

THE ASSOCIATION OF ADHERENCE WITH ANTIEPILEPSY DRUG CONSUMPTION ON SEIZURE CONTROL IN EPILEPSY PATIENTS AT THE NEUROLOGY POLYCLINIC OF REGIONAL PUBLIC HOSPITAL SANJIWANI

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ABSTRACT

Background: Epilepsy is the most common neurological disease in the world. Treatment with antiepileptic drugs (AEDs) is important to achieve optimal quality of life. Non-adherence with medication consumption is known to contribute to increased mortality and morbidity rates in epilepsy patients due to uncontrolled seizures. This study aims to determine the association between drug consumption adherence and seizure control in epilepsy patients at the Neurology Polyclinic at Sanjiwani Regional Hospital. This research is a cross-sectional analytical study.

Methods: The sampling technique used was consecutive sampling with a measuring instrument in the form of the MMAS-8 questionnaire. Statistical tests carried out included univariate analysis, chi-square, and binary logistic regression.

Results: The results of the study found that the majority of participants had uncontrolled seizures (57.8%) and high level of medication adherence (50%). In the chi-square analysis, a significant association was obtained between drug consumption adherence and participants' seizure control. In addition, adherence to medication consumption had a dominant influence compared to other variables in binary logistic regression analysis ($p=0.017$; AOR=12.83, CI 95% 1.57-104.51).

Conclusion: This study concludes there is a significant association between adherence to OAE consumption and seizure control. Patients who have low adherence have a 12.83 times greater chance of experiencing uncontrolled seizures than medium-high adherence. However, this result lacks precision seen from the wide confidence interval value.

Keywords: Antiepileptic Drugs, Adherence, Seizure Control

INTRODUCTION

Epilepsy is one of the most common chronic neurological diseases in the world. Approximately 50 million people worldwide suffer from epilepsy, and nearly 80% of them live in low- and middle-income countries.¹ The incidence of epilepsy in Indonesia is relatively high, with at least 700.000 – 1.400.000 cases of epilepsy in the country and an addition of 70.000 new cases each year.² According to the health profile of Bali Province, epilepsy ranked among the top 10 diagnoses for outpatient care in Primary Health Facilities and Advanced Level services of the National Health Insurance (JKN) program in 2018.³ In

2016, epilepsy was the third most common disease for outpatient visits to hospitals in Gianyar Regency, following diabetes mellitus and hypertension. A total of 2.306 cases were recorded from data obtained from Sanjiwani Regional Hospital.⁴ Apart from the high number of cases, the prevalent culture and traditions in Gianyar Regency, along with the high reliance on traditional healers, pose challenges to adherence to epilepsy treatment.^{5,6}

The adherence rate to antiepileptic drugs (AEDs) varies significantly according to several studies compiled in Chunsong Yang et al.'s research in 2018, ranging from 22.1% to 96.5%.⁷ Non-adherence to AED medications can result in uncontrolled seizures which can contribute to

increased morbidity and mortality, poor quality of life, and increased health care costs.⁷ Other studies also report that non-adherence to treatment significantly impacts an increased occurrence of seizures compared to patients compliant with their medication regimens.⁸ Therefore, this study aimed to analyze the association between adherence to antiepileptic drug consumption and seizure control in epilepsy patients at the Neurology Clinic of Sanjiwani Regional Hospital, Gianyar.

METHODS

This research is an analytical cross-sectional study conducted at the Neurology Clinic of Sanjiwani Regional Hospital from April to June 2023, in Gianyar. The research subjects were epilepsy patients at the Neurology Clinic of Sanjiwani Regional Hospital who met the inclusion criteria, including patients previously diagnosed with epilepsy, aged between 20-60 years old, undergoing a minimum of 6 months of AED treatment, and willing to participate as respondents. Patients who had achieved therapy targets or had been seizure-free for 2 years and patients with mental disorders were excluded. The total number of patients meeting the inclusion criteria was 90 participants selected through consecutive sampling techniques.

The dependent variable in this study is the adherence to antiepileptic drug consumption, while the independent variable is the seizure control of epilepsy patients. Confounding variables include age, gender, level of education, income, duration of illness, drug side effects, treatment duration, comorbidities, number of medications, duration of travel to the hospital, family history of epilepsy, pre-treatment seizure count, pre-treatment duration, alcohol consumption, and smoking habits.

The data used comprise both primary and secondary data. Primary data regarding participants' adherence levels to drug consumption were measured using the MMAS-8 questionnaire (Morisky Medication Adherence Scale – 8). The MMAS-8 questionnaire consists of 8 questions. For questions 1 to 7, except for question number 5, a response of "Yes" is scored as 0 and "No" is scored as 1. For question number 5, the scoring is reversed, with 0 for "No" and 1 for "Yes." In question number 8, if the response is "never"

(not even once in a week), the score is 1; occasionally (once a week) is scored 0.75, sometimes (two to three times a week) is scored 0.5, frequent is scored 0.25, and always is scored 0. Respondents scoring < 6 are interpreted as having low drug consumption adherence, those with scores between 6 – 7 have moderate adherence, and a score of 8 indicates high adherence. Secondary data include seizure frequency in the last year, disease duration, and medical history obtained from participants' medical records/seizure diaries.

Data analysis was conducted using the SPSS (Statistical Package for the Social Sciences) application. Analyses included univariate, bivariate (chi-square test), and multivariate analysis (binary logistic regression). The multivariate analysis included variables with a p-value < 0.25 in the chi-square test. Variable with p-value < 0.05 means there is a significant association between dependent and independent variable.

This research has undergone ethical review twice: first by the Research Ethics Commission Unit of the Faculty of Medicine, Udayana University, with number 357/UN14.2.2.VII.14/LT/2023, and secondly, by the Ethics Committee for Health Research of RSUD Sanjiwani Gianyar with number 42/PEPK/IV/2023.

RESULTS

Sociodemographic Characteristics of Study Participants

The distribution of sociodemographic characteristics of the participants in this study is presented in Table 1. According to the table, the majority of participants fall within the age range of 26-45 years (42.2%). The most frequent gender is male (55.6%). The majority of the participants had a high school education (38.9%). The most prevalent marital status is married (72.2%). The predominant occupation among respondents is working in the private sector (26.7%). The most of participants had income < Gianyar Regency Minimum Wage/UMR (85.6%). The most common travel duration to the hospital is less than 1 hour (80%).

Table 1. Sociodemographic characteristics of study participants

Characteristics	N(90)	%
Age (years)		
20 - 25	20	22.2
26 - 45	38	42.2
> 45	32	35.6
Gender		
Male	50	55.6
Female	40	44.6
The last education level		
College graduate	9	10
High school	35	38.9
Junior high school	28	31.1
Elementary school	14	15.6
Didn't go to school/didn't finish Elementary school	4	4.4
Marital status		
Married	65	72.2
Single	25	27.8
Occupation		
PNS/TNI/POLRI	4	4.4
Private sector employee	24	26.7
Self-employed	20	22.2
Farmer	13	14.4
Labor (farming, construction, etc.)	2	2.2
Student	11	12.2
Housewife	14	15.6
Unemployed	2	2.2
Monthly income		
< Gianyar Regency UMR	77	85.6
≥ Gianyar Regency UMR	13	14.4
Distance from hospital (hours)		
< 1	72	80
≥ 1	18	20

Clinical Characteristic

The participants' disease characteristics are distributed in frequencies and percentages in Table 2. The majority of participants had a disease duration of > 5 years (52.2%), experienced ≤ 5

seizure occurrences in the last year (95.6%), did not have any other accompanying diseases (85.6%), did not have a family history of epilepsy (94.4%), and had uncontrolled seizure status (57.8%).

Table 2. Clinical characteristics of study participants

Characteristics	N (90)	%
Duration of epilepsy (years)		
1-5	43	47.8
>5	47	52.2
Number of seizures (last 1 year)		
≤ 5	86	95.6
> 5	4	4.4
Comorbid		
Yes	13	14.4
Hypertension	6	6.7
DM	1	1.1
Toxoplasma	2	2.2
SNH	2	2.2
No	77	85.6
Family history of epilepsy		
Yes	5	5.6
No	85	94.4
Seizure control		
Controlled	38	42.2
Uncontrolled	52	57.8

Treatment History Characteristics of Study Participants

The participants' treatment characteristics in this study are outlined in Table 3. The predominant participants had a treatment duration of 1-5 years (52.2%), started treatment < 1 year after diagnosis (88.9%), experienced 1-5 seizures

before taking OAE (81.1%), took 1 type of OAE (monotherapy) (72.2%), did not experience drug side effects (86.7%), and regularly attended hospital visits (93.3%).

Table 3. Treatment-related characteristics of participants

Characteristics	N (90)	%
Treatment duration (years)		
1-5	47	52.2
> 5	43	47.8
Pre-treatment duration (years)		
< 1	80	88.9
≥ 1	10	11.1
Pre-treatment number of seizure		
1-5	73	81.1
> 5	17	18.9
Number of ASM		
Monotherapy	65	72.2
Polytherapy	25	27.8
Side effect		
Yes	12	13.3
Allergy	1	1.1
Fatigue	3	3.3
Headache	2	2.2
Sleepy	1	1.1

Heartburn	3	3.3
Gum swelling	1	1.1
Blurred vision	1	1.1
No	78	86.7
Follow-up visit		
Regular	84	93.3
Irregular	6	6.7

Behavioral Characteristics of Participants

Participant behavior factors are outlined in Table 4. The majority of research participants demonstrated high

adherence to medication (50%), did not consume alcohol (97.8%), did not smoke (91.1%), and had a sleep duration of 7-9 hours (76.7%).

Table 4. Behavioral characteristics related to uncontrolled seizures

Characteristics	N (90)	%
Medication adherence		
High	45	50.0
Moderate	28	31.1
Low	17	18.9
Alcohol consumption		
Yes	2	2.2
1x/week	1	1.1
4x/week	1	1.1
No	88	97.8
Smoking		
Yes	8	8.9
16 cigarettes/day	1	1.1
12 cigarettes/day	3	3.3
6 cigarettes/day	3	3.3
3 cigarettes/day	1	1.1
No	82	91.1
Sleep duration (hours)		
< 7	20	22.2
7 - 9	69	76.7
> 9	1	1.1

Factors Associated with Seizure Control among Epileptic Patients

In the chi-square test, no significant association was found between variables regarding sociodemographic characteristics, clinical characteristics, and treatment history concerning the seizure control of epilepsy patients (Table 5). In the determinants of patient behavior and habits, a significant association was found between variables such as medication adherence and sleep duration concerning the seizure control of epilepsy patients. Several variables with $p < 0.25$ qualified for entry into multivariate analysis using binary logistic regression, including gender, marital status, income, drug side effects, medication adherence, and sleep

duration. The multivariate analysis revealed that medication adherence had the most dominant impact on seizure control, with an Exp(B)/Odd Ratio of 12.83 (95% CI: 1.57-104.51). Meanwhile, sleep duration also significantly influenced seizure control, with an Exp(B)/Odd Ratio of 4.16 (1.05-16.47). However, the CI value for sleep duration was more precise compared to medication adherence, possibly due to the small sample size.

Distribution of MMAS-8 Answers by Participants

The distribution of participant responses to the MMAS-8 questionnaire can be seen in Table 6 and Table 7. According to the distribution, participants mostly answered

"Yes" to questions 1, 4, and 7, indicating that most participants feel uncomfortable taking medication every day and sometimes forget to take their medication or bring it when traveling.

Table 5. Bivariate analysis of characteristic and behavioral factors of study participants with seizure control among epilepsy patients in Policlinic Neurology RSUD Sanjiwani, Gianyar

Variable	Uncontrolled		Controlled		COR (CI 95%)	p-value
	N	%	N	%		
Age (years)						
20-45	35	60.3	23	39.7	1.34 (0.56-3.21)	0.51
46-60	17	53.1	15	46.9		
Sex						
Male	32	64.0	18	36.0	1.78 (0.76-4.15)	0.18
Female	20	50.0	20	50.0		
Education						
High	28	63.6	16	36.4	1.60 (0.69-3.73)	0.27
Low - moderate	24	52.2	22	47.8		
Marital Status						
Single	35	53.8	30	46.2	0.55 (0.21-1.45)	0.22
Married	17	68.0	8	32.0		
Occupation						
Employed	37	58.7	26	41.3	1.14 (0.46-2.83)	0.78
Unemployed	15	55.6	12	44.4		
Monthly Income						
< Gianyar regency UMR	42	54.5	35	45.5	0.36 (0.09-1.41)	0.13
≥ Gianyar regency UMR	10	76.9	3	23.1		
Distance from hospital (hours)						
< 1 hours	40	55.6	32	44.4	0.62 (0.21-1.85)	0.39
≥ 1 hours	12	66.7	6	33.3		
Duration of epilepsy (years)						
1-5	27	62.8	16	37.2	1.48 (0.64-3.45)	0.36
>5	25	53.2	22	46.8		
Comorbidity						
Yes	6	46.2	7	53.8	0.58 (0.18-1.88)	0.36
No	46	59.7	31	40.3		
Family history of epilepsy						
Yes	4	80.0	1	20.0	3.08 (0.33-28.76)	0.39
No	48	56.5	37	43.5		
Treatment duration (years)						
1 – 5	29	61.7	18	38.3	1.40 (0.60-3.24)	0.43
> 5	23	53.3	20	46.5		
Pre-treatment duration (years)						
< 1	46	57.5	34	42.5	0.90 (0.24-3.45)	1
≥ 1	6	60.0	4	40.0		
Pre-treatment number of seizure						
1-5	43	58.9	30	41.1	1.27 (0.44-3.68)	0.65
>5	9	52.9	8	47.1		
Number of AEDs						
Monotherapy	39	60.0	26	40.0	1.38 (0.55-3.50)	0.49
Polytherapy	13	52.0	12	48.0		
Side effect						
Yes	9	75.0	3	25.0	0.41 (0.10-1.63)	0.19
No	43	55.1	35	44.9		
Follow-up visit						
Regular	48	57.1	36	42.9	0.67 (0.12-3.84)	1
Irregular	4	66.7	2	33.3		
Medication adherence						
Low	16	94.1	1	5.9	16.44 (2.07-130.54)	0.001
Moderate - high	36	49.3	37	50.7		
Alcohol consumption						

Yes	3	98.3	1 [#]	1.7 [#]	2.25 [#] (0.23-22.91)	0.63 [#]
No	51	56.8	39	43.2		
Smoking						
Yes	4	50.0	4	50.0	0.71 (0.17-3.03)	0.72
No	48	58.5	34	41.5		
Sleep duration (hours)						
< 7	17	85.0	3	15.0	5.67 (1.52-21.08)	0.005
≥ 7	35	50.0	35	50.0		

[#]Correction was carried out using the Woolf-Haldane Correction method to overcome the presence of 0 cells

COR: Crude Odds Ratio; AEDs: Antiepileptic Drugs; UMR: regional minimum wage; Gianyar regency UMR = Rp.2.837.680

Table 6. Distribution of MMAS-8 answers by participants No. 1 – 7

No.	Questions	Answer	
		Yes (%)	No(%)
1.	Do you sometimes forget to take your medicine?	16.7	83.3
2.	During the last two weeks, has there been a day when you did not take medication?	14.4	85.6
3.	Have you ever reduced or stopped using medication without your doctor's knowledge because you experienced worse conditions/discomfort while using the medication?	14.4	85.6
4.	When traveling or leaving the house, do you sometimes forget to take your medicine with you?	20.0	80.0
5.	Did you take all your medicines yesterday? [#]	96.7	3.3
6.	When you feel things are getting better, do you sometimes choose to stop taking medication?	11.1	88.9
7.	Some people feel uncomfortable if they have to take medication every day, have you ever felt disturbed by a situation like that?	21.1	78.9

[#]Reverse scoring

Table 7. Distribution of MMAS-8 answers by participants No. 8

No.	Questions	Never (%)	Occasionally (%)	Sometimes (%)	Often (%)	Always (%)
8.	How often do you forget to take your medicine?	77.8	20.0	1.1	0.0	1.1

Table 8. Multivariate analysis of variables with p<0,25 from bivariate analysis

Variable	AOR (CI95%)	p-value
Sex		
Male	1.08	0.880
Female	(0.40-2.94)	
Marital status		
Single	0.54	0.256
Married	(0.18-1.57)	
Monthly income		
< Gianyar Regency UMR	0.40	0.215
≥ Gianyar Regency UMR	(0.09-1.71)	
Side effect		
Yes	1.49	0.656
No	(0.25-8.68)	
Medication Adherence		
Low	12.83	0.017
Moderate – high	(1.57-104.51)	
Sleep duration		
< 7 hours	4.16	0.042

≥ 7 hours

(1.05-16.47)

AOR: Adjusted Odds Ratio

DISCUSSION

Medication adherence is defined as an individual's behavior in consuming medication according to the prescribed dose and interval.⁹ Non-adherence to AEDs can impact the clinical outcome of the disease and increase mortality in epilepsy patients (Sudden Unexpected Death in Epilepsy/SUDEP). In this study, participants tended to have a high level of medication adherence, with 45 individuals (50%). Meanwhile, 28 participants (31.1%) exhibited moderate adherence, and 17 participants (18.9%) showed low adherence (Figure 1). These results align with a study by Mawuntu et al. (2020), which reported that a majority of

participants exhibited high levels of medication adherence (41.2%), compared to moderate (30.9%) and low adherence (27.8%)¹⁰. However, the results in this study were lower than other research by Malek et al. (2017) that reported the range of medication non-adherence in epilepsy patients is between 26-79%.¹¹ This difference may stem from factors such as lower education levels, low income, polytherapy, drug side effects, duration of disease and treatment, and comorbidities in epilepsy patients. Additionally, some studies found that age and gender have a statistically significant association with medication adherence.¹²⁻¹⁶

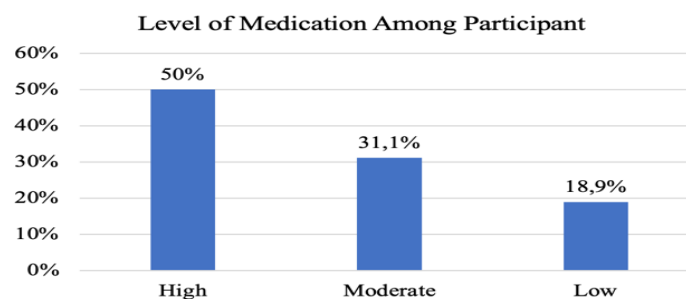


Figure 1. Characteristics of study participants' adherence to AEDs

The target of treatment with AEDs in epilepsy patients is to achieve controlled/seizure-free and minimal drug side effects. In this study, participants tended to have uncontrolled seizures, with 52 participants (57.8%), while 38 participants (42.2%) experienced controlled seizures (Figure 2). This aligns with Dawit Zena et al.'s study (2022), which reported a higher incidence of uncontrolled seizures (56.9%) compared to controlled seizures (43.1%) in

epilepsy patients at Gondar Hospital, Northwest Ethiopia.¹⁷ However, these numbers can vary because the seizure control status of epilepsy patients can be influenced by various factors such as the number of seizures before treatment, treatment duration, number of AEDs, medication adherence, travel duration to the hospital, smoking habits, alcohol consumption, sleep duration, and mental health disorders (stress, depression, anxiety).¹⁷⁻²²

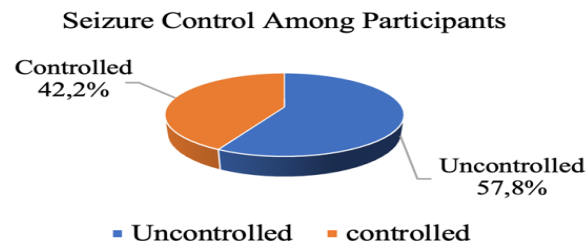


Figure 2. Distribution of participants' seizure control

In bivariate analysis, significant results were obtained between medication adherence and sleep duration concerning seizure control in epilepsy patients. To determine the most dominant variables, binary logistic regression analysis was performed on variables with p-value < 0.25. The results indicated that medication adherence (p=0.017; AOR 12.83; CI 95% 1.57-104.51) had a more

dominant effect compared to sleep duration (p=0.042; AOR 4.16; CI95% 1.05-16.47) on seizure control. These findings imply that patients with low-to-moderate medication adherence have a 12.83 times higher chance of experiencing uncontrolled seizures compared to patients with high medication adherence. These results align with several studies showing a significant association between

medication adherence and seizure control in epilepsy patients.²³⁻²⁸ However, the OR results in this study were less precise as seen from the wide confidence interval values. This could be due to adjustments to the effect size made by the researcher in calculating the sample size.

Furthermore, participants with low medication adherence were reported to have a higher percentage of uncontrolled seizures (94.1%) compared to controlled seizures (5.9%). Conversely, participants with moderate-to-high medication adherence showed a lower percentage of uncontrolled seizures (49.3%) compared to controlled seizures (50.7%). These findings support the notion that good medication adherence results in better seizure control in epilepsy patients and vice versa.^{15,24,26} Antiepileptic drugs (AEDs) are the primary treatment for epilepsy patients. Several drugs and their mechanisms in preventing seizures in epilepsy patients: (1) voltage-gated modulation (e.g. phenytoin, carbamazepine, lamotrigine, ethosuximide, retigabine); (2) increasing GABA-mediated inhibitory neurotransmission (e.g. tiagabine, vigabatrin, and benzodiazepine); (3) reduction of excitatory neurotransmission mediated by glutamate (e.g. perampanel); (4) Modulating neurotransmitter release through a pre-synaptic mechanism (e.g. Levetiracetam, gabapentin, pregabalin, brivaracetam).²⁹ These AEDs are known to provide a 70% chance for patients to achieve seizure freedom after effectively administering treatment.³⁰

On the other hand, a significant relationship was also found between sleep duration and seizure control in epilepsy patients. Participants with a sleep duration < 7 hours were 4.16 times more likely to experience uncontrolled seizures compared to those sleeping ≥ 7 hours. The association between sleep and epilepsy has long been recognized but not well understood. Research indicates that lack of sleep among individuals with epilepsy potentially triggers seizures while they are asleep, notably during the non-rapid eye movement (NREM) phase.³¹ Other studies reported that longer sleep provides a protective effect on patients with refractory focal epilepsy, reducing the risk of seizures. Additionally, patients experiencing less sleep in the past 2 months were reported to have a 41% higher incidence of seizures.^{24,32}

Based on the collected MMAS-8 questionnaire data, patients tend to answer "Yes" to questions asking about the tendency to feel uncomfortable taking medication every day and the tendency to forget to take or bring medication when traveling. This indicates that patients feel uncomfortable with the long-term treatment duration they have to undergo. These findings align with several other studies indicating a significant association between treatment duration and patient medication adherence. Patients undergoing treatment for 6 years were reported to have a 3.47 times greater chance of non-adherence compared to patients undergoing treatment for 3 months to 1 year.³³⁻³⁵ Additionally, similar results were reported in the study by Govil N et al. (2021), where the highest percentage of intrinsic reasons for

epilepsy patient non-adherence to medication was forgetting to take medication.³⁶

Strategies to improve epilepsy patient medication adherence to treatment include ensuring easy access to medication and implementing team-based services, educating and empowering patients to improve their understanding of treatment regimens and their benefits, reducing the financial burden of purchasing medication, using technological devices for communication and treatment monitoring, and understanding the root causes of patient non-adherence.³⁷ In this study, three main factors were found to play a role in patients' medication adherence: patients tend to feel uncomfortable taking medication every day and frequently forget to bring and take their medication. Therefore, clinicians are expected to provide education regarding the importance of treatment and conduct health education effectively so that patients do not feel bored with taking their medication daily. Furthermore, the urgency of treatment and educating the patient's family are crucial to remind each other about taking and carrying medication wherever the patient travels. In the study by Singh J et al. (2021), one of the recommended strategies to improve patient medication adherence is to establish a positive doctor-patient relationship.³⁸ Hence, the doctor's role in communication and building doctor-patient relationships is essential in enhancing medication adherence in epilepsy patients in the future.

CONCLUSION AND SUGGESTION

Among epilepsy patients at the Neurology Clinic of RSUD Sanjiwani, there tends to be a high level of adherence, with 45 individuals (50%), and majority experience uncontrolled seizures, totaling 52 participants (57.8%). Based on the analysis, a significant relationship was found between medication adherence and seizure control among epilepsy patients at the neurology clinic of RSUD Sanjiwani. However, the wide CI value indicates that more samples are needed to make the study more precise. Therefore, it is recommended for future researchers to use a larger sample size to make the research results more representative.

CONFLICT OF INTEREST

The author(s) stated that there is no conflict of interest related to the research, creation, and/or publication of this article.

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