0.25)	1.11 (0.96-1.28)
Oxcarbazepine	6.44 (5.79-7.16)	0.36 (0.31-0.43)	0.32 (0.26-0.4)	0.29 (0.24-0.36)	0.58 (0.45-0.73)
Phenytoin	3.41 (2.97-3.91)	0.55 (0.46-0.66)	0.27 (0.2-0.37)	0.31 (0.24-0.41)	0.83 (0.64-1.09)
Valproate	1.74 (1.61-1.87)	0.48 (0.44-0.52)	0.59 (0.53-0.65)	0.64 (0.58-0.7)	0.67 (0.58-0.77)
Topiramate	0.52 (0.45-0.59)	1.21 (1.11-1.33)	1.46 (1.32-1.62)	0.56 (0.49-0.64)	0.71 (0.6-0.84)
Non-SCBs					
Clonazepam	0.38 (0.33-0.44)	0.77 (0.7-0.85)	3.05 (2.8-3.33)	0.95 (0.86-1.06)	0.84 (0.72-0.99)
Gabapentin	0.25 (0.24-0.27)	1.24 (1.18-1.29)	1.38 (1.31-1.46)	1.92 (1.83-2.02)	1.23 (1.15-1.32)
Levitiracetam	1.93 (1.78-2.09)	0.37 (0.33-0.41)	0.96 (0.86-1.06)	0.64 (0.58-0.71)	0.67 (0.58-0.78)
Phenobarbital	4.62 (3.58-5.96)	0.15 (0.08-0.26)	0.47 (0.29-0.75)	0.22 (0.12-0.4)	1.21 (0.79-1.87)
Pregabalin	0.19 (0.17-0.2)	2.37 (2.27-2.48)	1.01 (0.96-1.07)	1.47 (1.4-1.55)	1.12 (1.04-1.2)

CNS: central nervous system; PNS: peripheral nervous system; SCB: sodium channel blocker; SOC: system organ classes; RES: reticulo endothelial system; ROR: reporting odds ratio; CI: confidence interval .

ROR >1 <1 Not significant

3.3. Types of Antiepileptic Drug-Related ADRs by Drug Mechanisms

3.3.1. The 20 Most Commonly Reported Adverse Drug Reactions

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

At the preferred term (PT) level, the top five ADRs observed in SCBs were rash (17.8%), pruritus (8.2%), dizziness (6.7%), urticaria (6.2%), and somnolence (3.9%). In non-SCBs, the top five ADRs were dizziness (23.7%), somnolence (13.0%), nausea (6.3%), constipation (3.7%), and vomiting (3.6%) (Table 4).

Table 4. Top 20 adverse drug reactions reported to the KAERS.

Top	SCBs			Non-SCBs		
	ADR	Reports (n)	%	ADR	Reports (n)	%
1	Rash	2,644	17.8	Dizziness	7,597	23.7
2	Pruritus	1,219	8.2	Somnolence	4,184	13.0
3	Dizziness	999	6.7	Nausea	2,020	6.3
4	Urticaria	916	6.2	Constipation	1,193	3.7
5	Somnolence	577	3.9	Vomiting	1,172	3.6
6	Nausea	359	2.4	Mouth Dry	1,076	3.4
7	Hepatic Enzymes Increased	352	2.4	Rash	1,003	3.1
8	Fever	333	2.2	Dyspepsia	886	2.8
9	Thrombocytopenia	285	1.9	Pruritus	849	2.6
10	Paraesthesia	272	1.8	Headache	695	2.2
11	Vomiting	263	1.8	Urticaria	478	1.5
12	Headache	228	1.5	Asthenia	450	1.4
13	Leucopenia	210	1.4	Oedema Generalised	442	1.4
14	Drug Hypersensitivity Syndrome	207	1.4	Hepatic Enzymes Increased	429	1.3
15	Constipation	198	1.3	Face Oedema	426	1.3
16	Tremor	197	1.3	Oedema	384	1.2
17	Stevens Johnson Syndrome	170	1.1	Tremor	327	1.0
18	Dyspepsia	163	1.1	Insomnia	307	1.0
19	Weight Increase	145	1.0	Weight Increase	289	0.9
20	Anorexia	139	0.9	Oedema Peripheral	280	0.9
	Total of Top20	9,876	66.52	Total of Top20	24,487	76.25
	Others	4,971	33.5	Others	7,629	23.8

SCBs: sodium channel blockers; ADR: adverse drug reaction.

3.3.2. Onset Time of Adverse Drug Reactions

The median onset time of the top 10 ADRs was compared. The median onset time for dizziness, somnolence, nausea, vomiting, constipation, mouth dry, and dyspepsia induced by both SCBs and non-SCBs was 0 days. However, there was a difference in the median onset time for rash, pruritus, and urticaria between SCBs and non-SCBs (Table 5). To perform a sensitivity analysis, when the onset time was restricted to 8 weeks (onset 1), rash, pruritus, and urticaria induced by SCBs exhibited a delayed onset of 2 days compared to non-SCBs. When onset time was not restricted (onset 2), the time difference in occurrence of rash, pruritus, and urticaria between SCBs and non-SCBs increased by 6 days, 6 days, and 7 days, respectively.

Table 5. The median onset time of the top 10 adverse drug reactions.

	Median time to onset 1 Days (Q1, Q3)		Median time to onset 2 Days (Q1, Q3)	
ADR	SCBs	Non-SCBs	SCBs	Non-SCBs
Dizziness	0 (0, 2)	0 (0, 1)	1 (0, 10)	0 (0, 1)
Somnolence	0 (0, 1)	0 (0, 0)	0 (0, 10)	0 (0, 1)
Rash	3 (0, 9)	1 (0, 5)	9 (1, 84)	3 (0, 72)
Nausea	0 (0, 1)	0 (0, 1)	0 (0, 6)	0 (0, 1)

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

Pruritus	2 (0, 7)	0 (0, 2)	7 (0, 83)	1 (0, 10)
Vomiting	0 (0, 2)	0 (0, 1)	1 (0, 6)	0 (0, 1)
Urticaria	2 (0, 8)	0 (0, 2)	8 (0, 82)	1 (0, 8)
Constipation	0 (0, 5)	0 (0, 2)	3 (0, 20)	0 (0, 5)
Mouth Dry	0 (0, 0)	0 (0, 0)	0 (0, 5)	0 (0, 0)
Dyspepsia	0 (0, 1)	0 (0, 0)	0 (0, 14)	0 (0, 0)

SCBs: sodium channel blockers; ADR: adverse drug reaction.

The median onset time of ADRs was calculated using the date of ADR occurrence and the start date of ADR use. If either of these dates was missing, it was excluded from the analysis (n=5,684). The median time to onset 1 included results where the onset time was limited to 8 weeks (n=34,069), while the median time to onset 2 included all results where the onset time was not limited (n=41,252).

3.4. Sexual/Reproductive related Adverse Drug Reactions

With regard to sexual/reproductive ADRs, 64 cases (59.8%) were reported in SCBs and 43 cases (40.2%) were reported in non-SCBs, showing a statistically significant difference (Fisher's exact test, $p < 0.0001$) (Table 6).

In the SCB group, there were 44 cases of female reproductive disorders and 7 cases of male reproductive disorders. The non-SCB group had 28 cases of female reproductive disorders and 15 cases of male reproductive disorders. Neonatal and infancy disorders were reported in 2 cases in the SCB group, while no cases were reported in the non-SCB group. As a result of signal detection, amenorrhoea and menstrual disorder were identified for valproate, and menstrual disorder was identified for topiramate (Table S4).

Table 6. Sexual/reproductive adverse drug reactions reported in KAERS.

Sexual/Reproductive SOC **ADRs**	**SCBs** **Number of reports (%)**	**Non-SCBs** **Number of reports (%)**	***P-value***
Total	**64 (59.8%)**	**43 (40.2%)**	**<0.0001**
Reproductive disorders, male	7 (31.8%)	15 (68.2%)	0.4642
Balanoposthitis	0	1	
Ejaculation Disorder	0	2	
Ejaculation Failure	0	3	
Ejaculation Premature	2	1	
Priapism	0	1	
Semen Abnormal	1	0	
Sexual Function Abnormal	4	7	
Reproductive disorders, female	44 (61.1%)	28 (38.9%)	0.0081
Amenorrhoea	6	1	
Breast Discomfort	0	1	
Breast Engorgement	2	1	
Breast Enlargement	1	4	
Breast Pain	1	3	
Breast Pain Female	1	1	
Dysmenorrhoea	3	0	
Gynecological-Related Pain	1	0	
Lactation Nonpuerperal	1	3	
Leukorrhoea	1	1	
Menorrhagia	1	0	
Menstrual Disorder	23	8	
Post-Menopausal Bleeding	0	1	
Uterine Atony	0	1	
Vaginal Discomfort	0	1	

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

Vaginal Haemorrhage	0	2	
Vaginitis	3	0	
Foetal disorders	2 (100.0%)	0 (0.0%)	-
Drug Exposure In Pregnancy	2	0	
Neonatal and infancy disorders	11 (100.0%)	0 (0.0%)	-
Psychomotor Development Impaired	11	0	

SCB: sodium channel blockers; SOC: system organ class. The proportion of sexual/reproductive ADRs was compared between SCBs and non-SCBs using Fisher's exact test.

4. Discussion

The number of disability-adjusted life-years of epilepsies increased from 1990 to 2017 by 13.8%. However, the disease burden has been exacerbated by factors such as rapid aging, population growth, increased life expectancy, and a higher incidence of risk factors including infections, traumatic brain injury, and stroke [24]. Fortunately, pharmacotherapy can improve epilepsy, and 63.7% of newly diagnosed patients with epilepsy achieve seizure freedom within one year of AED monotherapy [25]. 88% of patients taking AEDs experience one or more adverse events. Adverse events are the primary reason for early treatment discontinuation and a barrier to seizure control [26]. Understanding the safety profile of AEDs is crucial due to the long-term pharmacotherapy required to control symptoms in patients with epilepsy. However, there is a limitation in using high-quality evidence on AED safety due to the lack of standardized reporting [20]. Therefore, our goal is to identify the major safety concerns associated with AEDs, including neurological, skin, and sexual/reproductive disorders. We analyzed the ADRs that occurred in real clinical settings using a real-world spontaneous reporting database. Between 2012 and 2021, there were 63,669 reports of adverse events associated with AEDs nationwide in Korea, resulting in 49,963 ADR-AED pairs. In the USA, 112,901 cases of adverse events related to AEDs were reported between July 2018 and March 2020 [27]. In Japan, there were 587,017 cases reported between 2004 and 2020 [28].

The odds of skin disorders occurring in SCBs (5,631/8,438, 66.7%) were higher than in non-SCBs. Specifically, carbamazepine (ROR 4.22), lamotrigine (ROR 10.96), oxcarbazepine (ROR 6.44), phenytoin (ROR 3.41), and valproate (ROR 1.74) were identified as major doubtful drugs in SCBs. In contrast, topiramate (ROR 0.52) had a significantly lower incidence of skin disorders. Skin disorders were statistically less likely to occur with clonazepam (ROR 0.38), gabapentin (ROR 0.25), and pregabalin (ROR 0.19) compared to phenobarbital (RPR 4.6) in non-SCBs. AEDs are classified as the primary cause of severe cutaneous adverse reactions (SCARs) [29]. Based on data from the FDA Adverse Event Reporting System (FAERS) between 2004 and 2021, AEDs belonged to the major drug classes that cause Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN), and 19.37% of all reports were related to AEDs. Specifically, phenytoin was identified as the most frequently reported drug [30]. The study analyzing 2,942 cases of drug eruption from KAERS DB between 2008 to 2017 found that lamotrigine, valproate, carbamazepine, oxcarbazepine, levetiracetam, and phenytoin were the cause of the eruptions [31]. In this study, we found that carbamazepine, oxcarbazepine, lamotrigine, phenytoin, and phenobarbital were doubtful drugs for skin disorders. These aromatic AEDs are known to be major causes of SCARs [32]. Also, we identified that epidermal necrolysis was the signal for carbamazepine and lamotrigine, valproate, and SJS was the signal for carbamazepine, lamotrigine, phenytoin and phenobarbital (Table S5).

On the other hand, there was no statistically significant ROR index for lacosamide in skin disorders (ROR 0.89; 95% CI=0.7-1.13). The effect of lacosamide on skin disorders remains a subject of debate. According to the pivotal study, the incidence of lacosamide-induced rash was 2.9%, which did not differ significantly from placebo and had a low risk [33]. However, another independent study, utilizing the FDA Adverse Event Reporting System (FAERS) database, demonstrated that lacosamide increased the risk of Stevens-Johnson syndrome (SJS) (ROR 2.16, lower limit of 95% CI=1.42). Women treated with lacosamide had a particularly high risk of skin disorder, including alopecia, rash maculopapular, rash pruritic and TEN [34]. Our study identified rash erythematous as a signal for lacosamide (Table S5). Drug hypersensitivity typically occurs between 1 and 8 weeks after

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

exposure to the drug. As most reactions happen within the first two months of treatment initiation, there is a possibility of underestimating the true incidence of the syndrome [35]. In this study, the onset of skin disorders such as rash, pruritus, and urticaria was delayed by 2 days in patients treated with SCBs compared to non-SCBs. Conversely, somnolence, nausea, mouth dry and dyspepsia occurred instantly regardless of mechanisms (Table 3). Therefore, it is crucial to monitor patients treated with SCBs for delayed idiopathic hypersensitivity reactions, which may occur.

Neurological disorders were more prevalent in patients treated with non-SCBs (10,007/12,484, 80.2%). Gabapentin (ROR 1.24; 95% CI=1.18-1.29) and pregabalin (ROR 2.37; 95% CI=2.27-2.48) were associated with a high risk of neurological ADRs. This finding is consistent with a previous study that reported a high frequency of somnolence with pregabalin [36]. It is important to take neurological disorders seriously, as they can increase the risk of falls in the elderly [37–39]. There was a study that examined the relationship between AEDs and falls [40], but there is still limited information available on the specific drugs that cause them. Gabapentin and pregabalin have been identified as having a high risk of causing central and peripheral nervous system disorders. Further research is needed to determine the risk of falls associated with non-SCBs.

Sexual/reproductive disorders were more commonly reported with SCBs compared to non-SCBs (64[59.8%] vs. 43[40.2%], Fisher's exact test, $p<0.0001$). The effect on both sexes differed depending on the mechanism of action. In male reproductive disorders, including ejaculation disorder, ejaculation failure, and premature ejaculation, the number of reported cases was 7 in SCBs and 15 in non-SCBs, respectively. But there was no statistically significant difference between the two groups ($p=0.4642$). Epilepsy can have an impact on sexual function [41], with 30% of male patients suffered experiencing sexual dysfunction. Additionally, AEDs can cause drug-induced sexual disorders. Valproate and phenobarbital have been shown to worsen sexual function, while oxcarbazepine, lamotrigine, and levetiracetam may improve it [42]. There were 44 cases of female reproductive disorders, including amenorrhoea, dysmenorrhea, menorrhagia, menstrual disorder, breast discomfort, breast engorgement, breast enlargement, and breast pain in SCBs, compared to 28 cases in non-SCBs. Female patients with epilepsy who are undergoing pharmacotherapy may experience sexual dysfunction due to alternating doses of sexual hormones[43]. Additionally, valproate has been known to induce polycystic ovary syndrome[44]. Hyperprolactemia is known to cause amenorrhea and ejaculation disorders. Drugs affecting the nervous system, such as phenothiazines, risperidone, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and some tricyclic antidepressants, can induce hyperprolactemia. However, there have been few studies investigating the relationship between AEDs and hyperprolactemia. Our findings suggest that AEDs may induce typical symptoms of hyperprolactemia.

The KAERS DB has limitations related to non-standardized data due to reporter bias, underreporting, and heterogeneity. Incidence rates cannot be calculated due to a lack of information on the total number of patients, seizure types, indications, and comorbidities [45,46]. Despite these limitations, we proposed a safety profile based on real-world data from spontaneous reporting. This study found that patients reported symptoms indicative of hyperprolactemia associated with sexual/reproductive disorders, underscoring the importance of monitoring AED-induced hyperprolactinemia in patients presenting with such symptoms.

5. Conclusions

We analyzed the safety profiles of AEDs using real-world spontaneous reporting of adverse events. Our findings indicate that SCBs have a higher likelihood of causing skin disorders, while non-SCBs have a higher likelihood of causing neurological disorders. Depending on the mechanism of AEDs, different monitoring strategies may be required, as skin disorders may occur as a delayed response when it induced by SCBs. Regarding sexual/reproductive disorders, SCBs and non-SCBs have different effects on both sexes.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

Author Contributions: Conceptualization, D.J.K and S.H.L; methodology, D.J.K and S.H.L; formal analysis, D.J.K.; writing—original draft preparation, D.J.K.; writing—review and editing, S.H.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. A grant (21153MFDS602) from the Ministry of Food and Drug Safety in South Korea.

Institutional Review Board Statement: This study was approved by the Institutional Review Board of Ajou University (202301-HB-EX-001).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to regulatory reasons.

Acknowledgments: This research was supported by a grant (21153MFDS602) from the Ministry of Food and Drug Safety.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Thijs, R.D.; Surges, R.; O'Brien, T.J.; Sander, J.W. Epilepsy in adults. *The Lancet* **2019**, *393*, 689-701, doi:10.1016/S0140-6736(18)32596-0.
2. Beghi, E. The Epidemiology of Epilepsy. *Neuroepidemiology* **2020**, *54*, 185-191, doi:10.1159/000503831.
3. Jeon, J.Y.; Lee, H.; Shin, J.Y.; Moon, H.J.; Lee, S.Y.; Kim, J.M. Increasing Trends in the Incidence and Prevalence of Epilepsy in Korea. *J Clin Neurol* **2021**, *17*, 393-399, doi:10.3988/jcn.2021.17.3.393.
4. Falco-Walter, J. Epilepsy-Definition, Classification, Pathophysiology, and Epidemiology. *Seminars in neurology* **2020**, *40*, 617-623, doi:10.1055/s-0040-1718719.
5. Holmes, G.L. *Consequences of Epilepsy Through the Ages: When Is the Die Cast?*; Epilepsy Curr. 2012 Jul-Aug;12(Suppl 3):4-6. doi: 10.5698/1535-7511-12.4s.4.
6. Goldenberg, M.M. Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment. *P & T : a peer-reviewed journal for formulary management* **2010**, *35*, 392-415.
7. Kim, H.; Kim, D.W.; Lee, S.T.; Byun, J.I.; Seo, J.G.; No, Y.J.; Kang, K.W.; Kim, D.; Kim, K.T.; Cho, Y.W.; et al. Antiepileptic Drug Selection According to Seizure Type in Adult Patients with Epilepsy. *J Clin Neurol* **2020**, *16*, 547-555, doi:10.3988/jcn.2020.16.4.547.
8. Hakami, T. Neuropharmacology of Antiseizure Drugs. *Neuropsychopharmacology Reports* **2021**, *41*, 336-351, doi:https://doi.org/10.1002/npr2.12196.
9. Golpayegani, M.; Salari, F.; Gharagozli, K. Newer Antiepileptic Drugs Discontinuation due to Adverse Effects: An Observational Study. *Annals of Indian Academy of Neurology* **2019**, *22*, 27-30, doi:10.4103/aian.AIAN_25_18.
10. Gaitatzis, A.; Sander, J.W. The Long-Term Safety of Antiepileptic Drugs. *CNS Drugs* **2013**, *27*, 435-455, doi:10.1007/s40263-013-0063-0.
11. Kennedy, G.M.; Lhatoo, S.D. CNS Adverse Events Associated with Antiepileptic Drugs. *CNS Drugs* **2008**, *22*, 739-760, doi:10.2165/00023210-200822090-00003.
12. Zaccara, G.; Gangemi, P.F.; Cincotta, M. Central nervous system adverse effects of new antiepileptic drugs. A meta-analysis of placebo-controlled studies. *Seizure* **2008**, *17*, 405-421, doi:10.1016/j.seizure.2007.12.003.
13. Yang, Y.; Wang, X. Sexual dysfunction related to antiepileptic drugs in patients with epilepsy. *Expert Opin Drug Saf* **2016**, *15*, 31-42, doi:10.1517/14740338.2016.1112376.
14. Najafi, M.R.; Ansari, B.; Zare, M.; Fatehi, F.; Sonbolestan, A. Effects of antiepileptic drugs on sexual function and reproductive hormones of male epileptic patients. *Iranian journal of neurology* **2012**, *11*, 37-41.
15. Tomson, T.; Battino, D.; Perucca, E. Teratogenicity of antiepileptic drugs. *Current opinion in neurology* **2019**, *32*, 246-252, doi:10.1097/wco.0000000000000659.
16. Hill, D.S.; Wlodarczyk, B.J.; Palacios, A.M.; Finnell, R.H. Teratogenic effects of antiepileptic drugs. *Expert review of neurotherapeutics* **2010**, *10*, 943-959, doi:10.1586/ern.10.57.
17. Ibi, D.; Fujiki, Y.; Koide, N.; Nakasai, G.; Takaba, R.; Hiramatsu, M. Paternal valproic acid exposure in mice triggers behavioral alterations in offspring. *Neurotoxicology and teratology* **2019**, *76*, 106837, doi:10.1016/j.ntt.2019.106837.
18. Tomson, T.; Muraca, G.; Razaz, N. Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden. *Journal of neurology, neurosurgery, and psychiatry* **2020**, *91*, 907-913, doi:10.1136/jnnp-2020-323028.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

19. Yang, F.; Yuan, W.; Liang, H.; Song, X.; Yu, Y.; Gelaye, B.; Miao, M.; Li, J. Preconceptional paternal antiepileptic drugs use and risk of congenital anomalies in offspring: a nationwide cohort study. *European Journal of Epidemiology* **2019**, *34*, 651-660, doi:10.1007/s10654-019-00509-2.
20. Mifsud de Gray, J. Novel considerations on drug safety in epilepsy. *Expert Opinion on Drug Safety* **2021**, *20*, 119-121, doi:10.1080/14740338.2021.1865913.
21. Brockow, K.; Przybilla, B.; Aberer, W.; Bircher, A.J.; Brehler, R.; Dickel, H.; Fuchs, T.; Jakob, T.; Lange, L.; Pfützner, W.; et al. Guideline for the diagnosis of drug hypersensitivity reactions: S2K-Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) in collaboration with the Association of German Allergologists (AeDA), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Swiss Society for Allergy and Immunology (SGAI), the Austrian Society for Allergology and Immunology (ÖGAI), the German Academy of Allergology and Environmental Medicine (DAAU), the German Center for Documentation of Severe Skin Reactions and the German Federal Institute for Drugs and Medical Products (BfArM). *Allergo journal international* **2015**, *24*, 94-105, doi:10.1007/s40629-015-0052-6.
22. Zhou, C.; Peng, S.; Lin, A.; Jiang, A.; Peng, Y.; Gu, T.; Liu, Z.; Cheng, Q.; Zhang, J.; Luo, P. Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. *EClinicalMedicine* **2023**, *59*, 101967, doi:10.1016/j.eclinm.2023.101967.
23. Koo, H.; Kwon, J.Y.; Choi, J.-H.; You, S.H.; Park, S.; Jeong, K.H.; Jung, S.-Y. Signal Detection of Alpha-adrenoceptor Antagonist using the KIDS-KAERS database (KIDS-KD). *Korean J Clin Pharm* **2023**, *33*, 86-96, doi:10.24304/kjcp.2023.33.2.86.
24. Hu, Y.; Shan, Y.; Du, Q.; Ding, Y.; Shen, C.; Wang, S.; Ding, M.; Xu, Y. Gender and Socioeconomic Disparities in Global Burden of Epilepsy: An Analysis of Time Trends From 1990 to 2017. *Frontiers in Neurology* **2021**, *12*, doi:10.3389/fneur.2021.643450.
25. Chen, Z.; Brodie, M.J.; Liew, D.; Kwan, P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurology* **2018**, *75*, 279-286, doi:10.1001/jamaneurol.2017.3949.
26. Alsfouk, B.A.A.; Brodie, M.J.; Walters, M.; Kwan, P.; Chen, Z. Tolerability of Antiseizure Medications in Individuals With Newly Diagnosed Epilepsy. *JAMA Neurology* **2020**, *77*, 574-581, doi:10.1001/jamaneurol.2020.0032.
27. Kamitaki, B.K.; Minacapelli, C.D.; Zhang, P.; Wachuku, C.; Gupta, K.; Catalano, C.; Rustgi, V. Drug-induced liver injury associated with antiseizure medications from the FDA Adverse Event Reporting System (FAERS). *Epilepsy Behav* **2021**, *117*, 107832, doi:10.1016/j.yebeh.2021.107832.
28. Kawada, K.; Ishida, T.; Jobu, K.; Ohta, T.; Fukuda, H.; Morisawa, S.; Kawazoe, T.; Tamura, N.; Miyamura, M. Association of Aggression and Antiepileptic Drugs: Analysis Using the Japanese Adverse Drug Event Report (JADER) Database. *Biological and Pharmaceutical Bulletin* **2022**, *45*, 720-723, doi:10.1248/bpb.b21-00954.
29. Park, C.S.; Kang, D.Y.; Kang, M.G.; Kim, S.; Ye, Y.M.; Kim, S.H.; Park, H.K.; Park, J.W.; Nam, Y.H.; Yang, M.S.; et al. Severe Cutaneous Adverse Reactions to Antiepileptic Drugs: A Nationwide Registry-Based Study in Korea. *Allergy, asthma & immunology research* **2019**, *11*, 709-722, doi:10.4168/aair.2019.11.5.709.
30. Fei, W.; Shen, J.; Cai, H. Causes of Drug-Induced Severe Cutaneous Adverse Reaction Epidermal Necrolysis (EN): An Analysis Using FDA Adverse Event Reporting System (FAERS) Database. *Clinical, cosmetic and investigational dermatology* **2023**, *16*, 2249-2257, doi:10.2147/ccid.s422928.
31. Kim, H.K.; Kim, D.Y.; Bae, E.K.; Kim, D.W. Adverse Skin Reactions with Antiepileptic Drugs Using Korea Adverse Event Reporting System Database, 2008-2017. *Journal of Korean medical science* **2020**, *35*, e17, doi:10.3346/jkms.2020.35.e17.
32. Yang, S.-C.; Chen, C.-B.; Lin, M.-Y.; Zhang, Z.-Y.; Jia, X.-Y.; Huang, M.; Zou, Y.-F.; Chung, W.-H. Genetics of Severe Cutaneous Adverse Reactions. *Frontiers in Medicine* **2021**, *8*, doi:10.3389/fmed.2021.652091.
33. Fowler, T.; Bansal, A.S.; Lozsádi, D. Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting. *Seizure* **2019**, *72*, 61-70, doi:https://doi.org/10.1016/j.seizure.2019.07.003.
34. Liu, P.; He, M.; Xu, X.; He, Y.; Yao, W.; Liu, B. Real-world safety of Lacosamide: A pharmacovigilance study based on spontaneous reports in the FDA adverse event reporting system. *Seizure: European Journal of Epilepsy* **2023**, *110*, 203-211, doi:https://doi.org/10.1016/j.seizure.2023.07.003.
35. Krivoy, N.; Taer, M.; Neuman, M.G. Antiepileptic drug-induced hypersensitivity syndrome reactions. *Current drug safety* **2006**, *1*, 289-299, doi:10.2174/157488606777934459.
36. Kaur, U.; Chauhan, I.; Gambhir, I.S.; Chakrabarti, S.S. Antiepileptic drug therapy in the elderly: a clinical pharmacological review. *Acta Neurologica Belgica* **2019**, *119*, 163-173, doi:10.1007/s13760-019-01132-4.
37. Iwasaki, S.; Yamasoba, T. Dizziness and Imbalance in the Elderly: Age-related Decline in the Vestibular System. *Aging and disease* **2015**, *6*, 38-47, doi:10.14336/ad.2014.0128.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 June 2024 doi:10.20944/preprints202406.0844.v1

38. Zhou, S.; Jia, B.; Kong, J.; Zhang, X.; Lei, L.; Tao, Z.; Ma, L.; Xiang, Q.; Zhou, Y.; Cui, Y. Drug-induced fall risk in older patients: A pharmacovigilance study of FDA adverse event reporting system database. *Frontiers in Pharmacology* **2022**, *13*, doi:10.3389/fphar.2022.1044744.
39. Homann, B.; Plaschg, A.; Grundner, M.; Haubenhofer, A.; Griedl, T.; Ivanic, G.; Hofer, E.; Fazekas, F.; Homann, C.N. The impact of neurological disorders on the risk for falls in the community dwelling elderly: a case-controlled study. *BMJ open* **2013**, *3*, e003367, doi:10.1136/bmjopen-2013-003367.
40. Haasum, Y.; Johnell, K. Use of antiepileptic drugs and risk of falls in old age: A systematic review. *Epilepsy Res* **2017**, *138*, 98-104, doi:10.1016/j.eplepsyres.2017.10.022.
41. Hellmis, E. Sexual problems in males with epilepsy—An interdisciplinary challenge! *Seizure* **2008**, *17*, 136-140, doi:https://doi.org/10.1016/j.seizure.2007.11.011.
42. Sureka, R.K.; Gaur, V.; Purohit, G.; Gupta, M. Sexual Dysfunction in Male Patients with Idiopathic Generalized Tonic Clonic Seizures. *Annals of Indian Academy of Neurology* **2021**, *24*, 726-731, doi:10.4103/aian.AIAN_1023_20.
43. Singh, M.; Bathla, M.; Martin, A.; Aneja, J. Hypoactive sexual desire disorder caused by antiepileptic drugs. *Journal of human reproductive sciences* **2015**, *8*, 111-113, doi:10.4103/0974-1208.158619.
44. Joffe, H.; Hayes, F.J. Menstrual cycle dysfunction associated with neurologic and psychiatric disorders: their treatment in adolescents. *Annals of the New York Academy of Sciences* **2008**, *1135*, 219-229, doi:10.1196/annals.1429.030.
45. Palleria, C.; Leporini, C.; Chimirri, S.; Marrazzo, G.; Sacchetta, S.; Bruno, L.; Lista, R.; Staltari, O.; Scuteri, A.; Scicchitano, F.; et al. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. *Journal of pharmacology & pharmacotherapeutics* **2013**, *4*, S66-S72, doi:10.4103/0976-500X.120955.
46. Toki, T.; Ono, S. Spontaneous Reporting on Adverse Events by Consumers in the United States: An Analysis of the Food and Drug Administration Adverse Event Reporting System Database. *Drugs - Real World Outcomes* **2018**, *5*, 117-128, doi:10.1007/s40801-018-0134-0.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.