

## Original Research Article

# Anti-epileptic drugs adherence of epilepsy patients in Indonesia

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## ABSTRACT

**Background:** Adherence to medication is an important component of successful epilepsy treatment. However, the disease's long-term treatment makes it difficult to achieve good adherence. This study aimed to assess the adherence level of anti-epileptic drugs (AEDs) among adult epilepsy patients in Indonesia and its associated factors.

**Methods:** We reviewed the medical records of epilepsy patients in a tertiary public hospital between September 2018 and August 2019. Subjects were patients who were electro-clinically diagnosed with any type of epilepsy, have been taken at least one AED for at least three months, have a record of Morisky medication adherence scale 8 items (MMAS-8) score, and aged 20 years old and above. The level of adherence was measured by the MMAS-8 Indonesian version.

**Results:** We found 97 eligible subjects and the majority were males (56.7%), unemployed (69.1%), and aged  $\geq 30$  years old (55.7%). Most subjects (41.2%) showed a high adherence level. The remaining 30.9% and 27.8% had a moderate and low adherence level respectively.

**Conclusions:** This study reveals that high AEDs adherence is associated with being male, younger than 30 years of age, received monotherapy instead of polytherapy, and no memory impairment. A further investigation related to the reason why these factors play roles in the Indonesian setting is important to design appropriate strategies to improve AEDs adherence of epilepsy patients.

**Keywords:** Epilepsy, Anti-epileptic drug adherence, MMAS-8, Indonesia

## INTRODUCTION

Epilepsy is a condition of recurrent epileptic seizures ( $\geq 2$ ) without known direct causes that trigger the events. It was estimated that the annual incidence of this disease in developed countries to be between 40-70 per 100,000 population. The number was higher in resource-limited countries, between 100-190 per 100,000 people.<sup>1,2</sup>

Epilepsy is chronic in nature. This is the reason why most epilepsy cases require long-term anti-epileptic drugs (AEDs) treatment. At a minimum, patients with epilepsy

have to take AEDs for at least three months in which could decrease medication adherence.<sup>3</sup> Adherence to medication is defined by WHO (2003) as 'the degree to which the person's behaviour corresponds with the agreed recommendations from a health care providers'.<sup>4</sup> Past studies show that low education, low economic status, adverse events, difficult access to medication, complicated AEDs regimens, caregiver factors, and negative beliefs about physicians and medications, contribute to low medication adherence. In epilepsy patients, AEDs non-adherence was estimated to be between 30-50%.<sup>5,6</sup>

Adult patients have different medication adherence characteristics in comparison to children. Adults are more independent to decide on whether to take or not the drugs, and older adults tend to have multiple diseases and cognitive decline that could influence their medication adherence. These characteristics influence their adherence to chronic medication, including AEDs. Further, some studies have identified that gender, level of education, and employment status play roles in medication adherence in the adult population.<sup>7,8</sup>

Non-adherence to AEDs has some serious consequences. It reduces the seizure control rate in which can worsen the disease, increases the number of hospital admission and healthcare cost, decreases the quality of life, and even increases the risk of death, including sudden unexpected death in epilepsy (SUDEP).<sup>9,10</sup> Therefore, it is important to explore the level of AEDs adherence in epilepsy patients.

AED medication adherence can be measured directly or indirectly. The direct method can be performed by measuring the drug level using biomarkers. This approach is infrequently used due to the higher cost and the inability to provide feedback at the point of care. Besides, other factors like physiological variability, drug's half-life, medication schedule, and interactions with other drugs or foods might influence the results.<sup>11</sup>

The indirect method can be done through electronic drug monitoring, pill counting and pharmacy refills, medical record review, directly observed therapy, physician's assessment, and patient's self-report. The application of electronic drug monitoring technique is limited by its high cost.<sup>12</sup> The problem of the pill counting technique involves the potential mismatch between the time of refilling the prescription and the actual time when a patient needs the medication. The patients may also not accurately recall the date when their medications started or the drugs may not be stored in their original containers.<sup>13</sup> The self-report technique has a potential risk of response bias but it still provides a reasonably accurate estimate of adherence.<sup>14</sup> Furthermore, this technique could be done briefly, is relatively inexpensive, and applicable in many situations. In self-reporting, the physicians can also provide feedback at the point of care and reveal the underlying problems of the non-adherent patients.<sup>11</sup>

Each method has its own advantages and limitations, thus there is no single method that has been accepted as 'gold standard' for measuring AEDs adherence.<sup>14</sup> In this study, we use the Morisky medication adherence scale eight items (MMAS-8) a self-report measure of medication-taking behaviour designed by Morisky et al.<sup>15</sup> The reason we used this method was some studies have provided evidence of good psychometric properties of the scale.<sup>16</sup> Its advantages are it only requires a short period of time for the patients to answer the questions and it is easy for the healthcare providers (physician, nurse, or pharmacist)

to do the scoring. It also provides information on unintentional (e.g. forgetfulness) or intentional (e.g. concerns about medication side effects) behaviours related to medication to facilitate the recognition of barriers to and behaviours associated with adherence to chronic medications.<sup>17</sup> The tool had been translated and validated in various languages such as Malay, French, Persian, and Indonesian.<sup>17-20</sup>

Our study is aimed to assess the AEDs adherence in adult epilepsy patients who visited the outpatient epilepsy clinic in a hospital in Indonesia.

## METHODS

### *Settings and participants*

This study was conducted in a tertiary referral public hospital, Dr. R. D. Kandou Hospital in Manado, the capital city of North Sulawesi province. This hospital serves as a referral hospital in North Sulawesi and nearby provinces. From September to November 2019, we examined all medical records of epilepsy patients prescribed with AEDs who visited the outpatient epilepsy clinic between September 2018 and August 2019.

We selected the eligible subjects based on these following inclusion criteria: electro-clinically diagnosed with any type of epilepsy, have been taken at least one AED for at least three months, have a record of MMAS-8 score, and aged 20 years old and above. When a patient had more than one MMAS-8 score, we only included the latest one. We divided the available AEDs in this hospital into old and new generations. The old generation is including phenytoin, valproic acid, phenobarbital, carbamazepine, and clobazam; and the new generation is levetiracetam, lamotrigine, zonisamide, and topiramate.

### *Instruments*

AEDs adherence was tested using the validated MMAS-8 Indonesian version.<sup>19</sup> MMAS-8 has a total of eight questions to be answered as 'yes' or 'no', except for the last question. The scoring method is as followed: for questions 1 to 4 and 6 to 7, every 'no' answer is scored as '1' and every 'yes' is scored as '0'. For question 5, it is the other way around. For question 8, the option is formed in a 5 points Likert scale ranged from 'never/rarely' (scored as 1), 'once in a while' (scored as 0.75), 'sometimes' (scored as 0.5), 'usually' (scored as 0.25), and 'all the time' (scored as 0). The total score of this questionnaire ranged from 8 to 0. AEDs adherence was divided into high adherence (score 8), moderate adherence (score 6 to 7), and low adherence (score <6).

### *Data analysis*

The bivariate analysis was made using the statistical package for the social science (SPSS®) version 23 (IBM, Armonk, NY, USA) software. Statistical significance was

tested according to data characteristics. A *p* value of <0.05 was determined as the limit for statistical significance. For categoric variables, we performed a chi-square test for normally distributed data and Fisher exact test for the data that is not distributed normally. For numeric variables, the normality was tested using the Shapiro-Wilk test. Normally distributed data were then analysed using the independent t-test and the data that is not distributed normally were tested using the Mann-Whitney test.

### Ethical approval

Ethical approval was obtained from the Health Research Ethical Committee R.D. Kandou Hospital (ethical approval number 065/EC-KEPK/VI/2019).

## RESULTS

### Characteristic of the subjects

We found 97 eligible subjects included in the study (Table 1). The majority were male (56.7%), unemployed (69.1%) and aged 30 years old or above (55.7%). Clinically, 83.5% were diagnosed with focal epilepsy, 50.5% did not have memory impairments, and 87.6% did not experience any significant adverse event. Related to AEDs, the majority of the subjects used monotherapy (67%), old generation AEDs as first-line treatment (92.8%), and had been taken AEDs for more than a year (52.6%).

### MMAS-8 score

The MMAS-8 score revealed 41.2% subjects showed a high level of adherence in comparison to the 30.9% and 27.8% who had moderate and low adherence levels, respectively. The median value was 7 (1-8) (Table 1).

### Medication adherence

We performed a statistical analysis of each factor to medication adherence using a dichotomous variable high adherence vs moderate to low adherence (Table 2). Our analysis showed that age, gender, memory impairment, and the number of AEDs taken have a significant association with medication adherence. Subjects aged <30 years old have higher adherence compared to ≥30 years old (*p*=0.03). Male gender showed a higher adherence compared to females (*p*=0.03). The use of one AED was related to higher medication adherence compared to >1 AEDs (*p*=0.01). Memory was only assessed in 79 subjects. From this group of subjects, 32 (40.5%) subjects have memory impairment. Having memory impairment was associated with moderate to low medication adherence (*p*=0.02). On the other hand the length of education (*p*=0.67), employment status (*p*=0.87), distance to hospital (*p*=0.29), epilepsy type (*p*=0.44), the use of other medications (*p*=0.18), using old generation of AEDs as first-line (*p*=0.23), using phenytoin (*p*=0.53), the occurrence of significant adverse events (*p*=1), and duration of AEDs (*p*=0.40) did not significantly associated with AEDs adherence.

**Table 1: Socio-demographic and clinical characteristics of the subjects.**

Variables	Category	Number (N)	Percentage (%)	Mean (±2 SD)	Median (min-max)
<b>Total subject</b>	-	97	100	-	-
<b>Age (years)</b>	-	-	-	36.22±14.39	31 (20, 78)
<b>Age group (years)</b>					
	<30	43	44.3	-	-
	≥30	54	55.7	-	-
<b>Gender</b>					
	Male	55	56.7	-	-
	Female	43	44.3	-	-
<b>Length of education (years)</b>	-	-	-	11.5±3.62	12 (1-17)
<b>Employment status</b>					
	Employed	30	30.9	-	-
	Unemployed	67	69.1	-	-
<b>Distance to hospital</b>					
	≤20 km	57	58.8	-	-
	>20 km	40	41.2	-	-
<b>Epilepsy type</b>	Focal	81	83.5	-	-
	General	16	16.5	-	-
	Not specific	0	0	-	-
<b>Memory impairment<sup>a</sup></b>	Yes	30	30.9	-	-
	No	49	50.5	-	-
	Not tested	18	18.6	-	-

Continued.

Variables	Category	Number (N)	Percentage (%)	Mean ( $\pm 2$ SD)	Median (min-max)
<b>Concomitant medication<sup>b</sup></b>					
Yes		57	58.8	-	-
No		40	41.2	-	-
<b>Significant adverse events<sup>c</sup></b>					
Yes		12	12.4	-	-
No		85	87.6	-	-
<b>Numbers of AEDs taken</b>					
1		65	67	-	-
2		29	29.9	-	-
3		3	3.1	-	-
<b>Using old generation AEDs as the first-line</b>					
Yes		90	92.8	-	-
No		7	7.2	-	-
<b>Using phenytoin</b>					
Yes		57	58.8	-	-
No		40	41.2	-	-
<b>Duration of AEDs (months)</b>					
$\leq 12$ months		46	47.4	-	-
$> 12$ months		51	52.6	-	-
<b>Adherence</b>					
MMAS-8 score	-	-	-	6.34 $\pm$ 1.86	7 (1, 8)
<b>Level of adherence</b>					
High		40	41.2	-	-
Moderate		30	30.9	-	-
Low		27	27.8	-	-

<sup>a</sup>Memory was tested as part of the Montreal Cognitive Assessment Indonesian Version (Ina-MoCA); <sup>b</sup>Concomitant medications were defined as prescribed medication as recorded in the medical records; <sup>c</sup>Significant adverse events were defined as any medical condition that is life-threatening, causing disability, and or causing hospital admission, that happened after the administration of the drug at any dose.

**Table 2: Medication adherence of the subjects.**

Variables	High				Moderate to low				P value
	No.	%	Mean $\pm$ SD	Median (min-max)	No.	%	Mean $\pm$ SD	Median (min-max)	
<b>Age (years)</b>	-	-	27.92 $\pm$ 14.55	24 (12, 68)	-	-	33.54 $\pm$ 15.71	31 (12,78)	0.01
<b>Age group (years)</b>									
$< 30$	23	23.7	-	-	20	20.6	-	-	0.03
$\geq 30$	17	17.5	-	-	37	38.1	-	-	
<b>Gender</b>									
Male	28	28.9	-	*	27	27.8	-	-	0.03
Female	12	12.4	-	*	30	30.9	-	-	
Length of education (years)	-	-	11.07 $\pm$ 3.59	12 (0, 17)	-	-	10.93 $\pm$ 3.39	12 (2, 17)	0.67
<b>Employment status</b>									
Employed	12	12.4	-	-	18	18.6	-	-	0.87
Unemployed	28	28.9	-	-	39	40.2	-	-	
<b>Distance to hospital</b>									
$\leq 20$ km	21	21.6	-	-	36	37.1	-	-	0.29
$> 20$ km	19	19.6	-	-	21	21.6	-	-	
<b>Epilepsy type</b>									
Focal	32	33	-	-	49	50.5	-	-	0.44
Non-focal	8	8.2	-	-	8	8.2	-	-	

Continued.

Variables	High				Moderate to low				
	No.	%	Mean±SD	Median (min-max)	No.	%	Mean ±SD	Median (min-max)	P value
Memory impairment (n=79)									
Yes	7	8.9	-	-	23	29.1	-	-	0.02
No	25	31.6	-	-	24	30.4	-	-	
Concomitant medication									
Yes	6	6.2	-	-	15	15.5	-	-	0.18
No	34	35.1	-	-	42	43.3	-	-	
Significant adverse events									
Yes	5	5.2	-	-	7	7.2	-	-	1
No	35	36.1	-	-	50	51.5	-	-	
Using old generation AEDs as first-line									
Yes	39	40.2	-	-	51	52.6	-	-	0.23
No	1	1.0	-	-	6	6.2	-	-	
Numbers of AEDs taken									
1	21	21.6	-	-	44	45.4	-	-	0.01
≥2	19	19.6	-	-	13	13.4	-	-	
Using phenytoin									
Yes	22	22.7	-	-	35	36.1	-	-	0.53
No	18	18.6	-	-	22	22.7	-	-	
Duration of AEDs (months)									
≤12	21	21.6	-	-	25	25.8	-	-	0.40
>12	19	19.6	-	-	32	33	-	-	

## DISCUSSION

Our study aims to assess the AEDs adherence of epilepsy patients who visited the outpatient epilepsy clinic in a tertiary referral public hospital in Indonesia using MMAS-8. We found age, gender, memory impairment, and the number of AEDs taken significantly associated with AEDs adherence.

A concave pattern of medication adherence has been identified in an overview of systematic reviews of medication adherence by Gast and Mathes.<sup>21</sup> Subjects who are too young or too old generally will have decreased adherence. However, Modi et al have shown that among epilepsy patients, the adherence of younger patients was more affected by other factors such as socioeconomic status and marital status of their parents.<sup>22</sup> Buck et al found that teenagers have a low level of adherence in the general population while Shetty et al found that among children aged ≤16 years old, increasing age was related to declined adherence.<sup>5,23</sup>

In our study, we found that high adherence was significantly associated with subjects in the age between 20 and <30 years old. This finding is similar to a cross-sectional study in India that included patients aged 18-60 years old. This study found the rate of adherence was the highest among participants aged 18-29 years old.<sup>24</sup> These findings, however, are contrary to Malek et al review that identified age <30 years old as an associated factor for non-adherence.<sup>6</sup> Ferrari et al study in Brazil also showed that a higher mean age is associated with high adherence.

This Brazilian study concluded 42.4 is the mean age for high adherence and 38.2 was the mean age for moderate-low adherence.<sup>25</sup> One study in Sudan found the eldest group (49-59 years old) was significantly the least adherent.<sup>26</sup> This is in-line with two studies in the United States which concluded that patients aged ≥65 years old were more likely to be non-adherent.<sup>8,27</sup>

Male subjects in our study significantly had higher adherence than the female ones. This finding is consistent with the study by Piper et al but contradictory with the study by Ferrari, et al where they found females were more adherent than males.<sup>8,25</sup> Nevertheless, other studies did not find a significant relationship between gender and adherence.<sup>28,29</sup>

The presence of memory impairment was found to be related to moderate to low medication adherence in our study. Forgetfulness and intellectual disability are associated with non-adherence in some studies as reviewed by Malek, et al and in a cross-sectional study among adult patients by Niriayo et al.<sup>6,30</sup> Nevertheless, McAuley et al found that objective memory measures were not strongly correlated with adherence and that depression was more likely to be correlated with non-adherence in their study.<sup>31</sup> Memory was not routinely assessed in our subjects so we advise a routine neurobehavioral examination that can assess memory impairment to be used in all epilepsy patients. Assistive tools or caregivers should be encouraged when the patient has memory impairment.



The AED monotherapy was associated with high adherence in this study. Monotherapy is associated with an easier effort to remember the pills taken and also fewer adverse event and this contributed to higher adherence.<sup>5,6</sup> Some studies have confirmed that complicated AEDs regimens, including polytherapy, contributed to non-adherence.<sup>6,32</sup> The finding in this study contrasted with our previous study that was looking at the AEDs adherence in both children and adults. In that study, subjects with polytherapy had higher adherence than those with monotherapy.<sup>33</sup> However, in that study, we found that seizure control was better in subjects with polytherapy. This might be related to the different results. Buck et al also found that polytherapy was associated with good adherence and provided a similar argument.<sup>5</sup>

Factors that showed no significant association with adherence in our study were the length of education, employment status, access to the hospital, epilepsy type, concomitant medication, significant adverse events, using old generation AEDs as the first-line, using phenytoin, and duration of AEDs. A cross-sectional study from USA found that high educational attainment contributed to high adherence.<sup>7</sup> Malek, et al also identified low educational attainment as a factor associated with medication non-adherence in epilepsy based on their review.<sup>6</sup> On the contrary, a study from the lao people's democratic republic showed that illiteracy was significantly associate with high adherence. In that study, the authors argued that this was due to the low concern of medication side effects by illiterate patients.<sup>34</sup> However, many studies suggested that education was mostly not considered to be significant to medication adherence among epilepsy patients.<sup>28,29</sup>

Being unemployed was an associated factor in medication non-adherence based on the review by Malek, et al and a cross-sectional study among adults by Paschal et al. Unemployment could lead to adverse socioeconomic and psychological factors like financial difficulty in purchasing medication, depression, anxiety, and low confidence.<sup>6,7</sup> These could contribute to non-adherence. However, other study failed to find this association.<sup>28</sup> Our study also did not find a significant association between employment status and adherence.

Related to epilepsy type, the majority of our subjects were diagnosed with focal epilepsy spectrum. This finding is similar to the results from studies that mostly use both clinical and EEG information to establish the diagnosis.<sup>35</sup> Epilepsy type in our study did not associate with adherence which is in-line with other studies.<sup>29,36</sup> However, in the adult population, one cross-sectional study also found an association between focal epilepsy with non-adherence.<sup>29</sup>

The use of other drugs besides AEDs was not associated with AEDs adherence. This is similar to the study by Paschal, et al.<sup>7,23</sup> The occurrence of significant adverse events also did not associate with adherence in our study

but the occurrence only found in 13 subjects (10.3%) and difficult to be interpreted. Further study should be made in larger subjects to study the types of significant adverse events they had and the received treatments.

Using old generation AEDs as the first-line was not an influencing factor for medication adherence in this study. This finding is similar to another study by Harimanana et al.<sup>29</sup> On the other hand, we found a retrospective study in adult population by Gollwitzer et al that found newer AEDs were linked to better adherence.<sup>37</sup>

In our study, 55.4% of the subjects were using phenytoin as monotherapy or in combination with other drugs even though phenytoin is linked to the occurrence of higher adverse events in epilepsy patients as shown by a study in the same hospital.<sup>38</sup> Despite the higher use of phenytoin, our study found very low significant adverse effects. This might because the level of adverse events related to this drug is mostly mild to moderate or can be tolerated by most of the patients.<sup>39</sup> Subjects using AEDs for a longer period tend to lose their adherence according to previous study.<sup>40</sup> However, this is not consistent with other studies that failed to find the association.<sup>25,32</sup> This pattern was also not found in our study.

### Limitations

There are two limitations to this study. First, patients cannot always accurately remember the definite answers of each item asked in the questionnaire and patients may give better answers to satisfy the physician. To minimize this limitation, we trained the physicians to encourage honest answers from the patients and give the patients sufficient time to think or modify the answer. Second, the data were obtained through non-electronic medical records and not linked to the pharmacy's drug records. Thus, we could not triangulate the AEDs adherence through this method.

### CONCLUSION

In conclusion, we used a validated Indonesian version of MMAS-8 to obtain data on AEDs adherence in epilepsy patients in a tertiary public hospital in Indonesia. From our data, factors that are associated with high AED adherence are being male, younger than 30 years of age, received monotherapy instead of polytherapy, and no memory impairment. A further investigation related to the reason why these factors play roles in the Indonesian setting is important to design appropriate strategies to improve AEDs adherence of epilepsy patients.

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