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The Relationship between Antiseizure Medications and Sleep Quality Among Epilepsy Patients: A Cross-Sectional Study

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Abstract

Background: Poor sleep quality and sleep deprivation provoke *epileptic seizures*, and sleep-related epilepsy and antiseizure medications (ASMs) affect sleep quality. There is still a limited study exploring the relationship between ASM consumption and the sleep quality of epilepsy patients in developing countries, and this study will be the first one conducted in Indonesia.

Methods: This cross-sectional study was conducted from April to June 2023. Subjects were patients aged 18-65 years old, electro-clinically diagnosed with any epilepsy, who had taken at least one ASM. They were seizure-free for at least three months, without a history of anxiety, depression, poor sleep hygiene, or medication adherence. Sleep quality is measured using the *Pittsburgh Sleep Quality Index* (PSQI). The *Fisher-exact* test is used to analyze the association. A p-value of <0.05 is considered statistically significant.

Results: A total of 64 subjects were included, consisting of 33 males (51.6%), with a median age of 37.8 ± 13.8 years. Poor sleep quality was found in 24 subjects (37.5%) with a median PSQI score of 4.8. Older-generation ASMs (p = 0.023), polytherapy (p = 0.02), and ASM use for less than 1 year (p = 0.003) were significantly associated with poor sleep quality.

Conclusions: ASM type, consumption duration, and the number of ASMs are significantly associated with sleep quality. Therefore, routine evaluation of sleep quality and appropriate ASM is recommended for epilepsy patients.

Conclusion: The study will be useful while performing surgical procedures around the axis vertebrae to prevent injury to vital structures.

Keywords: Sleep quality; PSQI; ASM; Epilepsy; Indonesia.

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Introduction

Epilepsy is one of the most common neurological diseases. The International League Against Epilepsy (ILAE) defines epilepsy as a brain disorder characterized by a continuous tendency to produce epileptic seizures with neurobiological, cognitive, psychological, and social consequences.[1,2]

More than half of the 50 million epilepsy patients are estimated to reside in Asia, and Indonesia alone has a yearly estimated number of new epilepsy cases at 250,000, with a prevalence of 0.5-4%. Antiseizure medication (ASM) is still used as the main epilepsy treatment with various adverse effects, including poor sleep quality, which worsens seizure control.[1,2]

Several previous studies have examined the effects of various antiseizure medications (ASMs) on sleep microstructure. Based on several studies in adult patients, ASMs can alter sleep microstructure and reduce sleep quality.[3,4] Some studies indicate that older-generation ASMs, such as Phenytoin, Valproic Acid, and Carbamazepine, have a worse impact on sleep compared to newer-generation ASMs.[4,5] Nonetheless, the use of these older-generation ASMs still dominates the choice of ASMs in daily practice in Indonesia.

The number and duration of ASM use also tend to affect the sleep phase. One study showed that polytherapy is an independent factor for the occurrence of excessive daytime sleep (EDS) in epilepsy patients (p <0.05).[6] The decrease in sleep quality is known to have a bidirectional relationship, leading to an increased risk of seizures, which can

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further deteriorate the sleep quality of individuals with epilepsy. Approximately 42.7% of patients with epilepsy have been reported to have poor sleep quality; furthermore, excessive daytime sleepiness (EDS) has also been reported in 24% of subjects.[5]

However, there is still a limited study exploring the relationship between ASM consumption from various aspects (type, quantity, and duration) and the sleep quality of epilepsy patients in Indonesia.

Some studies still include sedative medications and do not exclude psychological factors (depression and anxiety) affecting sleep quality. Therefore, this study aims to determine the relationship between the use of ASMs and sleep quality in epilepsy patients.

Materials and Methods

This cross-sectional study was conducted at the Neurology Clinic of Prof. Dr. R. D. Kandou Central General Hospital in Manado, the capital city of North Sulawesi. This hospital serves as a referral hospital in North Sulawesi and nearby provinces.

We included subjects who met the inclusion and exclusion criteria during the study period, with a minimum required sample size of 59 subjects, as formulated by the Lemeshow method using the non-random, consecutive sampling method. Patients diagnosed with epilepsy clinically according to ILAE criteria and electroencephalographic findings, aged ≥ 18 years and < 65 years, cooperative during the examination, willing to participate in the study, stable ASM consumption, and being seizure-free for at least the last three months were included in this study. We excluded patients taking stimulant or sedative drugs (including clobazam), experiencing nocturnal epilepsy, working night shifts, experiencing depression and anxiety, having poor sleep hygiene, pregnant, low medication adherence, and patients with a history of progressive intracranial lesions, dementia, and/or Parkinson's disease. In order to determine the exclusion criteria for depressive symptoms, anxiety, low medication adherence, and poor sleep hygiene, we used several questionnaires: depressive symptoms were assessed using the Indonesian version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) questionnaire; a total score of >15 is considered positive for depressive symptoms.[7] Anxiety was assessed using the Indonesian version of the General Anxiety Disorder-7 (GAD-7), in which a total score of >6 is considered anxiety.[8] Nonadherence ASM consumption was assessed using the Morisky Green Levine Medication Adherence Scale (MGLS), in which a score of 3-4 is considered nonadherence.[9] Finally, poor sleep hygiene was assessed using the Indonesian version of the Sleep Hygiene Index (SHI), in which subjects with a score of over 27 are considered moderate or severe.[10] In summary, we included subjects with an NDDI-E score of <15 (no depressive symptoms), a GAD-7 score of <6 (no anxiety), an MGLS score of 0-2 (good medication adherence), and an SHI score of 13-27 (good sleep hygiene).

Demographic data, including age, sex, and working status, were collected. Clinical characteristics included epilepsy syndrome, etiology, type of ASM used, sleep quality, duration of treatment, duration of seizure-free period, and number of ASMs used. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), with a score>5 indicating poor sleep quality.[11] Every questionnaire used is validated in Indonesian.

Data on ASM types were grouped into old-generation ASMs (phenytoin, valproic acid, and carbamazepine) and new-generation ASMs (Levetiracetam). The ASMs were divided into monotherapy and polytherapy (>1 ASM type). Furthermore, the duration of consumption was categorized into >1 year and >3 months-1 year. The relationships among the type, number, and consumption duration of ASMs and sleep quality were analyzed.

Data were presented as frequency and percentage. The association between new- and old-generation ASM, the number of ASM, treatment duration, and sleep quality was assessed using Fisher's Exact test. A p-value of <0.05 was determined as the limit for statistical significance. The analysis was conducted using SPSS.

Results

A total of 64 participants were included in the study. Among participants, 33 (51.6%) subjects were male, with a mean age of 37.8 ± 13.8 years (Table 1).

The most common type of epilepsy found was temporal lobe epilepsy in 32 subjects (50%), with no cases of generalized epilepsy identified. Intracranial lesions as the etiology of epilepsy were found in 28 subjects (43.8%). The median PSQI score was 4.8, with 40 subjects (62.2%) having good sleep quality. Regarding the treatment regimen, 58 (90.6%) subjects were on monotherapy, with phenytoin as the most commonly used drug, followed by Levetiracetam. The median treatment duration was 24 months (IQR 36.0), with 41 subjects (64,1%) having treatment for more than one year (Table 1)

The most commonly used medication was phenytoin in 29 subjects (45.3%) (Table 1). Table 2 shows the distribution of sleep quality among ASMs users and its relationship. This study indicates that the highest percentage of poor sleep quality is mostly found in subjects using phenytoin (41.4%). However, subjects with carbamazepine also have a high percentage of poor sleep quality (50%), although the total subjects are lower than those with phenytoin (12 subjects vs. 29 subjects). This study also demonstrates that patients consuming old-generation ASMs (phenytoin, valproic acid, and

carbamazepine) were significantly associated with poor sleep quality and were nine times more likely to have poor sleep quality (p = 0.023, OR=9.0, 95% CI: 1.079-75.05) (Table 3).

Our results indicate a significant relationship between sleep quality and the total ASMs used (p = 0.024, OR=10.26, 95% CI: 1.19-94.11) (Table 3), in which poor sleep quality is associated with polytherapy.

Table 1. Characteristics of the subjects.

Characteristics	N = 64 (%)
Gender	
- Male	31 (48.4)
- Female	33 (51.6)
Age (year)	
Mean ± SD	37.8 ± 13.8
Seizure-free duration (month)	
Median ± SD	12 (IQR 20.0)
Epilepsy syndrome	
- Temporal lobe	32 (50)
- Frontal lobe	16 (25)
- Parietal lobe	11 (17.2)
- Occipital lobe	7 (10.9)
- Generalized	0 (0)
Epilepsy etiology	
- Stroke/ vascular malformation	10 (15.6)
- Intracranial tumor	9 (14.1)
- Trauma	6 (9.37)
- Infection	2 (3.12)
- Hippocampal sclerosis	1 (1.56)
- Unknown	36 (56.25)
Sleep Quality	
- Poor	24 (37.5)
- Good	40 (62.2)
Median PSQI	4.8 (IQR 3.0)
Medication	
- Phenytoin	29 (45.3)
- Carbamazepine	12 (18.8)
- Valproic acid	3 (4.7)
- Levetiracetam	14 (21.0)
- Phenytoin – Levetiracetam	2 (3.1)
- Levetiracetam- carbamazepine	3 (4.7)

Table 2. The distribution of sleep quality in the use of ASMs.

ASM type	Sleep Quality		Total (n)
	Good (%) (n=39)	Poor (%) (n=19)	
Phenytoin	17 (58.6)	12 (41.4)	29
Carbamazepine	6 (50)	6 (50)	12
Valproic acid	3 (100)	0 (0)	3
Levetiracetam	13 (92.9)	1 (7.1)	14

ASM, antiseizure medication

The duration of ASM consumption is also significantly associated with sleep quality (p = 0.003, OR = 5.6, CI: 1.82-17.2), with shorter durations (>3 months - 1 year) linked to poor sleep quality. This result indicates that patients with shorter ASM consumption duration were 5.6 times more likely to develop poor sleep quality (Table 3).

Table 3. The association between new- and old-generation ASM, number of ASM, duration of treatment and sleep quality.

Variable	Sleep Quality		P *value*	OR (95%CI)
	Good (%) (n=39)	Poor (%) (n=19)		
ASM Generation				
New generation	13 (33.3)	1 (5.3)	0.023	9.0 (1.079-75.05)
Old generation	26 (66.67)	18 (94.7)		
Number of ASM				
Monotherapy	39 (97.5)	19 (79.2)	0.024	10.26 (1.19-94.11)
Polytherapy	1 (2.5)	5 (20.8)		
Duration of treatment				
>1 year	32 (80)	10 (41.67)	0.003	5.6 (1.82-17.2)
>3 months – 1 year	8 (20)	14 (58.33)		

Discussion

This study aims to assess the relationship between ASM consumption and sleep quality in epilepsy patients, including ASM type, number of ASMs, and treatment duration, who visited the outpatient epilepsy clinic at a tertiary referral public hospital in Indonesia, using the PSQI. We found that older-generation ASM, polytherapy, and shorter ASM consumption duration were associated with poor sleep quality.

In this study, the majority of subjects (55.7%) were males. This aligns with previous research findings suggesting that there is a greater capacity for managing intra-hemispheric neuronal communication in male brains, potentially contributing to the higher incidence of focal epilepsies diagnosed in men.[12] The mean age of the participants was 37.8 ± 13.8 years. In developing countries, children and young adults have a higher rate of epilepsy, while the elderly populations have a lower incidence rate.[13]

Clinical characteristics showed that focal epilepsy is the most common kind of epilepsy observed in the adult population. While it is possible to identify an etiologic agent, approximately 50% of epilepsy cases (17.5 instances per 100,000 per year) have unknown origins and exhibit a varied hereditary propensity to seizures,[14] as supported by the findings of this study (56.25%).[14–16] The main etiology of epilepsy in this study is intracranial lesions due to stroke or vascular malformation. This aligns with a prior study, which also identified stroke as the most prevalent factor contributing to seizures and epilepsy in older adults.[17] In this study, 62.2% of subjects had good sleep quality with a median PSQI score of 4.8; similar to other studies, epilepsy patients tend to have higher PSQI scores but still within normal limits. Factors that affected sleep quality other than ASM use in epilepsy patients were uncontrolled seizures, progressive intracranial lesions, neurodegenerative disease (dementia or Parkinson's disease), and a history of anxiety and depression, which were excluded from this study.[18]

The majority of participants in this study used phenytoin as their antiseizure medication (ASM) monotherapy, accounting for 45.3% of the sample. Phenytoin, an example of an old-generation ASM, continues to be extensively prescribed for the treatment of focal epilepsy in Indonesia due to its availability and coverage by the national health insurance.[16,19] In addition, our hospital was only provided with national health insurance coverage for a limited range of new-generation ASMs, with Levetiracetam among the medications included with constant availability. In this study, the use of Levetiracetam was the second-highest. In particular, 43.25% of the participants included in this study were diagnosed with focal symptomatic epilepsy, among which 32.8% of the cases were attributed to stroke, intracranial tumor, and infection. Levetiracetam is considered to be one of the recommended new-generation ASMs for such cases, with minimal drug interactions with other medications [20].

Previous studies have demonstrated that patients who use older ASMs are more likely to have poor sleep quality.[4,5,21] The present study also demonstrates a significant association between older-generation ASMs and poor sleep quality (p = 0.023, OR 9.0, 95% CI 1.079-75.05).

Old-generation ASMs have a more detrimental effect on sleep compared to newer-generation drugs. These older ASMs tend to decrease the duration of both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep phases.[21]

Old-generation ASMs in this study (i.e., phenytoin and carbamazepine) are sodium channel blockers. The antiseizure effects of sodium channel blockers are attributed to their ability to bind to and prolong the inactive state of sodium channels in cellular membranes. In addition, these ASMs are involved in inhibiting glutamate neurotransmitter release.[22] Sodium channel blockers have been reported to decrease the amounts of extracellular glutamate as well as the concentration of glutamate within the synaptic cleft. The decrease in glutamate levels not only reduces seizures but also contributes to decreased wakefulness.[23]

New-generation ASMs contain positive allosteric modulators (PAMs) that exhibit a greater degree of selectivity in inhibiting the breakdown of gamma-aminobutyric acid (GABA) compared to earlier versions of ASMs, which functioned as GABA receptor agonists and GABA transporter (GAT-1) inhibitors. The aforementioned characteristic enhances the selectivity of the new-generation ASMs towards specific epilepsy syndromes while reducing their sedative effects.[24] Levetiracetam, a new-generation ASM, interacts with SV2A, which controls the exocytosis of neurotransmitter-containing vesicles. In this mechanism, any conventional actions of old-generation ASMs, i.e., direct increases in brain GABA levels, inhibition of voltage-gated Na+-channels, or inhibition of low-voltage-gated Ca2+-currents, are not involved. The unique properties of Levetiracetam regulate both neuronal excitability (inhibiting ryanodine and IP3 receptor-dependent Ca2+ release from the endoplasmic reticulum) and indirectly affect GABA turnover, making Levetiracetam less sedative.[25] Levetiracetam promotes sleep stability without affecting daytime sleepiness, as evidenced by a notable improvement in sleep efficiency and the absence of significant alterations in subjective sleep indicators.[26]

Our study findings indicate a significant relationship between polytherapy and sleep quality, with a 10-fold higher rate of poor sleep quality (p = 0.024, OR 10.26, 95% CI 1.19-94.11) among individuals receiving polytherapy compared to monotherapy. The results of this study are consistent with previous studies reporting an association between polytherapy and poor sleep quality.[4,5,27] Polytherapy increases the risk of sleep disturbances, with Excessive Daytime Sleepiness (EDS) being the most common type. [28] Polytherapy is also linked to more intractable epilepsy with poorer seizure control, which affects sleep structure.[29]

The study also finds a significant relationship between the duration of ASM use and sleep quality. Treatment duration of more than three months to one year is associated with a 5.6-fold decline in sleep quality (p = 0.003). Another study suggests prolonged use of phenytoin. i.e., more than six months in duration, does not exhibit a substantial influence on sleep patterns. However, it is worth noting that hypnotic effects may occasionally present.[30] Carbamazepine also exhibits a similar pattern, with acute use having a sedative effect upon acute administration, which gradually reduces after a month. This may be attributed to endogenous adaptation, in which individuals experience improved sleep quality as a result of better-controlled seizures and lower seizure frequency.[31] Additionally, psychological considerations may play a role, as patients tend to exhibit increased acceptance of their diagnosis with prolonged usage of ASMs.[32]

The strength of this study is that the data were obtained through face-to-face interviews with qualified doctors, the use of reliable and validated questionnaires, and cautious data handling. This study also excluded several important associated factors of poor sleep quality (i.e., anxiety, depression, poor medication adherence, poor sleep hygiene, uncontrolled seizure, unstable ASM dose, and progressive/degenerative intracranial lesion), which provided more reliable information about the relationship

between ASM and sleep quality, especially in Indonesia, as a developing country with limited ASM availability. Furthermore, studies regarding this topic in Indonesia were still limited.

However, several weaknesses remain. One potential limitation of this study, as it is a cross-sectional study, is the lack of information on sleep quality before the use of ASM. Furthermore, the study did not use an objective method, such as polysomnography (PSG), due to resource limitations. The plasma concentration of the medication was also not measured. Finally, the sample size in this study was small; therefore, we could not determine which ASM combination is associated with poor sleep quality.

Conclusion

The findings of this investigation indicate a significant relationship between the use of old-generation ASMs and polytherapy and poor sleep quality. In addition, a significant relationship was identified between shorter ASM duration and reduced sleep quality. This result could prompt clinicians to promote sleep quality monitoring before treatment initiation and to choose the ideal ASM. New-generation ASM monotherapy is more recommended for treating epilepsy patients with poor sleep quality. Longer duration of ASM consumption is relatively safe.

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Ethical consideration

This study has been approved by the Ethics Committee of Prof. Dr. R. D. Kandou Manado Central General Hospital with the number 060.EC/KEPK-KANDOU/V/2023.

Competing Interests

The authors declare no conflict of interest.

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