ADVERSE DRUG REACTION IN PEOPLE WITH EPILPSY

Luqman Ogunjimi[1], Akinyinka Alabi[1], Aderonke Aderinola[1], Mojisola Bello[1], Yusuf Oladunjoye[1], Adeola Kasali[1], Emmanuel Kasumu[1], Ibironke Oyenuga[1], Akinbodu Shittabey[1], Modupeoluwa Onipede[1], Oludolapo Dele[1], and Bamidele Osalusi[1]

[1]Olabisi Onabanjo University Obafemi Awolowo College of Health Sciences

June 3, 2023

Abstract

OBJECTIVES: There is a need for early identification and intervention of Adverse Drug Reaction (ADR) to alleviate unacceptably growing burden, morbidity and mortality associated in People With Epilepsy (PWE). This study is aimed at identifying factors associated with ADR and medication adherence among patients in PWE. METHODS: It is a cross-sectional questionnaire-based study consisting of 940 consenting participants aged 16 years and above attending epilepsy clinics for period of 5years with diagnosis confirmed by International League against Epilepsy (ILAE) criteria and supported by Electroencephalography (EEG). 21-item Liverpool Adverse Effect Profile (LEAP) and 8-item. Morinsky Medication Adherence Scale (MMAS) were used to assess ADR and adherence respectively. RESULTS: The highest reported ADR in PWE were nervousness (34.3%), aggression (33.6%) and weight gain (32.3%). Specifically, (20.1%) of the participant complained of memory problem, while the lowest were hair loss (7.2%), trouble with mouth (8.9%) and problem with skin (9.3%). Using the MMAS, 545(90.2%), 28(4.6%) and 31(5.1%) of PWE in this study were classified as having high, medium, and low adherence, respectively. Duration of AEDs use and duration of epilepsy were the major determinant of ADR in PWE on regression model. CONCLUSION: Duration of AEDs use and duration of epilepsy are the major determinant of ADR in PWE. Effective strategies to identify and reduce ADR should be incorporated to management of PWE by Health Care Providers to improve their quality of life. Furthermore, physician should aim towards reducing the duration of AED use and the epilepsy.

ADVERSE DRUG REACTION IN PEOPLE WITH EPILPSY

Ogunjimi Luqman[1], Alabi Akinyinka[1], Aderinola Aderonke[1], Olusola-Bello Mojisola[3], Oladunjoye Yususf[1], Kasali Adeola[1], Kasumu Emmanuel[1], Oyenuga Ibironke[1], Akinbodu Shittabey[4], Onipede Modupeoluwa[1], Dele Oludolapo[1], Osalusi Bamidele[2].

1. Department of Pharmacology and Therapeutics, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu Ogun state, Nigeria.

2. Department of Medicine, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu Ogun state, Nigeria.

3. Radiology Department, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu Ogun state, Nigeria.

4. Department of Physiology, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu Ogun state, Nigeria.

Corresponding Author: Ogunjimi Luqman Opeoluwa. **Msc (Ib), MBChB (Ogun), FWACP (Neuro) FMCP (Neuro)**

Department of Pharmacology and Therapeutics, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu, Ogun State.

email: luqmanogunjimi@yahoo.com Telephone: +234-703-268-3222

ORCID iD. https://orcid.org/0000-0001-9185-9774.

Declarations

Ethical approval: This was obtained from joint review board of Olabisi Onabanjo University Teaching Hospital with assigned number of OOUTH/HREC/294/2019AP.

Consent to participate: Participants for this study were fully informed on the research protocol detailing the purpose, method, risks, and benefits of the research. Each of the participant then voluntarily gave a written and well understood informed consent. The consent was translated to the local language for those who did not understand English language and the services of interpreters were employed. Participants were free to decline participation or withdraw from the study at any time without reprisal or loss of benefit. There were sections for the person giving the consent, person obtaining the consent and witnesses in the informed consent.

Consent for publication : All the authors gave consent for publication of this manuscript. The corresponding author shall be Dr Ogunjimi Luqman of the department of Pharmacology and Therapeutics, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Ogun state, Nigeria.

Material and data availability statement : The data will be made available upon reasonable request, the principal investigator, will make the data available.

Conflict of interest: We declare that there are no conflict of interest

Source of funding: None

Author's contribution: Luqman, Yusuf and Oludolapo conceived the idea of the study. Ibironke, and Adeola were involved with statistical analysis. EEG interpretation was done by Luqman and Bamidele. Luqman, Akinyinka, Shittabey, Bamidele, Ibironke, Aderonke, Modupeoluwa and Adeola were involved in the study design, interpretation and also made significant intellectual contribution to the manuscript development. Mojisola and Luqman performed neuroimaging, recruited patients, and made significant intellectual contributions to the development of manuscripts. Luqman, Oludolapo, Aderonke, Emmanuel and Akinyinka provided the laboratory expertise and also contributed significantly in the manuscript development.

ABSTRACT

OBJECTIVES: There is a need for early identification and intervention of Adverse Drug Reaction (ADR) to alleviate unacceptably growing burden, morbidity and mortality associated in People With Epilepsy (PWE). This study is aimed at identifying factors associated with ADR and medication adherence among patients in PWE.

METHODS: It is a cross-sectional questionnaire-based study consisting of 940 consenting participants aged 16 years and above attending epilepsy clinics for period of 5years with diagnosis confirmed by International League against Epilepsy (ILAE) criteria and supported by Electroencephalography (EEG). 21-item Liverpool Adverse Effect Profile (LEAP) and 8-item. Morinsky Medication Adherence Scale (MMAS) were used to assess ADR and adherence respectively.

RESULTS: The highest reported ADR in PWE were nervousness (34.3%), aggression (33.6%) and weight gain (32.3%). Specifically, (20.1%) of the participant complained of memory problem, while the lowest were hair loss (7.2%), trouble with mouth (8.9%) and problem with skin (9.3%). Using the MMAS, 545(90.2%), 28(4.6%) and 31(5.1%) of PWE in this study were classified as having high, medium, and low adherence, respectively. Duration of AEDs use and duration of epilepsy were the major determinant of ADR in PWE on regression model.

CONCLUSION: Duration of AEDs use and duration of epilepsy are the major determinant of ADR in PWE. Effective strategies to identify and reduce ADR should be incorporated to management of PWE by

Health Care Providers to improve their quality of life. Furthermore, physician should aim towards reducing the duration of AED use and the epilepsy.

1.0 INTRODUCTION

Epilepsy is a major public health with serious physical, social and psychological consequences that relies heavily on antiepileptic drugs (AEDs), adherence to medication to achieve to seizure remission and improve quality of life while avoiding unwanted side-effects.(Abou-Khalil, 2016; Fadare et al., 2018; George et al., 2015; Lyseng-Williamson, 2011; Olusanya et al., 2017)In a systematic review among developing countries to determine magnitude, causes, and possible intervention strategies, the overall estimated Treatment Gap (TG) was 56/100. (Nwani et al., 2013) Inadequate skilled manpower, cost of treatment, cultural beliefs, unavailability of AEDs were some of the identified reason for the relatively high TG.(Nwani et al., 2013)Furthermore, Adverse Drug Reaction(ADR) contributes significantly to the TG and negatively impact on outcome, and quality of care, social and economic burden in People With Epilepsy (PWE).(Adedapo et al., 2021; Coleman & Pontefract, 2016; Habib et al., 2013)In a recent cohort study among adults admitted to medical wards in southwestern Nigeria, aimed at determining prevalence, incidence, risk factors and fatality of ADR, anticonvulsant therapy accounted for 2.9% with Carbamazepine (CAP) and phenytoin being the major culprit.(Adedapo et al., 2021)Cognitive dysfunction, somnolence, irritability, behavioral issues, drowsiness, gingival hyperplasia, depression, gastrointestinal disturbance, and fatigue are some of the common ADR in PWE.(Du et al., 2019; Fadare et al., 2018; Kaushik et al., 2019; Silvennoinen et al., 2019)ADR has been established as a key factor of non-adherence, poor treatment outcome, poor seizure control and increased hospitalizations and poor quality of Life.(Adedapo et al., 2021; Yang et al., 2014)Gender, sex, genetic influence, background chronic illness, polytherapy, inappropriate dose, idiosyncratic reactions, seizure type, duration of use and type of AEDs, idiosyncratic and dose dependent reaction are factors associated with ADR (Abou-Khalil, 2016; Du et al., 2019; Meador et al., 2009; St. Louis, 2009). Liverpool Adverse Effect Profile (LAEP) is a reliable instrument which has been tested as a good measure of ADR in PWE on AEDs across the globe and has been correlated with medication adherence, depression status and suicidal tendency, cognitive dysfunction, and level of education.(Du et al., 2019; Fadare et al., 2018; Lee et al., 2014; Olusanya et al., 2017; Yang et al., 2014) Morinsky Medication Adherence Scale (MMAS) is an 8-item scale which has been previously validated and extensively used severally in conditions like diabetes mellitus, psychiatric disorders and hypertension among Nigeria cohorts with description of good internal consistency and reliability. There is an increasing need to develop appropriate strategy for effective early identification and intervention to alleviate unacceptably growing burden, morbidity and mortality associated with ADR in PWE. This study is aimed at identifying factors associated with ADR and medication adherence among patients in PWE.

METHOD

A multicenter observational and descriptive study carried out in southwestern part of Nigeria among adults PWE after due ethical clearance has been obtained. The estimation of sample size was done by using the single population proportional formulation by taking 5% margin of error, 95% confidence level and proportion of reported adverse events as 0.5%. Using convenient sampling method, we included 940 consenting participants aged 16 years and above attending epilepsy clinics for period of 5years with diagnosis confirmed by International League against Epilepsy(ILAE) criteria and supported by Electroencephalography(EEG).(Brodie et al., 2018; Fisher, 2017; Hirsch et al., 2013; Scheffer et al., 2017) The case records of all patients attending/that attended neurology clinics in the last 5 years with diagnosis of epilepsy in the selected hospitals was reviewed with the use of a semi structured questionnaire, to extract information about clinical and socio demographic characteristics. These include age, age of onset, seizure characteristics, type, and duration of AEDs.

LEAP, a previously validated instrument was used to assess ADR. It is a 21- item self-reported questionnaire, designed to measure AEDs side effect which covers both Central Nervous System (CNS) and Non-CNS related adverse effects. The total score of LAEP ranges from 19 to 76, with higher score indicating more adverse effects burden. Scores [?]45 indicates mild to moderate adverse effects and reaches the toxic level if the total

score exceeds 45.(Fadare et al., 2018). (Fadare et al., 2018; Sakuma et al., 2014; Yang et al., 2014). MMAS a previously validated and extensively used adherence instrument was used to measure medication adherence. There are five expected responses in MMAS namely; never, rarely, sometimes, often and always respectively which are scored as 0, 1, 2, 3, 4 respectively and subsequently subdivided into 0 (high adherence), 1-2 (medium adherence) and >2 (poor adherence). These instruments were administered by Neurologist and trainees who are qualified Doctors at participating Centers. Data were cleaned, coded, and analyzed using the IBM Statistical Package of Social Sciences Version 23. Socio-demographic and clinical characteristics of patients were presented as frequency (percentage). Using Pearson chi square test. Independent T-test was used to examine the possible association between ADR with gender, AED therapy (monotherapy and polytherapy) and medication adherence. One-way ANOVA test was used to assess the association between type of seizure, duration of epilepsy and epileptiform pattern. The significance level of statistical measures was set at $p<0.05$.

3.0 RESULT

3.1. Relationship between socio-demographic level/ clinical profiles and adherence level in PWE

The mean age (SD) among the participant was 39.19(18.80). The mean (SD) of the female among participant was 38.07(18.35) compare to the mean (SD) value of 40.44(19.24) among male participant. The total number of male participants was 445(47.3%) while that of female participant was 495(52.7%). The number of participants that were never married, currently married, separated, widow/widower, cohabiting, divorce respectively was 383(40.7%), 539(57.3%), 2(0.2%), 11(1.2%), 2(0.2%), 3(0.3%) respectively. The number of participants that had none, primary, secondary, tertiary, postgraduate level of formal education respectively was 45(4.8%), 37(3.9%), 350(37.2%), 414(44.0%), 94(10.0%) respectively. The level of adherence (high, medium, low) in PWE were comparable with regards to gender, age, marital status, formal education, seizure remission, and seizure type. Using the MMAS, 545(90.2%), 28(4.6%) and 31(5.1%) of PWE in this study were classified as having high, medium, and low adherence, respectively. (see Table 1)

4.2: Comparison between the mean LAEP scores and social demographic/clinical profiles

There was significant association between drug adherence, duration, duration of AEDs, and epileptiform pattern with mean LEAP score of 45.25(9.36), 44.24(10.40), 40.98(9.30) respectively ranging from high adherence to low adherence respectively, 41.43(9.74), 41.05(9.70), 42.84(10.12), 46.10(9.98), 46.98(10.40) respectively in the duration of <1 Month, 1-5 months, 6 months -1year, 2-5year, >5 years respectively, 41.33(9.49), 47.21(10.59) respectively ranging from <2Years, >2Years respectively, 43.54(9.92), 41.51(10.52), 46.08(9.25), 42.47(10.10) respectively, for generalized, focal, focal to secondary generalized, none respectively. (see Table 2)

4.3: Frequency and prescription pattern of AEDs among participants

The frequency of participants on medication were 604(64.2%) with those on monotherapy and polytherapy respectively been 498(52.9%) and 106(11.2%) respectively. The frequency of participants that were on CAP, LVC, Gabapentin, Valproate, Phenytoin, Clonazepam, Phenobarbiturate, CAP+LVC respectively were 414(68.5%), 56(9.2%), 1(0.1%), 11(1.8%), 11(1.8%), 1(0.1%), 4(0.6%), 55(9.1%) respectively. The mean (SD) of the participant on medication, monotherapy, polytherapy, CAP, LVC, Gabapentin, Valproate, Phenytoin, Clonazepam, Phenobarbiturate, CAP+LVC respectively were 44.43(10.48), 44.08(10.65), 46.10(9.52), 44.26(10.59), 44.63(10.58), 65, 37.91(13.40), 38.91(9.44), 36, 45.50(3.00), 47.44(8.61) respectively. (See Table 3)

4.4 Frequency of reported adverse effects of PWE.

The highest reported ADR in PWE were nervousness (34.3%), aggression (33.6%) and weight gain (32.3%). Specifically, (20.1%) of the participant complained of memory problem, while the lowest were hair loss (7.2%), trouble with mouth or gum (8.9%) and problem with skin (9.3%). (see Table 4)

4.5 Determinant of ADR in PWE

There was significant association between medication adherences (p0.000), duration of epilepsy (p0.000), duration of AED (p0.000), epileptiform pattern (p0.019) with mean LEAP score. (See Table 3) However on regression model, only duration of AEDs used and duration of epilepsy, were the major determinant of ADR in PWE. (see Table 5)

4.0 DISCUSSION

We reported a significant association between medication adherence, duration of epilepsy, duration of AED use, Epileptiform pattern with mean LAEP score. Furthermore, the mean LAEP from this study was higher compared to values previous studies. The mean age of our participant is 39.19±8.80, with higher values in male compared to female participants. The female preponderance among participants was like findings from previous studies among PWE. Furthermore, the mean (SD) between ages 13-20, 21-35, 36-50, >50 respectively is 175(18.6), 298(31.7), 201±21.4, and 266(28.3), respectively. Paul et al found that the prevalence of active epilepsy was very similar for 0-39 age group but higher among women in the age group of 40-50 years. When the prevalence trend of lifetime epilepsy was analyzed by sex, the peak in the 20-39 age group is higher for men, but the second peak in the 50-59 age group is seen only in women.(Paul et al., 2012)The mean LAEP score among cohorts from this study is higher than reported values from previous studies conducted in Nigeria, Italy, and India.(Du et al., 2019; Fadare et al., 2018; Lee et al., 2014) This difference might be due to pharmacogenomics, drug interaction, inter and intra racial disparity, under reporting of ADR, varied doses of AEDs, different number of participants and duration of treatment but more importantly different methodological approach. For instance, Fadare and his colleagues in a Nigeria study aimed at determining medication adherence and adverse effect profile of AEDs among Nigerian cohorts, reported a lower mean LAEP score with highest value of those on phenobarbital.(Fadare et al., 2018)This finding which is similar to that of this study, is not unexpected as Phenobarbitone has been associated with several significant adverse effect profile ranging cognitive dysfunction, enzyme inductions, drowsiness, headache, dizziness and psychomotor disturbance.(Abou-Khalil, 2016; Goodman et al., 2015; Roy et al., 2016)In a study to access the extent of ADR of CBZ and its potential associated factors, memory, headache, restlessness, tiredness and depression were most frequently reported ADR and identified female gender, lower level of formal education has factors associated with ADR.(Olusanya et al., 2017) Nasopharyngitis, agitation, hyperkinetic muscle activity, outburst of anger, agitation has been associated with ADR of LVC.(Bates et al., 1995; Belcastro et al., 2008; Joshi et al., 2017)In a review recently published by Cochrane evaluated the effectiveness of LVC, six most common ADR in a decreasing order: somnolence, headache, asthenia, accidental injury, dizziness and infection were reported. Only somnolence and infection were significantly associated with LVC.(Kaushik et al., 2019) Routine evaluation for known ADR that is specific for AEDs should be incorporated to management of PWE by physician and Health Care Providers (HCP) to improve their quality of life. In previous studies, age, gender, multiple drugs, disease state, allergy, genetic factors, and large doses of drugs were identified as determinants of ADR in PWE. In this study, adherence, duration of epilepsy, duration AEDs use, presence of Epileptiform pattern, drug adherence and duration of seizures were identified as significant factors associated with high mean LEAP which increase the possibility of the occurrence of high ADRs in PWE. In-tandem with previous studies,(Du et al., 2019; Fadare et al., 2018; Kaushik et al., 2019)the present study reported higher mean LAEP score for patients on polytherapy compared to those on monotherapy, though not statistically significant. This is not unexpected as polypharmacy or use of more than one medication for epilepsy has been linked to increase ADR.(Adedapo et al., 2021; St. Louis, 2009)This is the reason why PWE, therapy should be started with a single AEDs and then titrate as appropriate after due consideration of other factors that govern choice of AEDs. Combination therapy should be considered only when monotherapy fails.(Assadeck et al., 2019; Joshi et al., 2017; Stephen & Brodie, 2012)It is recommended that AED can be gradually withdrawn after 2 years of seizure freedom, and this must be carried out under the guidance of a physician.(Assadeck et al., 2019; Brodie & Sills, 2011; St. Louis, 2009)

Using the MMAS-8, 4(0.43%), 571(61.7%), and 351(37.9%) respectively, of the participants were identified as highly adherent, medium adherent and no adherent to AEDs, respectively. This shows that, majority

of PWE in this study had reduced number of highly adherence patients compared to findings in previous studies.(Du et al., 2019)This underscores the importance of compliance for better seizure controls and extent of TG. The use of alternatives to medicine such as healing homes, herbalists, and other spiritual mission houses, have been ascribed for low adherence in previous studies which account for the high rate of treatment gap in observed low- and middle-income countries.(Assadeck et al., 2019; Nwani et al., 2013; Owolabi et al., 2020) There is a dramatic global disparity in the care for epilepsy between high- and low-income countries, and between rural and urban settings. The reported size of the epilepsy treatment gap in Sub Sahara African varies widely, ranging from 23% in Senegal to 100% in Uganda, Tanzania, Gambia, and Togo.(Adeloye, 2014; Ding et al., 2021; Owolabi et al., 2020) A similar study in eastern Nigeria, reported overall treatment gap of 76%, diagnosed gap in 38% (n=11/29) and those who were diagnosed but discontinued AED treatment of their own volition accounting for a therapeutic gap of 38% (n=11/29).(Nwani et al., 2013) An online survey among 408 adults with epilepsy and 175 neurologists who treat epilepsy revealed that 29% of patients self-reported non-adherent to medications in a one-month period. Surprisingly from this study, there was no significant association between medication adherence and age, gender, marital status, level of education, seizure remission, seizures, and type of seizure in this study. However, there was a significant association between adherence and mean LAEP score. Nervousness, aggression, and memory problems were the most common ADRs previously reported in PWE. This finding is similar to findings from this study which revealed nervousness, aggression, weight gain, unsteadiness, restlessness and tiredness are the most common ADR. Furthermore, we reported that Carbamazepine (68%) was the most frequently prescribed monotherapy AEDs used, followed by Levetiracetam (9%) in this study, like other published studies in India and Nigeria.

CONCLUSION

We reported a significant association between medication adherence, duration of epilepsy, duration of AED use, Epileptiform pattern with mean LAEP score. Furthermore, the mean LAEP from this study was higher compared to values from previous studies. Duration of epilepsy and AEDs usage are the major determinant of adverse drug reaction in PWE. Routine evaluation for known ADR that is specific for AEDs should be incorporated to management of PWE by physician and Health Care Providers (HCP) to improve their quality of life. Overall goal of seizure management should be aimed at achieving early seizure control and remission with the aim of attaining a seizure free stage period of more than 3-5years so that AEDs might not be needed.

REFERENCES

1. A Yassine, I., M Eldeeb, W., A Gad, K., A Ashour, Y., A Yassine, I., & O Hosny, A. (2018). Cognitive functions, electroencephalographic and diffusion tensor imaging changes in children with active idiopathic epilepsy. *Epilepsy & Behavior: E&B* , *84* , 135–141. https://doi.org/10.1016/j.yebeh.2018.04.024
2. Abou-Khalil, B. W. (2016). Antiepileptic Drugs. *Continuum (Minneapolis, Minn.)* , *22* (1 Epilepsy), 132–156. https://doi.org/10.1212/CON.0000000000000289
3. Adedapo, A. D. A., Adedeji, W. A., Adedapo, I. A., & Adedapo, K. S. (2021). Cohort study on adverse drug reactions in adults admitted to the medical wards of a tertiary hospital in Nigeria: Prevalence, incidence, risk factors and fatality. *British Journal of Clinical Pharmacology* , *87* (4), 1878–1889. https://doi.org/10.1111/bcp.14577
4. Adeloye, D. (2014). An estimate of the incidence and prevalence of stroke in Africa: A systematic review and meta-analysis. *PloS One* , *9* (6), e100724. https://doi.org/10.1371/journal.pone.0100724
5. Assadeck, H., Toudou Daouda, M., Moussa Konate, M., Mamadou, Z., Hassane Djibo, F., Douma Maiga, D., & Sanoussi, S. (2019). Clinical and etiological characteristics of epilepsy in people from Niger: A hospital-based study from a tertiary care referral center of Niamey, Niger. *Epilepsia Open* , *4* (2), 318–327. https://doi.org/10.1002/epi4.12325
6. Bates, D. W., Cullen, D. J., Laird, N., Petersen, L. A., Small, S. D., Servi, D., Laffel, G., Sweitzer, B. J., Shea, B. F., & Hallisey, R. (1995). Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group.*JAMA* , *274* (1), 29–34.
7. Belcastro, V., Costa, C., Galletti, F., Autuori, A., Pierguidi, L., Pisani, F., Calabresi, P., & Parnetti, L.

(2008). Levetiracetam in newly diagnosed late-onset post-stroke seizures: A prospective observational study. *Epilepsy Research* , *82* (2–3), 223–226. https://doi.org/10.1016/j.eplepsyres.2008.08.008

8. Brodie, M. J., & Sills, G. J. (2011). Combining antiepileptic drugs—Rational polytherapy? *Seizure* , *20* (5), 369–375. https://doi.org/10.1016/j.seizure.2011.01.004
9. Brodie, M. J., Zuberi, S. M., Scheffer, I. E., & Fisher, R. S. (2018). The 2017 ILAE classification of seizure types and the epilepsies: What do people with epilepsy and their caregivers need to know? *Epileptic Disorders: International Epilepsy Journal with Videotape* , *20* (2), 77–87. https://doi.org/10.1684/epd.2018.0957
10. Coleman, J. J., & Pontefract, S. K. (2016). Adverse drug reactions. *Clinical Medicine* , *16* (5), 481–485. https://doi.org/10.7861/clinmedicine.16-5-481
11. Ding, D., Zhou, D., Sander, J. W., Wang, W., Li, S., & Hong, Z. (2021). Epilepsy in China: Major progress in the past two decades. *The Lancet. Neurology* , *20* (4), 316–326. https://doi.org/10.1016/S1474-4422(21)00023-5
12. Du, Y., Lin, J., Shen, J., Ding, S., Ye, M., Wang, L., Wang, Y., Wang, X., Xia, N., Zheng, R., Chen, H., & Xu, H. (2019). Adverse drug reactions associated with six commonly used antiepileptic drugs in southern China from 2003 to 2015. *BMC Pharmacology and Toxicology* , *20* (1), 7. https://doi.org/10.1186/s40360-019-0285-y
13. Fadare, J. O., Sunmonu, T. A., Bankole, I. A., Adekeye, K. A., & Abubakar, S. A. (2018). Medication adherence and adverse effect profile of antiepileptic drugs in Nigerian patients with epilepsy.*Neurodegenerative Disease Management* , *8* (1), 25–36. https://doi.org/10.2217/nmt-2017-0044
14. Fisher, R. S. (2017). An overview of the 2017 ILAE operational classification of seizure types. *Epilepsy & Behavior: E&B* ,*70* (Pt A), 271–273. https://doi.org/10.1016/j.yebeh.2017.03.022
15. George, J., Kulkarni, C., & Sarma, G. R. K. (2015). Antiepileptic Drugs and Quality of Life in Patients with Epilepsy: A Tertiary Care Hospital-Based Study. *Value in Health Regional Issues* ,*6* , 1–6. https://doi.org/10.1016/j.vhri.2014.07.009
16. Goodman, N. F., Cobin, R. H., Futterweit, W., Glueck, J. S., Legro, R. S., Carmina, E., American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), & Androgen Excess and PCOS Society. (2015). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ANDROGEN EXCESS AND PCOS SOCIETY DISEASE STATE CLINICAL REVIEW: GUIDE TO THE BEST PRACTICES IN THE EVALUATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME - PART 2. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* , *21* (12), 1415–1426. https://doi.org/10.4158/EP15748.DSCPT2
17. Habib, M., Khan, S. U., Hoque, M. A., Mondal, M. B. A., Hasan, A. H., Chowdhury, R. N., Haque, B., Rahman, K. M., Chowdhury, A. H., Ghose, S. K., & Mohammad, Q. D. (2013). Antiepileptic drug utilization in Bangladesh: Experience from Dhaka Medical College Hospital. *BMC Research Notes* , *6* , 473. https://doi.org/10.1186/1756-0500-6-473
18. Hirsch, L. J., LaRoche, S. M., Gaspard, N., Gerard, E., Svoronos, A., Herman, S. T., Mani, R., Arif, H., Jette, N., Minazad, Y., Kerrigan, J. F., Vespa, P., Hantus, S., Claassen, J., Young, G. B., So, E., Kaplan, P. W., Nuwer, M. R., Fountain, N. B., & Drislane, F. W. (2013). American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society* , *30* (1), 1–27. https://doi.org/10.1097/WNP.0b013e3182784729
19. Joshi, R., Tripathi, M., Gupta, P., Gulati, S., & Gupta, Y. K. (2017). Adverse effects & drug load of antiepileptic drugs in patients with epilepsy: Monotherapy versus polytherapy. *The Indian Journal of Medical Research* , *145* (3), 317–326. https://doi.org/10.4103/ijmr.IJMR_710_15
20. Kaushik, S., Chopra, D., Sharma, S., & Aneja, S. (2019). Adverse Drug Reactions of Anti-Epileptic Drugs in Children with Epilepsy: A Cross-Sectional Study. *Current Drug Safety* , *14* (3), 217–224. https://doi.org/10.2174/1574886314666190311112710
21. Lee, S.-J., Kim, J.-E., Seo, J.-G., Cho, Y. W., Lee, J.-J., Moon, H.-J., & Park, S.-P. (2014). Predictors of quality of life and their interrelations in Korean people with epilepsy: A MEPSY study.*Seizure* , *23*

(9), 762–768. https://doi.org/10.1016/j.seizure.2014.06.007
22. Lyseng-Williamson, K. A. (2011). Levetiracetam: A review of its use in epilepsy. *Drugs* , *71* (4), 489–514. https://doi.org/10.2165/11204490-000000000-00000
23. Meador, K. J., Penovich, P., Baker, G. A., Pennell, P. B., Bromfield, E., Pack, A., Liporace, J. D., Sam, M., Kalayjian, L. A., Thurman, D. J., Moore, E., Loring, D. W., & NEAD Study Group. (2009). Antiepileptic drug use in women of childbearing age. *Epilepsy & Behavior: E&B* , *15* (3), 339–343. https://doi.org/10.1016/j.yebeh.2009.04.026
24. Nwani, P. O., Nwosu, M. C., Enwereji, K. O., Asomugha, A. L., Arinzechi, E. O., & Ogunniyi, A. O. (2013). Epilepsy treatment gap: Prevalence and associated factors in Southeast Nigeria. *Acta Neurologica Scandinavica* , *128* (2), 83–90. https://doi.org/10.1111/ane.12096
25. Olusanya, A., Ogunleye, O., Godman, B., Fadare, J., & Danesi, M. (2017). Adverse effects of carbamazepine monotherapy among patients in Nigeria: A pilot study and implications. *Journal of Comparative Effectiveness Research* , *6* (1), 33–42. https://doi.org/10.2217/cer-2016-0057
26. Owolabi, L. F., Owolabi, S. D., Adamu, B., Jibo, A. M., & Alhaji, I. D. (2020). Epilepsy treatment gap in Sub-Saharan Africa: Meta-analysis of community-based studies. *Acta Neurologica Scandinavica* ,*142* (1), 3–13. https://doi.org/10.1111/ane.13246
27. Paul, A., Adeloye, D., George-Carey, R., Kolčić, I., Grant, L., & Chan, K. Y. (2012). An estimate of the prevalence of epilepsy in Sub-Saharan Africa: A systematic analysis. *Journal of Global Health* , *2* (2), 020405. https://doi.org/10.7189/jogh.02.020405
28. Roy, S., Goud, N. R., & Matzger, A. J. (2016). Polymorphism in phenobarbital: Discovery of a new polymorph and crystal structure of elusive form V. *Chemical Communications (Cambridge, England)* ,*52* (23), 4389–4392. https://doi.org/10.1039/c6cc00959j
29. Sakuma, M., Ida, H., Nakamura, T., Ohta, Y., Yamamoto, K., Seki, S., Hiroi, K., Kikuchi, K., Nakayama, K., Bates, D. W., & Morimoto, T. (2014). Adverse drug events and medication errors in Japanese paediatric inpatients: A retrospective cohort study. *BMJ Quality & Safety* , *23* (10), 830–837. https://doi.org/10.1136/bmjqs-2013-002658
30. Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G. W., Moshé, S. L., Nordli, D. R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y.-H., & Zuberi, S. M. (2017). ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology.*Epilepsia* , *58* (4), 512–521. https://doi.org/10.1111/epi.13709
31. Silvennoinen, K., de Lange, N., Zagaglia, S., Balestrini, S., Androsova, G., Wassenaar, M., Auce, P., Avbersek, A., Becker, F., Berghuis, B., Campbell, E., Coppola, A., Francis, B., Wolking, S., Cavalleri, G. L., Craig, J., Delanty, N., Johnson, M. R., Koeleman, B. P. C., ... EpiPGX Consortium. (2019). Comparative effectiveness of antiepileptic drugs in juvenile myoclonic epilepsy. *Epilepsia Open* , *4* (3), 420–430. https://doi.org/10.1002/epi4.12349
32. St. Louis, E. (2009). Minimizing AED Adverse Effects: Improving Quality of Life in the Interictal State in Epilepsy Care.*Current Neuropharmacology* , *7* (2), 106–114. https://doi.org/10.2174/157015909788848857
33. Stephen, L. J., & Brodie, M. J. (2012). Antiepileptic drug monotherapy versus polytherapy: Pursuing seizure freedom and tolerability in adults. *Current Opinion in Neurology* ,*25* (2), 164–172. https://doi.org/10.1097/WCO.0b013e328350ba68
34. Yang, A., Wang, B., Zhu, G., Jiao, Z., Fang, Y., Tang, F., Ma, C., Zhao, Y., Cheng, C., & Zhong, M. (2014). Validation of Chinese version of the Morisky medication adherence scale in patients with epilepsy. *Seizure* , *23* (4), 295–299. https://doi.org/10.1016/j.seizure.2014.01.003

TABLE 1: Showing relationship between adherence level and clinical profiles in PWE.

Variables	N (%) Total=940	High adherence N=545	Medium adherence N=28	Poor adherence N=31	Total adherence N=604	x^2 value	p value
Gender Male	40.44(19.24)	259(47.5)	12(42.9)	12(38.7)	283(46.9)	1.103	0.5766
Mean (SD)	38.07(18.35)	286(5.5)	16(57.1)	19(61.3)	321(53.1)		
Female							
Mean (SD)							
Age Mean	39.19(18.80)	39.6(19.1)	38.1(19.3)	43(20.1)	39.7(19.1)	f=0.577	0.562
(SD)	175(18.6)	102(18.7)	7(25.0)	5(16.1)	114(18.9)	1(3118	0.757
13-20	298(31.7)	172(31.6)	9(32.1)	8(25.8)	119(19.7)		
21-35	201(21.4)	108(19.8)	6(21.4)	5(16.1)	182(30.0)		
36-50 >50	266(28.3)	163(29.9)	6(21.4)	13(41.9)			
Marital	383(40.7)	214(39.3)	11(39.3)	15(48.4)	240(39.7)	7.320	0.695
Status Never	539(57.3)	318(58.3)	17(60.7)	15(48.4)	350(57.9)		
married	2(0.2)	1(0.2) 9(1.7)	0(0.0) 0(0.0)	0(0.0) 0(0.0)	1(0.2) 9(1.5)		
Currently	11(1.2)	1(0.2) 2(0.4)	0(0.0) 0(0.0)	0(0.0) 1(3.2)	1(0.2) 3(0.5)		
married	2(0.2) 3(0.3)						
Separated							
Widow/widower							
Cohabiting							
Divorce							
Formal	45(4.8)	27(5.0)	1(3.6) 1(3.6)	0(0.0) 3(9.7)	28(4.6s)	7.405	0.494
Education	37(3.9)	26(4.8)	9(32.1)	15(48.4)	30(5.0)		
None	350(37.2)	210(50.0)	16(57.1)	12(38.7)	234(38.7)		
Primary	414(44.0)	235(43.1)	1(3.6)	1(3.2)	263(43.5)		
Secondary	94(10.0)	47(8.6)			49(8.1)		
Tertiary							
Postgraduate							
Seizure	146(15.5)	86(15.8)	2(7.1)	6(19.4)	94(15.6)	6.502	0.591
remission	290(30.9)	166(30.5)	9(32.1)	7(22.6)	182(30.0)		
<1 month	266(28.3)	162(29.7)	12(42.99)	8(25.8)	182(30.0)		
1-5 months	194(20.6)	108(19.8)	5(17.9)	9(29.0)	122(20.2)		
6months-1	44(4.7)	23(4.2)	0(0.0)	1(3.2)	24(4.0)		
year 2-5							
years >5							
years							
Seizures	226(24.0)	135(24.8)	5(17.9)	8(25.8)	148(24.5)	1.746	0.782
types Focal	686(73.0)	394(72.3)	23(82.1)	22(71.0)	439(72.7)		
onset	28(3.0)	16(2.9)	0(0.0)	1(3.2)	17(2.8)		
Generalized							
onset							
Unknown							
onset							
Epilepsy	704(74.9)	58(10.6)	2(75.8)	5(16.1)	65(10.8)	5.680	0.460
classification	216(23.0)	388(71.2)	23(82.1)	24(77.4)	435(72.0)		
focal	17(1.8)	76(13.9)	3(10.7)	1(3.2) 1(3.2)	80(13.2)		
Generalized	3(0.3)	23(4.2)	0(0.0)		24(4.0)		
Combined							
Unknown							

TABLE 2: Showing comparison of the mean LAEP scores and social demographic/clinical profiles.

Variables	LAEP Mean (SD)	Statistical value	P value
Gender Male Female	42.74(10.35) 43.11(9.90)	T=0.564	0.573
Number of AEDs Monotherapy Polytherapy	44.08(10.65) 46.09(9.52)	T=-1.788	0.074
Drug adherence High adherence Medium adherence Low adherence	45.25(9.36) 44.24(10.40) 40.98(9.30)	F=11.563	**0.000***
Duration <1 Month 1-5 Months 6 months -1year 2-5year >5years	41.43(9.74) 41.05(9.70) 42.84(10.12) 46.10(9.98) 46.98(10.40)	F=10.120	**0.000***
Duration of AED <2Years >2Years	41.33(9.49) 47.21(10.59)	T=-7.141	**0.000***
Epileptiform Pattern Generalized Focal Focal to Secondary generalized None	43.54(9.92) 41.51(10.52) 46.08(9.25) 42.47(10.10)	F=3.342	**0.019***
Seizure type Focal onset Generalized Unknown	42.11(9.24) 43.33(10.33) 40.14(10.88)	F=2.330	0.098

AEDs – Anti-epileptic Drugs

*statistically significant.

TABLE 3: Showing frequency and distribution pattern of AEDs used.

Variables	**N**	**Mean±SD**
Total number of patients on meds	604	44.43(10.484)
Monotherapy	498	44.08(10.65)
Polytherapy	106	46.10(9.52)
CAP	414	44.26(10.59)
LVC	56	44.63(10.58)
GBP	1	65.00
VLP	11	37.91(13.40)
PNT	11	38.91(9.44)
CNP	1	36.00
PNT	4	45.50(3.00)
CAP+LVC	55	47.44(8.61)

Carbamazepine (CAP), Levetiracetam (LVC), Gabapentin (GBP), Valproate (VLP), Phenytoin (PNT), Clonazepam (CNP), Phenobarbiturate (PB).

TABLE 4: Frequency of reported adverse effects of PWE.

Variables	**Frequency**	**Percentage**
Unsteadiness	251	26.7
Tiredness	213	22.7

Variables	Frequency	Percentage
Restlessness	216	23.0
Feeling anger or aggression to others	316	33.6
Nervousness and or agitation	322	34.3
Headache	123	13.1
Hair loss	68	7.2
Problem with skin	87	9.3
Double or blurred vision	117	12.4
Upset stomach	152	16.2
Difficulty in concentrating	178	18.9
Trouble with mouth or gums	84	8.9
Shaky hands	165	17.6
Weight gain	304	32.3
Dizziness	105	11.2
Sleepiness	116	12.3
Depression	187	19.9
Memory problems	189	20.1
Disturbed sleep	184	19.6

TABLE 5: Determinant of ADR in PWE

Variable	B	t-test	p value	95% CI Lower – Upper
DRUG ADHERENCE	2.199	1.310	0.199	-1.097 – 5.494
DURATION OF EPILEPSY	1.269	3.231	**0.001***	0.498 – 2.040
DURATION OF AED	5.119	5.972	**0.000***	3.436 – 6.802
EPILEPTIFORM PATTERN	0.036	0.105	0.917	-0.633 – 0.705

Anti-epileptic Drug (AED)