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Association of side effects to medication adherence of antiepileptic drug use in epileptic patients

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ABSTRACT: Epilepsy is a chronic neurological disorder with symptoms characterized by seizures, arising spontaneously with brief episodes with the main symptom of decreased or loss of consciousness. This study aims to examine the effect of side effects of medication adherence to antiepileptic drug use in epilepsy patients. This research is an observational study that was analyzed using quantitative descriptive methods in Neurology patients at the Airlangga University Hospital from March until May 2022. Side effects were measured using the LAEP (Liverpool Adverse Effects Profile) questionnaire and adherence was measured using a pill count. Results showed that the influence of side effects on medication adherence (pill count method) to antiepileptic drugs using linear regression, it is known that the *P*-value is 0.501. There is no significant relationship between the category of side effects and medication adherence to antiepileptic drugs. Another factor that influences compliance with medication use is the appearance of seizures. Based on the results of this study, it is known that the greater the frequency of seizures, the more likely patients are to be non-compliant (*P*-value 0.006). To increase adherence, it is necessary to pay attention to other factors such as knowledge, economy, and type of therapy in epilepsy patients so that therapeutic outcomes can be achieved.

KEYWORDS: Adverse event, antiepileptic drug, compliance.

INTRODUCTION

Epilepsy is a chronic neurological disorder with typical symptoms characterized by epileptic seizures, arising spontaneously with short episodes with the main symptom of decreased consciousness until it disappears [1]. Epileptic conditions occur when seizures are unprovoked with symptoms of recurrent seizures without improvement in each seizure episode [1],[2]. Epilepsy can be primary or spontaneous which usually occurs in childhood and has a genetic predisposition. The onset of seizures in adults usually occurs due to hypoxemia, head injury, infection, stroke, or tumors of the central nervous system [3]. According to the World Health Organization (WHO) an estimated 50 million people in the world are currently diagnosed with epilepsy, and around 40 million are in developing countries [4]. In 2019, data on the prevalence of epilepsy in high-income countries ranged from 49 per 100,000 people, while in low and middle-income countries, this figure could reach 139 per 100,000 people [5]. One of the treatments for epilepsy patients is using AED (Anti-Epilepsy Drugs), where the use of AED reduced the incidence of seizures by as much as 67% [6]. One of the important things in the use of antiepileptic drugs in patients with epilepsy that affects the outcome of seizure control and remission is the level of adherence to drug use. Patients who use it regularly for 6 to 24 months have better seizure control and seizure remission than those who do not adhere to using AED [7]. Medication adherence is a person's obedience to directions regarding the rules for use and how to use drugs given to health practitioners (physician or pharmacist) [8].

Medication adherence in epilepsy patients is determined by many factors such as socioeconomic factors and type of epilepsy [9]. Other studies showed that non-adherence was influenced by the emergence of side effects from the use of antiepileptic drugs for a long time [10]. Low adherence is found in many patients who experience side effects including nervousness and aggressive conditions that lead to depression, which is around 52.7% [11]. A study conducted by Hovinga et al. [12], found that non-adherence accounted for only 29% of seizure control. This is understandable because many factors can trigger seizures and non-adherence is only one of them [13]. Based on this background, researchers wanted to know how the relationship between

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side effects and adherence to the use of antiepileptic drugs in epilepsy patients.

MATERIALS AND METHODS

Materials

This study was an observational study that was analyzed using quantitative descriptive methods. This research is prospective observations using data obtained from medical records and interviews with Neurology Polyclinic patients at Airlangga University Hospital (RSUA). This research has received ethical clearance from the Airlangga University Hospital ethical committee with document numbers 008/KEP/2022 and 009/KEP/2022.

The research was carried out at the Neurology Polyclinic at Airlangga University Hospital with data collection carried out from March to May 2022. The research sample in this study should comply with inclusion criteria.

Inclusion criteria

a) Adult patients aged 18 to 60 years who are registered at the Neurology Polyclinic at Airlangga University Hospital.
b) Patients with a diagnosis of epilepsy
c) The patient is receiving anti-epileptic drugs.

Exclusion criteria

a) Patients who are receiving AED for the first time

The sample size in this study was calculated using total sampling from the time of data collection.

Methods

Data collection technique

Data were carried out through the following stages:

1. Collecting patient data according to the inclusion criteria,
2. Ensuring that the patients were fully informed and comfortable with the process. The patients were asked to sign an informed consent and provide them with additional information for their consent
3. Collecting the data in the first month in the form of:
   a) Medical record number.
   b) Patient identity (name, age, sex, date of birth, diagnosis, and weight)
   c) arrival date
   d) Diagnosis of patient type of drug.
   e) Data on the use of other drugs (name of the drug, drug dosage, amount of drug, dosage form, frequency of use, and date of administration).
4. In the following month the patients were given a paper containing the LAEP side effect profile and interviewed about remaining drugs (pill count) then it was expected that the patients could fill it out individually.
5. The LAEP questionnaire was assessed based on the total score obtained, a higher score indicates a more severe side effect reaction.

Side Effects were measured using LAEP (Liverpool Adverse Effects Profile). LAEP Indonesian version was translated and adapted by Budikayanti et al. [14], in 2016 culturally according to WHO standard guidelines. The final version of the Indonesian LAEP was obtained and considered as valid and reliable because the translated and adapted questionnaires were also validated. A questionnaire assessment was carried out to determine the consistency and feasibility of the questionnaire. All 19 items are valid and reliable

with a correlation coefficient ranging from 0.456 to 0.690 (moderate to strong correlation) and a significance level of less than 0.01 [14]. The internal consistency of the overall score as measured by Cronbach's alpha coefficient is 0.846. The prevalence of side effects in the study was 91%. Cognitive complaints, emotional complaints, weight changes, and hair loss tend to be ignored by patients and are not considered a special problem. Therefore, the use of a structured self-screening instrument is necessary to determine the prevalence of side effects [10].

▪ RESULTS

This research is a cross-sectional observational study to evaluate the relationship between side effects and adherence to drug use which was measured using the pill count method. Pill count is a measurement of adherence to drug use which is carried out by calculating the remaining drug [15]. In this study, 30 research respondents were patients diagnosed with epilepsy who used antiepileptic drugs. Data showed that the majority have side effects with an LAEP score between 20-38 (side effects that appeared 3 days in the last 4 weeks) (Figure 1).

Table 1. Distribution of research subject characteristics.

Patient characteristics	N (amount)	Percentages (%)	*P- value*
Gender			0.129
Male	19	63.3	
Female	11	36.7	
Age (years)			0.638
17-25	10	33.3	
26-35	6	20.0	
36-45	4	13.3	
46-55	7	23.3	
56-59	3	10.0	
Educational background			0.365
Elementary School	1	3.3	
Junior High School	4	13.3	
Senior High School	19	63.3	
Diploma degree	2	6.7	
Bachelor's degree	4	13.3	
Diagnose			0.065
Epilepsy +Stroke Infarc	5	16.7	
Epilepsy + Hypertension	1	3.3	
Epilepsy (without comorbids)	24	80	
Duration of epilepsy (years)			0.221
≤1	7	23.3	
2-10	21	70.0	
≥10	2	6.7	
Type of therapy			0.742
Monotherapy	27	90.0	
Polytherapy	3	10.0	
Duration of therapy (years)			0.746
< 1	6	20.0	
≥ 1	24	80.0	
Seizure (in one last a month)			0.006
Yes	8	26.67	
No	22	73.33	
Medication adherence (pill count)			
adherents (90-100%)	21	70	-
Non-adherents (<90%)	9	30	

The level of adherence was found at percentage of 90-100% (Table 1). In thisstudy, epilepsy patients used the antiepileptic drug Phenytoin (60%) and type of therapy is monotherapy (90%) (Table 2). Data also showed that in general patients experienced side effects (86.7%) with the most common side effectbeing fatigue (Table 3).

Table 2. Data on the use of anti-epileptic drugs.

No	Antiepileptic Drugs	N (amount)	Percentages (%)
1	Phenytoin 100 mg	18	60.0
2	Divalproex Sodium ER 500 mg	6	20.0
3	Divalproex sodium 250 mg	2	6.7
4	Divalproex Sodium ER 250 mg	1	3.3
5	Divalproex Sodium 250 mg +Clobazam 100 mg	1	3.3
6	Phenytoin 100 mg + clobazam 10 mg	1	3.3
7	Phenytoin 100 mg +Divalproex sodium ER 500 mg	1	3.3

Table 3. Prevalence of adverse events (using LAEP Questionnaire).

No	Adverse Events (AE)	N	Percentages (%)
1	Presence AE	26	86.7
2	No Presence AE	4	13.3

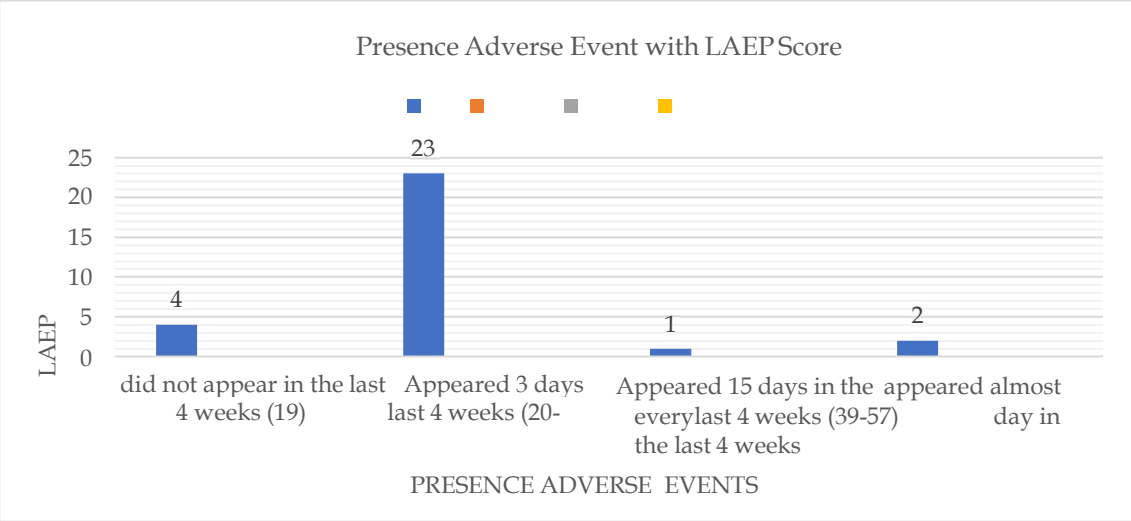

Figure 1. Presence adverse events in epileptic patient.

DISCUSSION

Non-adherence to take medication can be intentional or unintentional. Several factors affect medication adherence such as side effects, dosage regimens, daily doses, the lack of drug efficacy, social stigma, and costs. The forms of non-adherence to the medication include not adding medication when the drug runs out, stopping self-medication, forgetting to take medication, and taking medication not according to the schedule [13],[16]. Failure to control seizures is strongly influenced by disease factors such as the type of seizure, the presence or absence of comorbidities, and non-adherence to treatment. The occurrence of seizures/seizures can be influenced by several other factors including the presence or absence of trauma, fractures, and psychological problems (depression, anxiety, decreased quality of life) [13]. Medication adherence is one of the factors that can support the success of therapy, and conversely, non-adherence is one of the problems that arise in the treatment of epilepsy patients [17]. Monitoring adherence is very important in epilepsy patients. Non-adherence of epilepsy patients to medication leads to uncontrolled seizures, and suboptimal doses of antiepileptic drugs, and this also leads to drug resistance in epilepsy patients [18].

Side effects are major problems that often occur in the use of antiepileptic drugs which significantly reduce the quality of life of epilepsy patients [17]. Side effects that often occur in the therapeutic management of epilepsy patients include those due to idiosyncratic, neurocognitive reactions related to dose and effects or complications of long-term use [19],[20]. Consideration of side effects greatly influence the selection of drugs in the management of epilepsy therapy [21],[22]. The presence of side effects also affects the success of therapy. Patients who experience side effects affect adherence to drug use and discontinuing treatment hinders the success of therapy [23],[24]. Therapeutic efficacy in the therapeutic management of epilepsy patients is being able to control seizures and improve quality of life without side effects [20]. Reporting of side effects on long-term medication such as epilepsy is needed, to explore what problems from the consumption [25]. Monitoring side effects and adherence are some of the things that pharmacists should do in the management of epilepsy patient therapy that focuses on patient health and safety[26].

The relationship between the presence of side effects and compliance with medication use (pill counting method) which was carried out using binary logistic regression obtained results that were not statistically significant with a P-value of 0.501. There is no significant relationship between the category of side effects of using antiepileptic drugs and the level of adherence. The results of this study are in line with previous research by Das et al.[27], that the presence of side effects does not have a significant effect on adherence. However, Elsayed et al. [10] reported that side effects in the use of antiepileptic drugs have a significant effect on adherence to drug use (*P*- value=0.000). Indicators of poor adherence will help clinicians to identify patients most in need of interventions to improve adherence. This indicator can identify factors that affect adherence including depression, cognitive impairment, side effects, lack of confidence in the benefits of treatment, lack of patient understanding of the disease, poor relationship between health workers and patients, or the presence of other barriers to care and treatment, the complexity of treatment, and medical expenses [10],[28],[29],[30].

In another study by Sunny *et al*. [31], it is known that the use of anti-seizure drugs hasan incidence of side effects of around 29.9% with the majority experiencing side effects of drowsiness and weight gain. The existence of side effects influences negative behavior in non-adherence with drug use [31]. Side effects also increase in the use of combination drugs (polytherapy) and affect increasing non-adherence with drug use [32]. In this study, the factor that affected adherence was the presence of seizures, whereas the frequency of seizures increased, patients tended to be disobedient. The results of this study are in line with previous research by Gabr *et al*. (33) and a review article by Ernawati *et al.* [13], that the high presence of seizures is in line with non-adherence in drug use. The weakness of this research is that it did not examine factors that influence compliance with drug use, including economic factors. Another factor that affects adherence is related to economic factors, where some patients experience economic difficulties, so they do not take back/refill drugs [34].

CONCLUSION

There was no significant relationship between the categories of side effects of antiepileptic drug use and medication adherence (pill count method). The factor that affected adherence was the presence of seizures, where the more convulsions, the more disobedient the patients. To improve adherence, it is necessary to pay attention to the factors that influence adherence, especiallyin epilepsy patients so that therapeutic outcomes can be achieved.

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