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Prevalence and factors associated with adverse therapeutic outcomes of antiseizure medication therapy in people with epilepsy

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Abstract

Background: Antiseizure medication (ASM) therapy has been the mainstay of the pharmacological management of epilepsy. The goal of treatment includes achieving good seizure outcomes while minimising the risk of adverse effects (AE). In developing countries, the therapeutic outcomes remain suboptimal. This study aimed to determine the prevalence of ASM therapeutic outcomes and its associated factors. *Methods:* This study was conducted in a public, hospital-based specialist clinic. People with epilepsy (PWE) who were prescribed at least one ASM were screened for eligibility. The therapeutic outcomes were assessed using established tools: the Seizure Severity Questionnaire (SSQ) and Liverpool Adverse Events Profile (LAEP), respectively. The patient's information and responses were recorded, and all relevant data was collected. *Results:* Three hundred and ninety-seven PWE were included in the analysis, of which 105 were included in the face-to-face outcome assessment. It was found that 79.3% of the PWE had poor seizure control. The mean SSQ score was 1.44 (±SD:1.34), and the mean LAEP score was 24.0 (±SD:5.91). Epilepsy duration of >10 years (OR: 1.87, 95%CI:1.10-3.17), generalised onset (OR:7.42, 95%CI:2.95-18.66), focal onset (OR:8.24, 95%CI:2.98- 22.77), non-adherence (OR:3.55, 95%CI:1.52, 8.27) and having ≥3 ASM (OR:3.29 (95%CI:1.32-8.24) were factors associated with poor seizure control. For seizure severity, younger age at onset (OR:3.29, 95%CI:1.32-8.24) and neurological deficit (OR:3.55, 95%CI:1.52-8.27) increased the tendency to have more severe seizures. The factors associated with AE occurrence were advancing age (OR:0.12, 95%CI:0.03-0.20), shorter epilepsy duration (OR:2.89, 95%CI:0.50-5.29), and PWE who had changes in their ASM regimen within the past year (OR:2.93, 95%CI:0.24-5.62).
Conclusion: Factors related to individuals' demographic and clinical characteristics are associated with adverse outcomes of ASM therapy. Recognising PWE at risk of adverse outcomes is crucial for improving overall epilepsy management.

Keywords: Epilepsy; seizures; therapeutic outcomes; seizure severity; adverse effects

INTRODUCTION

Over the last decades, there has been a transition in policy, moving away from the conventional biomedical care model towards more patient-centred care that prioritises people with epilepsy (PWE) and encompasses concepts like medication concordance.[1] Parallel to the core aspects of patient-centred care, several components of disease management need to be subdued. In a nutshell, it depicts overall therapeutic outcomes that comprise symptom control and remission, drug-related issues such as medication adherence, adverse drug reactions, and risk factors for poor therapeutic outcomes.

With the appropriate use of pharmacological interventions, most PWE can achieve seizure freedom. However, the therapeutic outcome remains suboptimal, particularly in developing and resource-limited countries.[2] Several concerns

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that hamper the provision of adequate epilepsy treatment in developing countries include lack of qualified and specialised medical personnel, limited availability of treatment options, stigma, cultural beliefs, poor awareness and financial instability.[3] These are among the factors that lead to the majority of PWE (80-90%) in developing countries not receiving appropriate treatment, as shown from previous studies.[4,5]

Therapeutic outcomes can be divided into the outcome measures related to i) the drugs' effectiveness and ii) the drug's safety and tolerability (potential adverse drug reactions). Primarily, treatment effectiveness is measured in terms of changes in clinical manifestation, i.e., seizure counts (frequency) and seizure severity.[6,7] Achieving good seizure control can vary from one individual to another, as each individual's response to treatment is unique. A good number of studies investigated the factors associated with seizure freedom. Several studies reported a relatively high proportion of PWE achieved seizure freedom (60-70%)[8-11], while other studies reported less than half of individuals achieved seizure freedom.[12-14] Assessment and recognition of this outcome are crucial to developing treatment optimization optimisation strategies in providing responsible care of PWE.[15]

Determining seizure frequency involves a straightforward calculation of the number of seizures within a specified timeframe, whereas assessing seizure severity can pose more complexity and uncertainty. There has been a growing interest in assessing possible changes in seizure severity following drug therapy. An accurate assessment of seizure severity can function effectively both as a marker for clinical outcomes and as a means of evaluating the interplay between seizures and the psychosocial challenges associated with epilepsy.[6] Likewise, a comprehensive understanding of potential adverse effects, continuous monitoring, patient education, and addressing physical and psychosocial considerations are necessary to ensure the safety of ASM utilisation.[16,17] Consequently, the drugs' safety and tolerability outcome serves as a vital domain within the broader landscape of treatment outcomes for ASM in epilepsy.[18]

In general, achieving the desired therapeutic outcome has been the primary aim of disease management with medication therapy. Failure to accomplish these adverse therapeutic outcomes would lead to reduced quality of life, extensive physical injury, social stigma, limited educational opportunities, neuropsychological limitations, decreased marriage and employment rates and ultimately, a shortened life expectancy.[13] Recognizing the risks and predictors of adverse outcomes would be of great value and beneficial for healthcare providers to strategise and optimise the pharmacological management of epilepsy.[19] In the Southeast Asian region, studies on ASM treatment outcomes are still scarce. Hence, this study investigated the prevalence of adverse therapeutic outcomes and associated factors among PWE prescribed with ASM.

METHODS

Study design and setting

This cross-sectional, observational study was conducted among PWE in the ambulatory setting of Tengku Ampuan Rahimah Hospital, Klang. It is a public tertiary care centre located in the central region of Malaysia under the Selangor State Health Department.

Study population and sampling method

The PWEs who were under follow-up for epilepsy treatment for at least 1 year in either general medical or neuromedical outpatient clinics and were prescribed at least one ASM were included in the study. The minimum age eligible for inclusion was 16 years old at the point of data collection. The list of subjects was retrieved from an electronic database, i.e., Pharmacy Information System (PhIS). At least 384 subjects were required for hypothesis testing.[20] Subjects were randomised using Microsoft Excel's Random sampling function.

Data collection and study instruments

All prescriptions received from the Medical Outpatient Clinic from January 2019 to December 2022 were screened. Prescriptions containing at least one ASM were extracted and sorted according to the respective ASM. After identifying the number of samples needed for each ASM, the randomised sampling function of the Excel spreadsheet was employed to select the corresponding subjects at random. The selected subjects from one ASM dataset were then combined with the other ASM datasets. The overall dataset was screened for duplicates.

There were two modes of data collection. Retrospective data collection on the subjects' medical records and assisted self-administered assessment using a pre-identified validated

research instrument. The data collection was mostly researcher-assisted, whereby the researcher guided the subjects in completing the questionnaire. The completed questionnaires were sorted out and compiled according to the study instrument:

i. The Seizure Severity Questionnaire (SSQ)

This questionnaire was developed by Cramer *et al*.[21] and was constructed from previously established seizure severity assessment tools. It consisted of 24 items with a 7-point scale gauging the severity of symptoms. These items were subdivided into 4 components based on seizure activity, namely, "before seizures", "during seizures", and "after seizures", which correspond to the phases of seizure, which are warning, activity and recovery. The fourth component asked for an overall assessment, whereas the final item, probing the overall severity and bothersomeness after changing seizure treatment, was omitted because of its non-applicability in this study. The total score ranged from 0 to 7, with a higher score indicating more severe seizures. The total score was calculated as the sum of the average of the items in respective components. The Malay Language version[22] of this questionnaire was utilised and permission to use was obtained from the main author prior to data collection.

ii. The Liverpool Adverse Events Profile (LAEP)

The assessment of adverse effects was carried out using LAEP, which is a validated tool developed in 1993 by Baker *et al*. In this study, the validated Indonesian version was employed, considering the similarity of the language used with that of the study population.[23] The LAEP tool comprised 19 items inquiring about the symptoms and frequency of adverse events (AE) within the past four weeks of the data collection date (patient-researcher encounter). Each item is tagged with a four-point Likert scale with the lowest score of 1 (no adverse events within four weeks), 2 – AE appeared for three to four days within four weeks, 3 – AE appeared for 15 days within four weeks and 4 – AE occurred almost every day within four weeks. The lowest score, 19, indicates that the patient never experienced any adverse effect within the past four weeks. Conversely, higher scores correlate with higher prevalence and intensity of adverse effects, with a maximum score of 76. Permission to use the tool was granted by the main author via email response.

Variables and definition of terms

Several potential independent variables, such as epilepsy duration, age at onset, aetiology, and types of seizures, were identified. Seizure types were categorised according to ILAE classification guidelines[24], including unknown onset, generalised onset, and focal onset seizures. These data and other clinical conditions were gathered from the medical records. In practice, neurological deficit status was assessed through observation and physical examination, covering gait, deep tendon reflexes, meningeal signs, motor exam (range of motion, muscle strength, and tone), mental status (cognitive function, awareness, orientation), visual function (acuity, field of vision), and cranial nerve function.[25-27]

Further categorisation followed guidelines and findings from previous studies.[13,28] For multivariate analysis of seizure severity, age at onset was categorised into two groups: i) more than 40 years old and ii) less than or equal to 40 years old, based on previous reports by Kaur *et al*.[29] and Asadi-Pooya *et al*.[30], aligning with the mean age of the studied population, 39.4 years old (±15.07). For adverse effect outcome analysis, epilepsy duration was dichotomised with a cut-off point of 13 years, corresponding to the average epilepsy duration associated with the mean LAEP score (24.0 ±5.39). This was determined from bivariate correlation analysis. Information on medication adherence was obtained through direct assessment by attending medical officers, as documented in the medical records.

The outcome variables for this study are seizure freedom, seizure severity as measured by SSQ score and adverse effect profile using LAEP score. Subjects were considered as having seizure freedom if the subjects had no seizure within the preceding year and poor seizure control if the subjects had at least one seizure (all seizure activities including auras) within the same timeframe.[31]

Data analysis

Data were tabulated, and analysis was performed using SPSS (Inc., Chicago, IL) version 27. Means and standard deviations (SD) were used for parametric continuous data. Frequencies and percentages were used for categorical variables. A probability (p) value of <0.05 was considered statistically significant. For the categorical outcome (seizure freedom), the chi-square test was used to determine the association between categorical variables, whereas binary logistic

regression was used to establish the factors associated with poor seizure control. Similarly, linear regression was applied to determine the factors associated with continuous outcome variables, i.e., SSQ and LAEP scores, respectively. Significant independent variables from univariate analysis and all the important variables based on established literature were then included in the multivariate analysis.

All assumptions for regression analysis were checked using various analyses, e.g., linearity of residuals (for continuous dependent variables using Q-Q plot), homoscedasticity (variance-residual plot), interactions (bivariate correlation analysis and Durbin-Watson statistic) and multicollinearity (bivariate correlation analysis and Variance Inflation Factor - VIF value) were checked.[32,33] A VIF value of <5 to 10 indicates that the model is free from multicollinearity issues.[34] Outliers for SSQ (n=3) and LAEP (n=7) were included as these were legitimate extreme values representing the true variations of the subjects' scores.

Ethical considerations

Ethical approval was obtained from the Medical Research and Ethics Committee (MREC) of the Ministry of Health, Malaysia (NMRR-21-1087-59121) and Universiti Kebangsaan Malaysia (JEP-2022-040). Permission to conduct a study from the site of the investigation was obtained from the Director of Tengku Ampuan Rahimah Hospital. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles. Written informed consent was obtained from all subjects who participated in the SSQ and LAEP assessment. All information about the participants will be kept strictly confidential.

RESULTS

A total of 3,856 prescriptions containing at least one ASM prescribed at the Medical Outpatient Department (MOD) were retrieved from PhIS. After preliminary screening of the prescriptions, only 2,258 prescriptions corresponding to 2,258 subjects were still actively followed up in MOD within the past two years. Subjects were further screened for eligibility as per inclusion and exclusion criteria. Throughout the data collection period, we meticulously reviewed and incorporated 397 medical records into our analysis. Among these subjects, 105 visited the MOD for specialist follow-up within the study timeframe and were eligible for face-to-face assessment using the aforementioned questionnaires.

Therapeutic outcome 1: Seizure freedom

From the information collected through medical records, 315 PWE (79.3%) had at least one seizure episode, while the remaining 20.7% had no seizure within the past year. All the relevant variables were regressed with seizure freedom, and the analysis revealed at least 10 variables had a p-value of <0.25 (Table 1). When these variables were regressed into multivariate analysis, only four variables were statistically significant ($p<0.05$) after adjusting to one another. These are the duration of epilepsy, type of seizure, medication adherence and the number of current ASMs (Table 2).

Therapeutic outcome 2: Seizure severity

From the analysis, the mean SSQ score was 1.44 (± 1.34) with a minimum score of 0 (no seizure within the past 4 weeks) and a maximum score of 5.4. Out of 62 subjects who had seizures within 4 weeks, about half (56.5%) felt that overall, the most bothersome aspect of their seizures was the ictal activity (during seizure event). The remaining 41.9% perceived that the most bothersome was the condition after the seizure event (post-ictal) and only one patient felt that the seizure part that bothered the patient most was the aura (pre-ictal) activity.

The variables that were selected for this analysis were based on the relevant demographic and intrinsic clinical characteristics, as highlighted by previous studies mentioned earlier. It was found that age, age at symptom onset and duration of epilepsy had p-values of <0.25, which would qualify these variables into multivariate analysis with other significant categorical variables such as other comorbidities (diabetes mellitus, hypertension), neurological deficit status and medication adherence. This analysis revealed only neurological deficit status has a p-value of <0.05 in the multivariate analysis. Multiple linear regression analysis was applied and the result showed only neurological deficit status and age at onset were significantly associated with seizure severity (Table 3).

Therapeutic outcome 3: Adverse effects of ASM

Out of 105 PWE assessed for adverse effects (AE) of ASM using LAEP, 75.2% (n=79) reported at least 1 symptom of AE with a minimal frequency of symptoms occurrence of three to four days in four weeks. From this study (n=105), the minimum LAEP score was 19 (no AE), whilst the maximum

Table 1: Descriptive data and univariate associations of variables with seizure control

Statistical test	Descriptive analysis		Univariate analysis	
	Seizure-free within 1 year		OR (95% CI)	p-value
Variables	Yes (n=82)	No (n=315)		
Age, years	n (%)	n (%)		
16-19	2 (2.4)	28 (8.9)	5.52(1.15-26.56)	0.033
20-59	67 (81.7)	254 (80.6)	1.49(0.75-3.00)	0.259
≥60	13 (15.9)	33 (10.5)	1	
Sex				
Male	42 (51.2)	163 (51.8)	1	
Female	40 (48.8)	152 (48.3)	0.98 (0.60-1.59)	0.932
Ethnicity				
Malay	35 (42.7)	114 (36.2)	1	
Chinese	13 (15.9)	69 (21.9)	1.63 (0.80-3.30)	0.174
Indian	34 (41.5)	127 (40.3)	1.15 (0.67-1.96)	0.616
Others	0 (0)	5 (1.6)	999 (0)	0.999
Smoking status				
Non/ex-smoker	73 (89.0)	284 (90.2)	1	
Smoker	9 (11.0)	31 (9.8)	1.13 (0.52-2.48)	0.761
Alcohol consumption				
Never	77 (93.9)	291 (92.4)	1	
Ever	5 (6.1)	24 (7.6)	1.27 (0.47-3.44)	0.638
Employment status				
Employed	31 (37.8)	94 (29.8)	1	
Student	7 (8.5)	32 (10.2)	1.51 (0.61-3.78)	0.378
Unemployed	32 (39.0)	159 (50.5)	1.64 (0.94-2.86)	0.082
Clinical Characteristics				
Seizure Type (based on ILAE)				
Unknown	15 (18.3)	9 (2.9)	1	
Generalized	50 (61.0)	218 (69.2)	7.27 (3.00-17.55)	<0.001
Focal	17 (20.7)	88 (27.9)	8.63 (3.25-22.89)	<0.001
Age at onset, years				
≥ 20	54 (65.9)	148 (47.0)	1	
10 – 19	18 (22.0)	89 (28.3)	1.80 (1.00-3.27)	0.520
0 – 9	10 (12.2)	78 (24.8)	2.85 (1.37-5.90)	0.005
Duration of epilepsy, months				
<120 months	47 (57.3)	132 (41.9)	1	
≥120 months	35 (42.7)	183 (58.1)	1.86 (1.14-3.04)	0.013
Etiology (based on ILAE)				
Unknown	50 (61.0)	190 (60.3)	1	
Structural	27 (33.0)	100 (31.8)	0.98 (0.58-1.65)	0.924
Others	5 (6.1)	25 (7.9)	1.32 (0.48-3.61)	0.594
Family history				
No	68 (82.9)	271 (86.0)	1	
Yes	6 (7.3)	16 (5.1)	0.67 (0.25-1.77)	0.419
Comorbidity				
None	24 (29.3)	124 (39.4)	1	
At least 1	58 (70.7)	191 (60.6)	0.64 (0.38-1.08)	0.094

Renal profile				
Normal	73 (89.0)	298 (94.6)	1	
At least 1 deranged	8 (9.8)	12 (3.8)	0.367 (0.15-0.93)	0.035
Liver function test				
Normal	79 (96.3)	290 (92.1)	1	
At least 1 deranged	2 (2.4)	18 (5.7)	2.45 (0.56-10.79)	0.236
Diabetes Mellitus				
No	63 (76.8)	279 (88.6)	1	
Yes	19 (23.1)	36 (11.4)	0.43 (0.23-0.80)	0.007
Hypertension				
No	63 (76.8)	270 (85.7)	1	
Yes	19 (23.2)	45 (14.3)	0.55 (0.30-1.00)	0.054
No. of ASM				
< 3	76 (92.7)	243 (77.1)	1	
≥ 3	6 (7.3)	72 (22.9)	3.75 (1.57-8.98)	0.003
Adherence				
Yes	75 (91.5)	240 (76.2)	1	
No	7 (8.5)	75 (23.8)	3.35 (1.48-7.58)	0.004

ASM – Antiseizure Medication
ILAE – International League Against Epilepsy
OR – Odds Ratio

score was 51. The mean score was 24.0 (±5.91). The most commonly reported AE among the studied PWE was drowsiness (33.3%, n=35), followed by sleep disturbances (31.4%, n=33), memory problems (27.6%, n=29), shaky hands (19.0%, n=20) and dizziness (18.1%, n=19). On the descriptive level, we observed that subjects with three or more ASMs had a higher proportion of reported adverse events (Figure 1). However, the results were not statistically significant, which may be due to the lack of a true difference in the population caused by the probable inherent variability of the sample.

Table 2: Multivariate analysis using binary logistic regression

Variable	Regression coefficient (B)	Adjusted Odds Ratio (95% CI)	Wald Statistic	P-value
Epilepsy duration				
< 10 years	0	1		
≥ 10 years	0.625	1.87 (1.10, 3.17)	5.355	0.021
Type of seizure				
Unknown	0	1		
Generalized onset	2.004	7.42 (2.95, 18.66)	18.162	<0.001
Focal onset	2.108	8.24 (2.98, 22.77)	16.507	<0.001
ASM adherence				
Yes	0	1		
No	0.40	3.55 (1.52, 8.27)	8.629	0.003
Number of ASM				
< 3	0	1		
≥ 3	1.192	3.29 (1.32, 8.24)	6.501	0.011

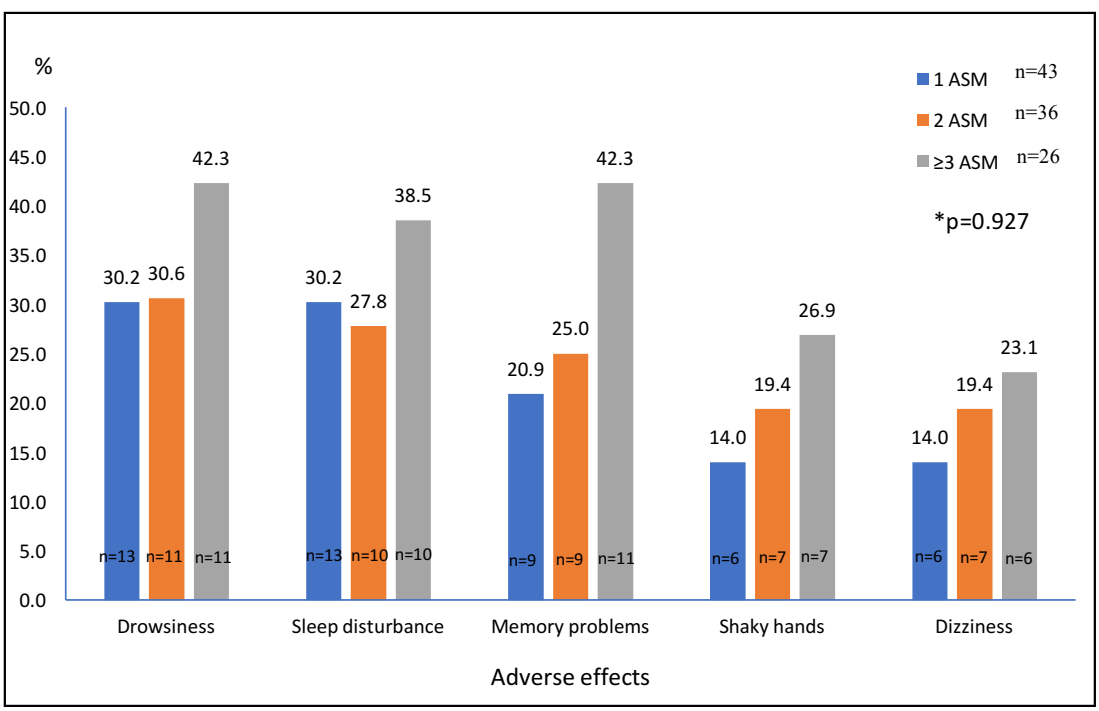
ASM – Antiseizure Medications
CI – Confidence Interval

Table 3: Result of multivariate linear regression of patients' variables and SSQ score

Variable	Regression coefficient (B)	Standard Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper bound
(Constant)	-0.457	0.700	-0.653	0.515	-1.847	0.932
Duration	0.005	0.011	0.504	0.615	-0.016	0.026
Neuro-deficit	1.659	0.668	2.485	**0.015**	0.334	2.983
Age onset	1.332	0.435	3.065	**0.003**	0.469	2.194
Generalized	0.670	0.659	1.016	0.312	-0.639	1.978
Focal onset	0.467	0.659	0.709	0.480	-0.840	1.775
Structural	-0.070	0.288	-0.241	0.810	-0.642	0.503
Psychiatric comorbid	0.196	0.358	0.547	0.585	0.196	0.907

Linear regression analysis was carried out to determine the factors associated with the LAEP score. Seven variables were identified that may potentially be associated with adverse effects. These are the patient's age, age at onset, epilepsy duration, the number of ASM prescribed, changes in ASM regimen within the past year, newer generation ASM and combination of the older plus newer generation of ASM. The type of ASM regimen variables (newer ASM, older + newer ASM) were removed to determine the best model since both of these variables were not statistically significant.

The variables included in the repeated multivariate analysis were the number of ASMs, age, duration of epilepsy (categorical) and changes in ASM regimen. All the five important assumptions in linear regression were checked. The final model in the regression analysis illustrated that advancing age, epilepsy duration of less than 13 years and changes in ASM regimen within the past year were the factors associated



ASM – Antiseizure medications *Chi-square test

Figure 1. The proportion of patients reporting adverse effect symptoms according to the number of ASM prescribed

with higher prevalence of adverse effects of ASM (Table 4).

DISCUSSION

Factors associated with seizure freedom status

Among the 397 subjects included in this study, more than two-thirds (79.3%) had poor seizure control, and the remaining 20.7% achieved seizure freedom. Several studies have investigated the factors associated with uncontrolled seizures, and more than half of these studies originated from low to lower-middle-income countries. These countries have a relatively low magnitude of seizure freedom status (25% to 56%), and this is due to social, economic and cultural issues apart from suboptimal accessibility to medication and healthcare.[35] The most commonly reported factor associated with uncontrolled seizures was non-adherence to medication, with the adjusted odds ratio (OR) value ranging from 2.04 to 11.52.[3,9,13,14,35] This is consistent with the current finding from this study where subjects who were non-adherent to ASM regimen were 3.55 times more likely to have uncontrolled seizures (95% CI: 1.52, 8.27). Not adhering to the prescribed medication and doses could cause a reduction in serum drug concentration, consequently causing the ASM to be ineffective and subsequently lead to uncontrolled seizure.[36] The reasons for non-adherence vary from one particular studied population to another and it is important to recognise and address the issues to attain the optimal benefit of ASM therapy.[19,37]

Other significant factors that contributed to uncontrolled seizures were ≥10 years of epilepsy duration. To date, there is no published evidence that proved epilepsy duration, per se, was a direct determinant of seizure freedom. However, epilepsy duration can indirectly influence seizure freedom status based on various presumptive factors that could occur as the individuals undergo age-related changes, such as changes in treatment response, neurological changes, underlying conditions and comorbidities.[38] A study done by Adal *et al*.[39] found that PWE who used ASM for two to five years and more than five years duration was almost 6 times and 4.8 times more likely to have seizure freedom as compared to PWE who took ASM for one to two years respectively. This showed that a longer duration of ASM use is associated with seizure freedom, which contradicts the findings from this current study. In another study, PWE with less than two years of ASM were observed to have a higher chance of poor seizure control (8.64, 95%CI: 3.27-22.85), and this could be related to the patient's inexperience in managing medication and the possibility of under-optimized ASM regimens.[35]

The possible explanation for the longer duration of epilepsy associated with uncontrolled seizures is non-adherence among this group. Chowdhury *et al*.[40] found that patients who had epilepsy for less < than 5 years and 5-10 years were 6.49 and 3.25 times more likely to adhere to PSM, respectively, as compared to patients with more than 10 year-epilepsy duration. This indicated that patients who were taking ASM for a longer duration were poorly adherent, and this could be due to possible factors such as clinical (comorbidities, advancing age), socio-economic issues (unemployment, lack of social support) and/or experiencing side effects for prolonged periods of time.

Generalised and focal onset seizures were both independently significant factors associated

Table 4: Result of multivariate linear regression of patients' variable and LAEP scores

Variable	Regression coefficient (B)	Standard Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
(Constant)	15.396	2.425	6.349	<0.001	10.584	20.209
No. of ASM	0.698	0.695	1.005	0.317	-0.681	2.078
Age	0.115	0.044	2.628	**0.010**	0.028	0.201
Duration <13 years	2.893	1.205	2.401	**0.018**	0.502	5.285
Changes in ASM regimen	2.932	1.355	2.164	**0.033**	0.244	5.620
Newer ASM regimen	-0.999	1.527	-.654	0.514	-4.029	2.031
Older + Newer ASM	-0.307	1.300	-.237	0.814	-2.886	2.272

with uncontrolled seizures in comparison with unknown onset seizures, as observed in this study. Seizure of unknown onset refers to individuals who had a seizure during sleep or had no witness during the episode. Inadequate information on seizure semiology, along with the absence of neuroimaging and EEG findings, render the patients such a diagnosis.[41] Therefore, unknown onset is not characteristic of the seizure itself; rather, it is a referral term for PWE who neither had a confirmed diagnosis of generalised nor focal onset type of seizure.[42] There is a lack of evidence-based reports with regard to seizure freedom in unknown onset populations. The possible explanation is that the diagnosis might only be temporary until further information and results of investigation is available. That would make it a less prioritised area to explore.

It was found that individuals with focal onset seizures had a higher likelihood of experiencing uncontrolled seizures than generalised onset seizures, with unknown onset as the reference (AOR: 8.24, 95%CI, 2.98-22.77 vs AOR: 7.42, 95%CI: 2.95-18.66). This finding is in line with results observed by Obiako *et al*.[11] where focal onset seizure has a higher rate of uncontrolled seizure (47%) in which those with generalised onset were more likely to have seizure freedom (OR:2.3, 95%CI: 2.2-3.8). From the result, it was concluded that seizure types and certain epilepsy syndromes, along with other clinical factors, were associated with treatment outcomes.[41]

In this study, the number of ASMs taken was also found to be the predictor of seizure control. The finding disclosed that subjects who were being prescribed three or more ASMs were 3.29 times more likely to have uncontrolled seizures compared to subjects with less than three ASMs (95%CI: 1.32-8.24, p=0.011). This finding can be related to a previous study by Zena *et al*.[35], where subjects with two or more ASM had a higher chance of uncontrolled seizure when compared to single ASM (AOR = 2.48, 95% CI: 1.23-5.02, p = 0.011). This finding was also supported by studies done in the UK, Saudi Arabia, and Ethiopia, which reported that taking two or more ASMs was a predictor of uncontrolled seizure.[13,43] A higher number of ASM prescribed translates not only higher pill burden but also a higher risk of adverse effects that could compromise the patient's medication adherence.[37]

Factors associated with seizure severity

There is a considerable variation with regards to age at symptoms onset among PWE. This is mainly due to multifaceted as well as complicated aetiologies that inevitably affect individuals at various points in life.[44,45] Younger age at onset is often associated with poor prognosis, both the morbidity and mortality outcomes in epilepsy.[44,46,47] In the years preceding adulthood, the human brain undergoes vast development in both structural and functional plasticity.[48] It has been explored that early disruptions in the brain's ability to organise, adapt and change its structure, which is known as neural plasticity, may result in poor seizure outcomes along with cognitive and behavioural impairments.[49] In adults where neural plasticity and synaptogenesis have decreased, seizure events may result in permanent impairment, particularly in cognitive function.[48,50] This may explain the mixed finding of the impact of different age at onset on seizure outcomes.

Park and colleagues[46] have investigated the prognostic implications of age at onset according to the relapse pattern in individuals who have already achieved seizure freedom. The study demonstrated that age 20-29 years was an independent factor predictive of poor prognosis along with failure to achieve seizure freedom within one year and more than 10 GTC seizures prior to initiation of therapy. In another study investigating epilepsy aetiologies with age at onset, the highest prevalence of post cerebrovascular accident (CVA) epilepsy was among individuals aged more than 40 years (95.6%).[29] Management of epilepsy in this population is relatively more straightforward compared to other aetiologies and, if initiated at the early onset, may lead to favourable outcomes.[46,50,51] These findings supported the revelation from the analysis where subjects who begin to have epilepsy symptoms at age 40 and younger were associated with the risk of poor seizure outcomes.

The other significant factor associated with seizure severity was neurological deficit or neurodeficit status. A possible explanation for the increased severity of neuro deficit status is the abnormality involving the central nervous system, its structure and functioning. This leads to abnormal functioning of a specific body area that is caused by insults to the brain, spinal cord, muscles or nerves that supply the impacted region.[52] The most commonly observed neurological deficit condition is among individuals with cerebral palsy. Identification of neuro deficit typically involves a comprehensive evaluation of the nervous system's functioning and should be tailored to and focused on specific disease presentation.[27]

Interestingly, there was no significant association between the patient's aetiologies and seizure outcomes. This could be due to the homogeneity of clinical characteristics of the study population, where the majority of patients (60.5%) had "Unknown" aetiology followed by "Structural" aetiology (32.0%). For "Other" aetiologies (genetic, infections, metabolic, immune origin), the observed proportion was only 7.5%. Since this study examines the overall clinical characteristics of patients, a separate study focusing on how various patient aetiologies affect ASM therapeutic outcomes would be valuable for a deeper understanding of the topic.

Factors associated with the adverse effect of ASM

Liverpool Adverse Event Profile tool in the assessment of AE of ASM has been widely utilised for its validity, availability and convenience to use.[53,54] In this study, 75.2% out of 105 subjects assessed for adverse effect occurrence reported to have at least one symptom of AE. This finding is consistent with the previous studies utilising LAEP as an AE assessment tool, with the range of 58.7 – 96% of subjects reported to have at least one AE symptom.[17,54-57]

In the multivariate analysis with the presence of other variables, namely, number of ASM, duration of epilepsy, gender and psychiatric comorbidities, the score of LAEP the score of LAEP increases by 11.5% for each increasing year of subjects' age (95% CI: 0.028-0.201, p=0.010). This could be interpreted as, as a patient gets older, he/she tends to have higher AE incidence and/or intensity. Generally, the older adult population is an important predisposing factor associated with the risk of developing adverse events from a drug.[56-58] Moreover, advanced age was found to be one of the risk factors for adverse drug events in hospitalised patients, as reported by Gomes *et al*.[59] in a systematic review. Advancing age may affect the way the body reacts with medication pharmacokinetically and pharmacodynamically due to the decline in renal and metabolic functions, impaired homeostatic mechanisms and increased sensitivity towards central nervous system active drugs.[57] Besides, interactions with medications for other comorbid conditions could also be a factor for the higher risk of developing AE in this population.[60]

The duration of ASM treatment also plays an important role as a factor for AE of ASM. A longer duration of epilepsy has been deliberately considered as a valid alternative to explain higher drug loads.[61] Thus, this variable was tested as a covariate and predictor of LAEP score together with other relevant predictors. It was found that subjects with <13 years of duration had higher LAEP scores as compared to subjects with ≥ 13 years of epilepsy duration. The possible explanation is that most of the common adverse effects, especially the ones involving the central nervous system, occur early at the beginning of treatment, then decrease over time.[62,63,64] The Type and intensity of adverse effects for each single ASM differ from one another, particularly during early treatment or the initiation phase. The concerns include pharmacodynamic reactions, which are frequently affected by the dose and rate of dose titration at the early introduction of a particular drug.[62] Over a certain period of time, individuals' physiologic adaptation to a single or combination of drugs would typically occur.[63] Researchers have evaluated AE symptoms at different points of time, and the findings demonstrated that adaptation or functional tolerance can be developed with the majority of ASM.[63,65,66]

As stated earlier, changes in ASM regimen within the last 1-year period were also factors associated with LAEP score. The term "change" includes the addition of one or more ASM into the existing regimen, transition to another ASM monotherapy (switching of 1 agent altogether), and rarely (n=2) removal of one ASM from the current ASM regimen. When switching from one ASM to another, there are a number of approaches with regard to tapering the baseline ASM. The main aim should be to cease the existing ASM to avoid increased toxicity as a result of the increased drug burden. Likewise, when adding an ASM to the existing therapy, flexible and slow adjustment and titration of the new and concomitant ASM may help improve the tolerability of the drug, with the target of achieving the lowest possible drug load.[62]

The main limitation with regard to data collection was identified. The subjects' data was obtained retrospectively from the follow-up record. This manual record contains information on patients' current and previous disease status as well as the doctor's assessment and plan for each encounter. Some variables, such as the precise date of ASM initiation, were lacking in detail. Therefore, we opted for a dependable substitute, selecting the date of epilepsy diagnosis at the centre as a reliable indicator of the overall course of epilepsy morbidity and healthcare interventions. A prospective cohort observation on the therapeutic outcomes among PWE is therefore

recommended for future research. Apart from that, the assessment of seizure severity and adverse effect profile was carried out by one researcher, which could cause researcher bias. This can be avoided by assigning trained, independent personnel to conduct the assessment for future works. Also, the sample size in this study was rather small. Therefore, to enhance statistical power and improve the generalizability of the findings, a larger sample size is recommended for future replications of the study.

The findings suggested that individuals' as well as medication-related factors can influence the therapeutic outcomes of epilepsy management with ASM therapy. A patient with a longer epilepsy history tends to have uncontrolled seizures. Conversely, a patient with an epilepsy duration shorter than 13 years had a tendency to have higher frequency and/ or intensity of adverse effects of ASM. Types of seizure, medication adherence and number of ASM prescribed were also positive predictors of uncontrolled seizure. In terms of seizure severity, age at onset and neurological deficit status were found to be significant predictors from the analysis of outcome measured using the SSQ assessment tool. Apart from that, advancing age and changes in ASM regimen within the past year had significant associations with a tendency to experience a higher burden of ASM adverse effects. Healthcare professionals should recognise the factors that could lead to adverse therapeutic outcomes and consequently undertake appropriate initiatives and approaches to ensure PWE receive optimal pharmacological management while minimising the risk of adverse drug reactions.

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REFERENCES

1. Gyllensten H, Fuller JM, Östbring MJ. Commentary: How person-centred is pharmaceutical care? *Int J Clin Pharm* 2022;44(1):270-75. doi: 10.1007/s11096-021-013320
2. Tefera G, Woldehaimanot T, Angamo M. Poor treatment outcomes and associated factors among epileptic patients at Ambo Hospital, Ethiopia. *Gaziantep Med J* 2015;21(1). doi: 10.5455/gmj-30-163442
3. Niriayo YL, Mamo A, Kassa TD, *et al*. Treatment outcome and associated factors among patients with epilepsy. *Sci Rep* 2018;8(1):17354. doi: 10.1038/s41598-018-35906-2
4. Abdullah JM, Abdullah MR, Tarakan J, Hussin Z. National response to neurological disease in Malaysia: Planning for the future. Southeast Asian. *J Trop Med Public Health* 2006;37(4):798-805
5. Trinka E, Kwan P, Lee B, Dash A. Epilepsy in Asia: Disease burden, management barriers, and challenges. *Epilepsia* 2019;60 (Suppl 1):7-21. doi: 10.1111/epi.14458
6. Todorova KS, Velikova VS, Kaprelyan AG, Tsekov ST. Seizure severity as an alternative measure of outcome in epilepsy. *J IMAB* - Annual Proceeding (Scientific Papers) 2013;19(3):433-37. doi: 10.5272/jimab.2013193.433
7. Aghaei-Lasboo A, Fisher RS. Methods for measuring seizure frequency and severity. *Neurol Clin* 2016;34(2):383-94, viii. doi: 10.1016/j.ncl.2015.11.001
8. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 2012;78(20):1548-54. doi: 10.1212/WNL.0b013e3182563b19
9. Dubale M, Gobena K, Aklog A, Ababu Y, Bose L. Treatment outcome and associated factors among adult epileptic patients at Hawassa University Specialized Hospital, Southern Ethiopia. *J Bioanal Biomed* 2018;12:7. doi: 10.37421/Jbabm.2020.12.236
10. Gidey K, Chelkeba L, Gemechu TD, Daba FB. Treatment response and predictors in patients with newly diagnosed epilepsy in Ethiopia: A retrospective cohort study. *Sci Rep* 2019;9(1):16254. doi: 10.1038/s41598-019-52574-y
11. Obiako OR, Sheikh TL, Kehinde JA, *et al*. Factors affecting epilepsy treatment outcomes in Nigeria. *Acta Neurol Scand* 2014;130(6):360-7. doi: 10.1111/ane.12275
12. Ahmed M, Nasir M, Yalew S, Getahun F, Getahun F. Assessment of treatment outcome and its associated factors among adult epileptic patients in public hospitals in the Southern Ethiopia: A Multi-center Cross-sectional Study. *Ethiop J Health Sci* 2023;33(2):327-36. doi: 10.4314/ejhs.v33i2.18
13. Nasir BB, Yifru YM, Engidawork E, Gebrewold MA, Woldu MA, Berha AB. Antiepileptic drug treatment outcomes and seizure-related injuries among adult patients with epilepsy in a tertiary care hospital in Ethiopia. *Patient Relat Outcome Meas* 2020;11:119-27. doi: 10.2147/prom.S243867
14. Zewudie A, Mamo Y, Feyissa D, Yimam M, Mekonen G, Abdela A. Epilepsy treatment outcome and its predictors among ambulatory patients with epilepsy at Mizan-Tepi University Teaching Hospital, Southwest Ethiopia. *Neurol Res Int* 2020;8109858. doi: 10.1155/2020/8109858
15. Munger Clary H, Josephson SA, Franklin G, *et*

al. Seizure frequency process and outcome quality measures: Quality improvement in Neurology. *Neurology* 2022;98(14):583-90. doi:10.1212/WNL.0000000000200239
16. Kanner AM, Bicchi MM. Antiseizure medications for adults with epilepsy: A review. *JAMA* 2022;327(13):1269-81. doi:10.1001/jama.2022.3880
17. Barnard SN, Chen Z, Kanner AM, *et al*. The adverse effects of commonly prescribed antiseizure medications in adults with newly diagnosed focal epilepsy. *Neurology* 2024;103(7):e209821. doi: 10.1212/WNL.0000000000209821
18. Ayalew MB, Muche EA. Patient reported adverse events among epileptic patients taking antiepileptic drugs. *SAGE Open Med* 2018;6. https://doi.org/ 10.1177/20503121187724712050312118772471
19. Bekele F. Non-adherence to antiepileptic drugs and associated factors among epileptic patients at ambulatory clinic of Southwestern Ethiopian Hospital: A cross-sectional study. *Patient Prefer Adherence* 2022;16:1865-73. doi: 10.2147/PPA.S377910
20. Cochran WG. Sampling techniques. 3rd ed. New York: John Wiley & Sons, 1977
21. Cramer JA, Baker GA, Jacoby A. Development of a new seizure severity questionnaire: initial reliability and validity testing. *Epilepsy Res* 2002;48(3):187-97. doi: 10.1016/s0920-1211(02)00003-7
22. Cramer JA, Baker GA, Jacoby A. Development of a new seizure severity questionnaire: initial reliability and validity testing. *Epilepsy Res* 2002;48(3):187-97. doi: 10.1016/s0920-1211(02)00003-7. [Baseline: Hak cipta JA. Cramer, 2006. Bahasa Melayu Malaysia Malaysia (Malay, Malaysia), November 6, 2006]
23. Budikayanti A, Qadri LM, Syeban Z, Indrawati LA, Octaviana F. Adverse events of antiepileptic drugs using Indonesian version of Liverpool Adverse Events Profile. *Neurol Res Int* 2018;2018:8490639. doi: 10.1155/2018/8490639
24. Fisher RS. The new classification of seizures by the International League Against Epilepsy. *Curr Neurol Neurosci Rep* 2017;17(6):48.
25. Shahrokhi M, Asuncion RMD. Neurologic exam. 2023. https://www.ncbi.nlm.nih.gov/ books/NBK557589/
26. Cheshire WP, Jr., Goldstein DS. The physical examination as a window into autonomic disorders. *Clin Auton Res* 2018;28(1):23-33. doi: 10.1007/s10286-017-0494-7
27. Fritz D, Musial MK. Neurological assessment. *Home Healthc Now* 2016;34(1):16-22. doi: 10.1097/nhh.0000000000000331
28. Beghi E. The epidemiology of epilepsy. *Neuroepidemiology* 2020;54 (2): 185-91. https://doi.org/10.1159/000503831
29. Kaur S, Garg R, Aggarwal S, Chawla SPS, Pal R. Adult onset seizures: Clinical, etiological, and radiological profile. *J Family Med Prim Care* 2018;7(1):191-7. doi:10.4103/jfmpc.jfmpc_322_16
30. Asadi-Pooya AA, Emami M, Sperling MR. Age of onset in idiopathic (genetic) generalized epilepsies: clinical and EEG findings in various age groups. *Seizure* 2012;21(6):417-21. doi: 10.1016/j.seizure.2012.04.004.
31. Kwan P, Hao XT. Update and overview of the International League Against Epilepsy consensus definition of drug-resistant epilepsy. *Eur Neurol Rev* 2011;6(1). doi: 10.17925/enr.2011.06.01.57
32. Steyerberg EW. Clinical prediction models: A practical approach to development, validation, and updating. Cham: Springer International Publishing; 2019:495-518.
33. Montgomery DC, Peck EA, Vining GG. Introduction to linear regression analysis. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2021
34. Shrestha N. Detecting multicollinearity in regression analysis. *Am J Appl Mathematics Statistics* 2020;8(2):39-42. doi: 10.12691/ajams-8-2-1.
35. Zena D, Tadesse A, Bekele N, Yaregal S, Sualih N, Worku E. Seizure control and its associated factors among epileptic patients at Neurology Clinic, University of Gondar hospital, Northwest Ethiopia. *SAGE Open Med* 2022;10:1-11. doi: DOI: 10.1177/20503121221100612
36. Johannessen Landmark C, Johannessen SI, Patsalos PN. Therapeutic drug monitoring of antiepileptic drugs: Current status and future prospects. *Expert Opin Drug Metab Toxicol* 2020;16(3):227-38. doi: 10.1080/17425255.2020.1724956.
37. Terman SW, Kerr WT, Marcum ZA, Wang L, Burke JF. Antiseizure medication adherence trajectories in Medicare beneficiaries with newly treated epilepsy. *Epilepsia* 2021; 62(11):2778-2789. doi: 10.1111/epi.17051
38. Piccenna L, O'Dwyer R, Leppik I, et al. Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the elderly. *Epilepsia* 2023;64(3):567-85. doi: https://doi.org/10.1111/epi.17426
39. Adal HD, Alemu K, Muche EA. Seizure control status and associated factors among pediatric epileptic patients at a neurologic outpatient clinic in Ethiopia. *PLoS One* 2021;16(11):e0259079. doi: 10.1371/journal.pone.0259079
40. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. *Fam Med Community Health* 2020;8(1):e000262 doi: 10.1136/fmch-2019-000262
41. Sarmast ST, Abdullahi AM, Jahan N. Current classification of seizures and epilepsies: Scope, limitations and recommendations for future action. *Cureus* 2020;12(9):e10549. doi: 10.7759/cureus.10549
42. Dhinakaran R, Mishra D. ILAE Classification of seizures and epilepsies: An update for the Pediatrician. *Indian Pediatrics* 2019;56(1):60-2. doi: 10.1007/s13312-019-1469-7
43. Hamdy NA, Alamgir MJ, Mohammad el GE, Khedr MH, Fazili S. Profile of epilepsy in a regional hospital in Al Qassim, Saudi Arabia. *Int J Health Sci* (Qassim) 2014;8(3):247-55. doi: 10.12816/0023977.
44. Riney K, Bogacz A, Somerville E, *et al*. International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task

Force on Nosology and Definitions. *Epilepsia* 2022;63(6):1443-74. doi: 10.1111/epi.17240.
45. Doerrfuss JI, Kowski AB, Holtkamp M. Etiology-specific response to antiseizure medication in focal epilepsy. *Epilepsia* 2021;62(9):2133-41. doi: 10.1111/epi.17017.
46. Park S, Lee M. Prognostic implications of epilepsy onset age according to relapse pattern in patients with four-year remission. *Diagnostics* (Basel) 2020;10(12). doi: 10.3390/diagnostics10121089.
47. Berg AT, Zelko FA, Levy SR, Testa FM. Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes: a prospective cohort study. *Neurology* 2012;79(13):1384-91. doi: 10.1212/WNL.0b013e31826c1b55.
48. Jarero-Basulto JJ, Gasca-Martínez Y, Rivera-Cervantes MC, Ureña-Guerrero ME, Feria-Velasco AI, Beas-Zarate C. Interactions between epilepsy and plasticity. *Pharmaceuticals* (Basel) 2018;11(1). doi: 10.3390/ph11010017
49. Doucet GE, Sharan A, Pustina D, Skidmore C, Sperling MR, Tracy JI. Early and late age of seizure onset have a differential impact on brain resting-state organization in temporal lobe epilepsy. *Brain Topography* 2015;28(1):113-26. doi: 10.1007/s10548-014-0366-6
50. Xu MY. Poststroke seizure: optimising its management. *Stroke Vasc Neurol* 2019;4(1):48-56. doi: 10.1136/svn-2018-000175
51. Fu Y, Feng L, Xiao B. Current advances on mechanisms and treatment of post-stroke seizures. *Acta Epileptologica* 2021;3(1):14. doi: 10.1186/s42494-021-00047-z.
52. Wasay M, Awan S, Shahbaz N, *et al*. Neurological disorders and disability in Pakistan: A cross-sectional multicenter study. *J Neurol Sci* 2023;452:120754. doi: 10.1016/j.jns.2023.120754.
53. Dang YL, Foster E, Lloyd M, *et al*. Adverse events related to antiepileptic drugs. *Epilepsy Behav* 2021;115:107657. doi: 10.1016/j.yebeh.2020.107657
54. Willems LM, van der Goten M, von Podewils F, *et al*. Adverse event profiles of antiseizure medications and the impact of coadministration on drug tolerability in adults with epilepsy. *CNS Drugs* 2023;37(6):531-44. doi: 10.1007/s40263-023-01013-8
55. Chen HF, Tsai YF, Shih MS, Chen JC. Validation of the Chinese version of the Liverpool Adverse Events Profile in patients with epilepsy. *Epilepsy Res* 2011;94(1-2):45-52. doi: 10.1016/j.eplepsyres.2011.01.008
56. Alom Zazzara, M.B., Palmer, K., Vetrano, D.L. *et al*. Adverse drug reactions in older adults: a narrative review of the literature. *Eur Geriatr Med* 2021; 12:463-73. https://doi.org/10.1007/s41999-021-00481-9
57. Yadesa TM, Kitutu FE, Deyno S, Ogwang PE, Tamukong R, Alele PE. Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: A systematic review and meta-analysis. *SAGE Open Med* 2021;9. doi:10.1177/20503121211039099
58. Cahir C, Curran C, Walsh C, *et al*. Adverse drug reactions in an ageing PopulaTion (ADAPT) study: Prevalence and risk factors associated with adverse drug reaction-related hospital admissions in older patients. *Front Pharmacol* 2023;13:1029067. doi: 10.3389/fphar.2022.1029067
59. Gomes IV, Muniz CR, Vieira RS, Reis RL, Carmo RF, Silva DT. Risk factors for adverse drug events in hospitalized patients: an overview of systematic reviews. *Rev Bras Farm Hosp Serv Saúde* 2022;13(1):738 doi: 10.30968/rbfhss.2002.131 .0738
60. Woo, SD., Yoon, J., Doo, GE. *et al*. Common causes and characteristics of adverse drug reactions in older adults: a retrospective study. *BMC Pharmacol Toxicol* 2020;21:87. https://doi.org/10.1186/s40360-020-00464-9
61. Witt J-A, Nass RD, Baumgartner T, *et al*. Does the accumulated antiepileptic drug load in chronic epilepsy reflect disease severity? *Epilepsia* 2020;61(12):2685-95. doi: https://doi.org/10.1111/epi.16720
62. Seiden LG, Connor GS. The importance of drug titration in the management of patients with epilepsy. *Epilepsy Behav* 2022;128:108517. doi: https://doi.org/10.1016/j.yebeh. 2021.108517
63. Meador KJ, Laloyaux C, Elmoufti S, *et al*. Time course of drug-related treatment-emergent adverse side effects of brivaracetam. *Epilepsy Behav* 2020;111:107212. https://doi.org/10.1016/j.yebeh.2020.107212
64. Klein P, Krauss GL, Aboumatar S, Kamin M. Long-term efficacy and safety of adjunctive cenobamate in patients with uncontrolled focal seizures: open-label extension of a randomized clinical study [poster]. American Epilepsy Society Annual Meeting, December 6–10, 2019, Baltimore, MD.
65. Loscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: From bromide salts to cenobamate and beyond. *CNS Drugs* 2021;35(9):935-63. doi: 10.1007/s40263-021-00827-8.
66. Löscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. *Epilepsia* 2006;47(8):1253-84. doi: 10.1111/j.1528-1167.2006.00607.