



Factors Influencing Antiepileptic Drug (AED) Nonadherence in a Tertiary Care Hospital: A Cross-Sectional Study

Majid Ali Khand¹, Shoaib Ahmed², Saifullah³, Lal Chand⁴,
Muhammad Asif Khaskheli⁵

¹Neurologist Neurology, Chandka Medical College Hospital at SMBBMU Larkana, Pakistan; ²Senior Registrar Neurology, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences Gambat, Pakistan; ³Neurologist Neurology, Chandka Medical College Hospital at SMBBMU Larkana Pakistan; ⁴Associate Professor Neurology, Ghulam Mohammad Mahar Medical College Sukkur Pakistan; ⁵Consultant Neurologist Neurology, KMC Civil Hospital Khairpur Mir's Pakistan.

ABSTRACT

Introduction: Epilepsy affects almost 50 to 70 million individuals worldwide, accounting for 0.75 percent of the worldwide illness burden. Every year, an approximate of 2.4 million individuals are afflicted with epilepsy. Due to a lack of accessibility and affordability of AEDs, up to three-quarters of patients with epilepsy in low-income nations are unable to receive the medication they require.

Aim: To determine the factors influencing antiepileptic drug (AED) nonadherence in a tertiary care hospital.

Methodology: According to the findings of a single center, cross-sectional investigation, we did a subgroup assessment. Patients have to be at least 18 years old to participate. The Morisky Medication Adherence Scale, which has four items, was employed to assess compliance to AEDs. To forecast parameters linked to AED nonadherence, researchers employed multivariable logistic regression assessment.

Results: This subgroup evaluation includes a total of 270 patients who met the eligibility criteria. Amongst the patients, 82 (31%) did not take their medication as prescribed. AED polytherapy, medication linked negative events, and medication length beyond 3 years were three characteristics linked to poor adherence.

Conclusion: Almost one third of the participants did not take their medicine as prescribed. Noncompliance may be minimized if patients' treatments are limited to monotherapy as much as feasible and patients are taught about the length of medication and potential side effects of AEDs.

Key Words: Epilepsy, Antiepileptic drugs, Compliance, Poly therapy, Potential side effects, Morisky Medication Adherence Scale

INTRODUCTION

Epilepsy affects almost 50 to 70 million individuals worldwide, accounting for 0.75 percent of the worldwide illness burden.^{1, 2, 3} Every year, an approximate of 2.4 million individuals are afflicted with epilepsy. Due to a lack of accessibility and affordability of AEDs, up to three-quarters of patients with epilepsy in low-income nations are unable to receive the medication they require.⁴ With presently accessible antiepileptic medicines, around two-thirds of epileptic sufferers can be effectively managed and made seizure-free. Antiepileptic medications (AEDs) can help 60 percent to 70 percent of epileptic patients to live seizure-free with the right medication.⁵ Unmanaged epilepsies, on the other hand, does

not automatically reflect treatment resistance.⁶ There can be a variety of reasons for the epilepsy's uncontrollability. It's possible that a person's episodes aren't epileptic. Uncontrolled epilepsy could also be the result of an individual being medicated with the incorrect AEDs, or with inadequate AED dosages, or it could be true drug-resistant epilepsy. At last, some individuals may have been appropriately identified, be on the right dose of the right AEDs, but still be uncontrollable due to noncompliance. According to a study, non-compliance ranged from 26% to 79 percent, with the wide variation among studies attributed to varied interpretations of compliance and cutoff values for identifying non-compliance.⁷ Epileptic individuals who do not follow their

Corresponding Author:

Majid Ali Khand, Neurologist Neurology, Chandka Medical College Hospital at SMBBMU Larkana, Pakistan.
Email: drmajidkhand@gmail.com

ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 03.03.2022

Revised: 16.03.2022

Accepted: 02.04.2022

Published: 19.04.2022

AED treatment programs risk recurrence⁸, status epilepticus⁹, hospitalization¹⁰, and higher health-care expenses.^{11, 12} In epilepsy, noncompliance may even be linked to abrupt, inexplicable death due to status epilepsy.¹³ With an epilepsy rate of at least 9.99 per 1000 people in Pakistan¹⁴, noncompliance and its consequences take on a significant dimension. There is a paucity of data on the incidence of AED non-compliance in the Pakistani epileptic patients, and much less is documented about the variables that contribute to it. Knowledge on the degree of non-compliance and the variables that may contribute to it could be useful in developing effective interventions. In this study, we determined the factors influencing antiepileptic drug (AED) nonadherence in a tertiary care hospital.

Study design: A cross-sectional study

Place and Duration: This study was conducted at Chandka Medical College Hospital at SMBBMU Larkana, Pakistan from January 2020 to January 2021.

METHODOLOGY

A predictive subgroup assessment to examine compliance was planned. In this study, all epileptic participants who presented to the Neurology outpatient department for the first session were recruited, but only those who were 18 years or above. We eliminated younger participants since compliance was measured using a self-reported scale, and its validity in younger participants was unknown. Treatment-naïve individuals, individuals using only conventional medicines, and individuals with cognitive decline severe enough to limit memory and/or contact with researchers were also excluded. The research was authorized by the institutional ethics review board after all participants signed a formal informed consent statement.

Epilepsy is a neurological illness that is characterized by frequent and unexpected disruptions of regular brain functioning, known as epileptic seizures.¹⁵ Adherence is defined as “The degree to which an individual’s behavior while consuming medicine coincides with agreed upon suggestions from a health care practitioner.”¹⁶ Nonadherence is described as any divergence from a recommended regimen’s instructions, both in terms of time and amount.¹⁷ An individual was identified with epilepsy if he or she experienced at minimum 2 uncontrolled seizures that occurred greater than 24 hours apart, or even a single uncontrolled seizure with a substantial risk of subsequent seizures. If the participant’s seizure semiology indicated that nonepileptic seizures were probable, it was defined as nonepileptic seizures. The revenue of the individual and his or her family was assessed and classified using modified Kuppaswamy and B G Prasad social economic levels to estimate income levels. M.I.N.I. (Mini International Neuropsychiatric Interview) was used to

evaluate psychiatric comorbidities. The intensity of negative medication occurrences was graded using the Common Terminology Criteria for Adverse Events (CTCAE) scoring system. The monthly expense of all recommended medications, comprising of AEDs, vitamins, and calcium, was totaled to determine the medical costs. We left out the expense of diagnostic testing, travel fees, and any other costs associated with patient treatment. Polytherapy was described as the simultaneous use of two or several antiepileptic medicines. Seizures were classified as “often” if they happened more than once per month, and “uncommon” if they occurred less than once per month.

The four-item Morisky Medication Adherence Scale, a standardized, established survey for monitoring self-reported medication compliance, was used to evaluate compliance to AED therapy. The MMAS4 assesses whether the participant: (a) has ever neglected to consume medicine; (b) has ever experienced difficulty recalling to administer medication; (c) has ever discontinued medication due to improved symptoms; and (d) has ever discontinued medicine owing to deteriorating symptoms. Each item is given a score of 0 (Yes) or 1 (No). The ratings of each item are then added together to get a spectrum of scores ranging from 0 through 4. A rating of 3–4 indicates that the individual is compliant, whereas a rating of 2 indicates that the individual is noncompliant. In order to avoid recall biases, we concentrated on compliance in the four weeks leading up to the present outpatient clinic appointment.

An already structured proposal was used to gather data on demographics, epilepsy kind, psychiatric disorders, number of AEDs, length of treatment, drug-related negative occurrences, monthly expense of medication, and self-reported medication compliance.

Two objectives were of particular relevance to us: (a) estimating the percentage of epileptic individuals who were non-compliant to medicine according on MMAS4 and (b) variables related with AED non-compliance.

Microsoft Excel spreadsheets were used to input the data. To summarize initial variables, descriptive statistics were employed. Averages were used to display uninterrupted data with a normal distribution. Figures and percentages were used to depict categorical variables. The independent ‘t’ test was used to evaluate uninterrupted data, and the Chi-square test was used to evaluate categorical data. Univariate analysis logistic regression analysis was used to look at possible indicators of non-compliance. To develop the multivariable model, we utilized Hosmer and Lemeshow intentional multivariable analysis with the goal of finding the most possible independent factors. All variables that indicated a possible effect in the bivariate analyses (i.e., variables with a P value just under 0.25 or medically meaningful) were incorporated in the multivariate analysis to develop the optimal model.

P-values less than 0.05 were considered significant in the final version. All of the statistical analyses were done with STATA version 13 program.

RESULTS

A total of 426 individuals were evaluated between the study duration. A total of 270 patients met the eligibility requirements and were enrolled in this subgroup study. Over the four weeks before the present outpatient clinic appointment, 82 (31%) of the individuals (n = 270) were noncompliant to medicine, whereas 188 (71%) were compliant. Table 1 shows the demographics of the individuals in the research. Using

univariate regression assessment, there was a statistically substantial variation between compliant and noncompliant groups in epilepsy kind, AED polytherapy, monthly medicine expense, recurrent seizures, associated with drug side events, and length of treatment [As shown in Table 1]. Only three characteristics were identified to be linked with poor compliance in a multivariable iterative logistic regression assessment [As shown in Table 2]. AED polytherapy participants [OR: 4.4 (2.1-9.4) P = 0.002], with drug-related side effects [OR: 3.9 (2.2-7.4) P = 0.002] and a duration of therapy of more than 3 years for epilepsy [OR: P= 0.001] were the ones most likely to be linked to Noncompliance with AEDs [As shown in Table 2].

Table 1: Participants' demographic and clinical features

Characteristics	Non-Compliant N=82	Compliant N=188	P-value	Univariate analysis
Age Mean (SD)	32.2 (±13.8)	31.5 (±12.4)	0.8	1.1 (0.9-1.1)
Male gender	44 (55.5)	111 (59.8)	0.4	0.7 (0.4-1.4)
Rural resident	36 (43.3)	78 (41.2)	0.5	1.0 (0.6-1.7)
Education less than matriculation	34 (43.1)	63 (34.1)	0.2	1.4 (0.8-2.3)
Unemployed	24 (28.5)	60 (31.6)	0.5	0.6 (0.5-1.4)
Low socio-economic class	37 (46.8)	76 (41.1)	0.6	1.1 (0.7-2.2)
Marital status (single)	44 (53.2)	97 (51.4)	0.7	1.2 (0.7-1.8)
Epilepsy duration mean (SD)	5.4 (±7.3)	5.3 (±5.2)	0.8	1.1 (0.9-1.05)
Focal epilepsy	63 (76.6)	120 (63.7)	0.05	1.7 (1.02-3.2)
Generalized epilepsy	12 (16.55)	48 (26.1)	0.06	0.5 (0.4-1.05)
Uncertain epilepsy	7 (7.5)	20 (10.2)	0.4	0.7 (0.3-1.7)
Recurrent seizures	30 (38.1)	49 (26.6)	0.07	1.7 (0.8-2.9)
AED Polytherapy	70 (85.2)	81 (42.9)	0.002	7.7 (3.8-15.1)
Expense of Medication	1385.5	1038.1	0.001	1.1 (1.01-1.06)
Length of treatment (>3 years)	56 (68.1)	54 (23.4)	0.002	5.2 (3.0-9.3)
Psychiatric comorbidity	15 (19.6)	26 (14.3)	0.26	1.2 (0.7-2.9)

Table 2: A multivariable logistic regression analysis was used to forecast factors linked to non-compliance to AEDs

Characteristics	Non-compliance	P-value
Focal epilepsy	1.4 (0.6-2.6)	0.41
AED Poly therapy	4.4 (2.1-9.4)	0.002
Expense of medication	1.1 (0.9-1.1)	0.10
Negative effects associated with drug use	3.9 (2.2-7.4)	0.002
Length of treatment (>3 years)	2.5 (1.4-5.0)	0.001
Recurrent seizure	1.1 (0.7-2.3)	0.50

DISCUSSION

Medicine adherence can be understood as a treatment partnership between the physician and the patient, in which the clinician prescribes a medical prescription and the patient is required to follow it.¹⁸ The important problems of significance, when evaluating compliance are that the definition(s) of compliance are apparent, that a differentiation is established between the many forms of non-compliance, that the means of evaluating compliance are transparent, and that the consequence of non-compliance is clearly understood.¹⁹

In the four weeks following the present outpatient clinic appointment, 31 percent of epilepsy patients were non-compliance to recommended AED medication. According to the research, lack of adherence ranged from 26 to 79 percent. This discrepancy could be due to differences in the study population's demographics, definition of terms, and compliance assessment scales. AED polytherapy, drug-related unpleasant outcomes, and length of treatment greater than 3 years were the three characteristics we observed to be linked with non-adherence.

Whenever a society reports a big treatment gap, one automatically wonders of individuals who have never been identified or begun AEDs. Whilst such patients are a significant part of the treatment gap, there are multiple layers to the issue. The term "secondary treatment gap" refers to people who were identified and began AEDs at some time but then stopped taking them. Noncompliance on a regular basis may also result in a subsequent therapy gap. This issue is exacerbated in areas where epileptic patients are impoverished and unable to afford AEDs, are typically uninformed about epilepsy, are skeptical of contemporary treatment, and are afflicted by superstitions and culturally stigma. Epilepsy awareness promotes compliance. Participants that were part of this research were new to our hospital. At least 40% of these individuals did not require tertiary care. Despite this, we observed that a considerable number of participants were presently on polytherapy—85% in the non-compliant group and 43% in the compliant group. Extensive and frequently unjustified usage of polytherapy reveals a lack of consistency in the nation's epilepsy prescription standards. Polypharmacy overuse gives little advantage in symptom control while increasing needlessly AED-related adverse consequences and raising medical costs. Although our study did not explicitly link medication costs to non-compliance, it is possible that non-compliance to polytherapy is partly due to the cost of healthcare. A higher cost is associated with a prolonged medication period. Individuals who have been on AED medication for a long time may have non-compliance as a result of not being educated about the necessity for continued treatment. Patients who are better educated about epilepsy, along with the anticipated length of therapy and the risk for AED-relat-

ed side effects and how to minimize them, are more probable to stick to their treatment regimens.²⁰

Individuals self-reported AED non-compliance, and some cases of skipping the medication may have been ignored or even purposely hidden, which limits our study. We attempted to reduce recall bias by analyzing noncompliance in the four weeks leading up to the present appointment. Individuals may suppress data concerning noncompliance owing to humiliation or a worry of upsetting the treating physician on rare occasions.

Completing suitable boxes on the MMAS4 form in relative confidentiality and security constitutes self-reporting the MMAS4. We expect that this has allayed any anxieties or apprehensions patients may have had about disclosing non-compliance. Other diseases and coexisting non-AED pharmacies were not considered in our analysis, which contained mental disorders and AED pharmacy information.

Although a planned study with a bigger sample number may produce more accurate data, we believe our findings are significant for two justifications: (1) There is little reliable information about poor adherence in Pakistani epileptic patients, and (2) the variables that cause non-compliance are, for the most part, reparable.

CONCLUSION

Almost one third of the participants did not take their medicine as prescribed. Nonadherence may be minimized if patients' treatments are limited to monotherapy as much as feasible and patients are provided ample knowledge, particularly about the length of treatment and the harmful consequences of AEDs.

ACKNOWLEDGEMENT

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Source of Funding

None

Conflict of interest

None

Permission

Permission was taken from the ethical review committee of the institute

Authors' Contribution:

All of authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published.

REFERENCES

1. World Health Organization. Epilepsy. Fact sheet. No. 999. 2012. Updated February 2016. <http://www.who.int/mediacentre/factsheets/fs999/en/>. Accessed March 12, 2016.
2. Katchanov J, Birbeck GL. Epilepsy care guidelines for low-and middle-income countries: From WHO mental health GAP to national programs. *BMC medicine*. 2012 Dec; 10(1):1-5.
3. Yemadje LP, Houinato D, Quet F, Druet-Cabanac M, Preux PM. Understanding the differences in prevalence of epilepsy in tropical regions. *Epilepsia*. 2011 Aug; 52(8):1376-81.
4. Mbuba CK, Ngugi AK, Newton CR, Carter JA. The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes, and intervention strategies. *Epilepsia*. 2008 Sep; 49(9):1491-503.
5. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology*. 2012 May 15; 78(20):1548-54.
6. Schmidt D, Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurologica Scandinavica*. 2005 May; 111(5):291-300.
7. Malek N, Heath CA, Greene J. A review of medication adherence in people with epilepsy. *Acta Neurologica Scandinavica*. 2017 May; 135(5):507-15.
8. Samsonsen C, Reimers A, Bråthen G, Helde G, Brodtkorb E. Nonadherence to treatment causing acute hospitalizations in people with epilepsy: an observational, prospective study. *Epilepsia*. 2014 Nov; 55(11):e125-8.
9. Alvarez V, Westover MB, Drislane FW, Dworetzky BA, Curley D, Lee JW et al. Evaluation of a clinical tool for early etiology identification in status *epilepticus*. *Epilepsia*. 2014 Dec; 55(12):2059-68.
10. Manjunath R, Davis KL, Candrilli SD, Ettinger AB. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. *Epilepsy & Behavior*. 2009 Feb 1; 14(2):372-8.
11. Davis KL, Candrilli SD, Edin HM. Prevalence and cost of non-adherence with antiepileptic drugs in an adult managed care population. *Epilepsia*. 2008 Mar; 49(3):446-54.
12. Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. *Epilepsia*. 2009 Mar; 50(3):501-9.
13. Faught E, Duh MS, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology*. 2008 Nov 11; 71(20):1572-8.
14. Khatri IA, Iannaccone ST, Ilyas MS, Abdullah M, Saleem S. Epidemiology of epilepsy in Pakistan: review of literature. *Journal-pakistan medical association*. 2003 Dec 1; 53(12):594-6.
15. Fisher RS, Boas WV, Blume W, Elger C, Genton P, Lee P et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*. 2005 Apr; 46(4):470-2.
16. World Health Organization. Adherence to long-term therapies: evidence for action. World Health Organization; 2003.
17. Malek N, Heath CA, Greene J. A review of medication adherence in people with epilepsy. *Acta Neurologica Scandinavica*. 2017 May; 135(5):507-15.
18. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB et al. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glyce-mic management. *Diabetes care*. 2007 Apr 1;30(4):807-12.
19. Hughes DA, Bagust A, Haycox A, Walley T. Accounting for noncompliance in pharmacoeconomic evaluations. *Pharmacoeconomics*. 2001 Dec; 19(12):1185-97.
20. Das K, Banerjee M, Mondal GP, Devi LG, Singh OP, Mukherjee BB. Evaluation of socio-economic factors causing discontinuation of epilepsy treatment resulting in seizure recurrence: A study in an urban epilepsy clinic in India. *Seizure* 2007; 16:601-7.