Epilepsy & Behavior 156 (2024) 109781

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Research Paper

Differences in factors associated with insomnia symptoms between patients with epilepsy with and without depressive symptoms

Sang-Ahm Lee [a,*], Eun Ju Choi [a], Hyun-Woo Kim [a], Ji-Ye Jeon [b], Su-Hyun Han [c], Gha-Hyun Lee [d], Han Uk Ryu [e], Boyoung Kim [a], Tae-Young Kim [a]

[a] Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Department of Neurology, Kyungpook National University Chilgok Hospital, Kyungpook National University School of Medicine, Daegu, Republic of Korea
[c] Department of Neurology, Chung-Ang University College of Medicine, Seoul, Republic of Korea
[d] Department of Neurology, Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea
[e] Department of Neurology and Research Institute of Clinical Medicine, Jeonbuk National University School of Medicine and Hospital, Jeonju, Republic of Korea

ARTICLE INFO

Keywords:
Epilepsy
Sleep disturbance
Insomnia
Depression
Daytime sleepiness
Perampanel

ABSTRACT

Objective: To determine if insomnia-related factors differ depending on the presence of depression in patients with epilepsy.

Methods: This cross-sectional multicenter study collected data on depressive symptoms, insomnia symptoms, and excessive daytime sleepiness, which were defined as a Patient Health Questionnaire-9 (PHQ-9) score of ≥ 10, an Insomnia Severity Index (ISI) score of ≥ 15, and an Epworth Sleepiness Scale (ESS) of ≥ 11, respectively. Further, uncontrolled seizures were defined as one or more seizures per month during antiseizure medications treatment. A stepwise logistic regression analysis was conducted, with a logistic regression with interaction terms performed to identify differences in insomnia-related factors depending on depressive symptoms.

Results: Of 282 adults with epilepsy (men, 58 %; mean age, 40.4 ± 13.9 years), a PHQ-9 score ≥ 10, an ISI score ≥ 15, an ESS score ≥ 11 were noted in 23.4 % (n = 66), 20.2 % (n = 57), and 12.8 % (n = 36), respectively. More patients with depressive symptoms had an ISI score ≥ 15 (56.1 % vs. 9.3 %; $p < 0.001$) than those without. In multiple logistic regression, uncontrolled seizures (odds ratio [OR], 4.896; $p < 0.01$), daytime sleepiness (OR, 5.369; $p < 0.05$), and a history of psychiatric disorders (OR, 3.971; $p < 0.05$) were identified as significant factors that were more likely to be associated with an ISI score ≥ 15; however, this was only true in patients without depressive symptoms. In contrast, use of perampanel (OR, 0.282; $p < 0.05$) was less likely associated, while female sex (OR, 3.178; $p < 0.05$) was more likely associated with an ISI score ≥ 15 only in patients with depressive symptoms.

Conclusions: Insomnia-related factors in patients with epilepsy may differ between patients with and without depression. Our findings of different insomnia-related factors based on the presence of depression may facilitate the management of patients with epilepsy.

1. Introduction

Epilepsy is a common brain disorder in which patients are prone to epileptic seizures which can inflict physical, psychological, cognitive, and social consequences [1]. Prior research has shown that patients with epilepsy are two to three times more likely to experience sleep problems than the general population [2–4]. One of the most frequent sleep-related complaints is insomnia, which affects 36 % to 74 % of adults with epilepsy [2]. Poor sleep comorbid with epilepsy may make seizures difficult to control [5], aggravate daytime sleepiness [6], and reduce quality of life in patients with epilepsy [4,6]; as such, early identification of sleep disturbances is important to facilitate the management of this patient population.

Several epilepsy-related factors have been reported to be associated with insomnia in patients with epilepsy, including: focal epilepsy [7,8], nocturnal seizures [9,10], epileptiform activity on electroencephalography [9], seizure freedom [6,9,11], uncontrolled epilepsy [7,8,12], duration of epilepsy [6,8,11], and polytherapy with antiseizure

* Corresponding author at: Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Republic of Korea.
E-mail address: salee@amc.seoul.kr (S.-A. Lee).

https://doi.org/10.1016/j.yebeh.2024.109781
Received 25 December 2023; Received in revised form 11 March 2024; Accepted 4 April 2024

medications (ASMs) [13,14]. However, reports regarding the relationships between individual epilepsy-related factors and insomnia have been inconsistent. For example, some studies have identified a significant association between uncontrolled seizures and insomnia [8,12], while others failed to show this relationship [10,13,14]. Similarly, in some studies, the duration of epilepsy was found to be significantly associated with insomnia; however, an opposite direction of this association was found in others [8,11]. In contrast, other studies did not find any correlation between the duration of epilepsy and insomnia [6,10,12]. Furthermore, a recent study failed to show that any epilepsy-related factors were related to insomnia after controlling for depression and anxiety [15]. The inconsistency of the results among these studies suggests that the effects of epilepsy-related factors on insomnia remain poorly understood in patients with epilepsy. Insomnia is one of the primary symptoms of depression, which is the most common psychiatric comorbidity among patients with epilepsy. Given that psychological distress is the most influential factor associated with insomnia in patients with epilepsy [8,10,15], its potential impact on insomnia should be considered when investigating the relationship between epilepsy-related factors and insomnia. However, this subject has not been investigated in prior research on insomnia in patients with epilepsy.

Thus, our study aimed to achieve the following: 1) to determine which factors, including epilepsy-related factors, are associated with insomnia symptoms in adults with epilepsy with and without depressive symptoms, and 2) to determine if insomnia-related factors differ depending on the presence of depressive symptoms in patients with epilepsy.

2. Participants and methods

2.1. Participants

This cross-sectional multicenter study used convenience sampling to enroll patients treated at the outpatient epilepsy clinics of six tertiary hospitals from November 2020 to July 2022. Study eligibility was contingent on patients meeting the following specific inclusion criteria: 1) age 19 years or older; 2) diagnosed with epilepsy in accordance with the diagnostic criteria established by the International League Against Epilepsy [1]; 3) currently using one or more ASMs, with no changes to their medication regimen for at least one month; and 4) possessing the necessary cognitive capacity to complete self-reporting questionnaires. Participation in the study was restricted to exclude individuals with psychogenic nonepileptic seizures, confusion associated with psychosis, delirium, amnestic disorders, intoxication, unstable somatic disorder, and/or previously diagnosed sleep disorders (such as obstructive sleep apnea, narcolepsy, restless leg syndrome, periodic limb movement disorder, and REM sleep behavior disorder). Taking into consideration the results of Kenner et al.'s study [16], which systematically evaluated postictal behavior symptoms, finding that the median duration of two thirds of postictal symptoms was 24 h, individuals who experienced generalized tonic–clonic seizures (GTCSs) or focal to bilateral tonic–clonic seizures (FBTCSs) during the 72 h before study enrollment were further excluded. Fundamental demographic details and clinical data were collected through interviews and reviews of the patients' medical records. Written informed consent was obtained from all participants prior to inclusion in the study. The Institutional Review Board of Asan Medical Center reviewed and approved this study (2020–1439), which was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (2008).

2.2. Assessment tools

The Insomnia Severity Index (ISI) is a seven-item questionnaire that was designed to evaluate the nature and symptoms of insomnia [17]. A five-point Likert-type scale (ranging from 0 to 4) was used, resulting in a total score between 0 and 28. ISI scores are classified as follows: no clinically significant insomnia (scores 0–7), subthreshold insomnia (scores 8–14), moderate severity of clinical insomnia (scores 15–21), and severe clinical insomnia (scores 22–28). In the present study, the presence of insomnia was defined as an ISI score of 15 or above [17]. Psychometric properties for the Korean version of the ISI were validated in a previous study [18].

The Epworth Sleepiness Scale (ESS) is an eight-item questionnaire in which respondents rate the frequency of dozing during regular daily activities [19]. Each response is assessed using a four-point scale ranging from 0 (never dozed) to 3 (high likelihood of dozing). The total score ranges from 0 to 24, with a higher score reflecting a greater inclination toward daytime drowsiness. Excessive daytime sleepiness was defined as an ESS score of 11 or above in this study [19].

The Patient Health Questionnaire-9 (PHQ-9) is a screening assessment tool designed to evaluate depression, which was originally developed by considering the nine diagnostic criteria for major depressive disorders outlined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [20]. Responses are scored using a four-point Likert-type scale ranging from 0 (no symptoms) to 3 (symptoms present almost every day for the past two weeks). The total score ranges from 0 to 27, with higher scores representing more severe depression. In our study, clinically significant depression was defined as a PHQ-9 score of 10 or above [20].

The Generalized Anxiety Disorder-7 (GAD-7) is a seven-item screening assessment tool designed to facilitate the swift identification of GAD [21], which uses a four-point Likert-type scale ranging from 0 (no symptoms) to 3 (symptoms present nearly every day during the preceding two weeks). The total score ranges from 0 to 21, with higher scores representing more severe anxiety. Clinically significant anxiety was defined as a GAD-7 score of 7 or above in this study [21].

2.3. Statistical analysis

Data are displayed as the mean and standard deviation, median and interquartile range (IQR), or number and percentage. Univariate analyses were conducted using the Student's t-test to compare the means between two groups, and the Pearson's chi-square test to assess the existence of differences in the trend of the proportions in the two groups. In the exploration of factors independently linked to insomnia symptoms, a logistic regression analysis with the backward elimination method was performed. The dependent variable was clinically significant insomnia (defined as an ISI score ≥ 15). The independent variables were age, sex, and factors with an association ($p < 0.05$) with the dependent variables in the univariate analysis. Factors considered independent variables included demographic (body mass index), psychological (history of psychiatric disorders and symptoms of depression and anxiety), sleep-related (daytime sleepiness), epilepsy-related (age at seizure onset, duration of epilepsy, type of predominant seizures and epilepsy, seizure freedom for at least one year, recurrence of GTCSs or FBTCSs in the last year, nocturnal seizures, uncontrolled seizures, ASM polytherapy, and use of individual ASMs shown in Table 1), and other (presence of medical comorbidities) variables. Uncontrolled seizures were defined as the occurrence of one or more seizures per month during ASM treatment. Nocturnal seizures were defined as more than 90 % of seizures occurring during nighttime sleep. With regard to psychological variables, categorical variables (an ESS score ≥ 11, a PHQ-9 score ≥ 10, and a GAD-7 score ≥ 7) were used for the logistic regression analyses. Regression analyses were conducted among all participants as well as groups divided according to the presence of depressive symptoms (defined as a PHQ-9 score ≥ 10).

To determine if insomnia-related variables differ depending on a PHQ-9 score ≥ 10, a logistic regression with interaction terms was conducted. The models were adjusted for the variables identified to be independently associated with insomnia symptoms in the multivariate regression analyses.

Multicollinearity among several independent variables was

Table 1
Subject characteristics (n = 282).

Age, years, mean (SD)	40.4 (13.9)
Women, n (%)	119 (42.2)
Body mass index, kg/m^2, mean (SD)	23.8 (3.7)
The unemployed, n (%)	72 (25.5)
Medical comorbidities, n (%)	46 (16.3)
History of psychiatric disorders, n (%)	39 (13.8)
ESS scores, median (IQR)	4.0 (2.0, 8.0)
ESS score of ≥ 11, n (%)	36 (12.8)
ISI scores, median (IQR)	6.0 (2.0, 12.0)
ISI score of ≥ 15, n (%)	57 (20.2)
PHQ-9 scores, median (IQR)	4.0 (1.0, 9.0)
PHQ-9 score of ≥ 10, n (%)	66 (23.4)
GAD-7 scores, median (IQR)	3.0 (1.0, 7.0)
GAD-7 score of ≥ 7, n (%)	73 (25.9)
Age at seizure onset, years, mean (SD)	26.2 (15.4)
Duration of epilepsy, years, mean (SD)	14.3 (12.5)
Epilepsy type, n (%)	
Generalized, idiopathic	46 (16.3)
Focal	219 (77.7)
Unknown	17 (6.0)
Predominant seizure type, n (%)	
Focal aware	27 (9.6)
Focal impaired awareness	152 (53.9)
GTCS or FBTCS	103 (36.5)
Seizure freedom for at least one year, n (%)	93 (33.0)
Seizure frequency ≥ 1 per month, n (%)	69 (24.5)
GTCS or FBTCS in the last year, n (%)	170 (60.3)
>90 % of seizures occurring during sleep, n (%)	35 (12.4)
ASM polytherapy, n (%)	141 (50.0)
Individual ASM prescribed, n (%)	
Levetiracetam	147 (52.1)
Valproic acid	90 (31.9)
Oxcarbazepine	69 (24.5)
Lamotrigine	50 (17.7)
Topiramate	42 (14.9)
Carbamazepine	41 (14.5)
Perampanel	41 (14.5)
Others*	42 (14.9)
History of epilepsy surgery, n (%)	13 (4.6)

ASM, antiseizure medication; ESS, Epworth Sleepiness Scale; FBTCS, focal to bilateral tonic clonic seizure; GAD-7, Generalized Anxiety Disorder-7; GTCS, generalized tonic clonic seizure; ISI, Insomnia Severity Index; IQR, interquartile range; N, number; PHQ-9, Patient Health Questionnaire-9.
* Zonisamide, pregabalin, gabapentin, lacosamide phenytoin, vigabatrin, clobazam, clonazepam, lorazepam, and phenobarbital were prescribed individually less than 10 % of subjects.

determined by calculating the variance inflation factor (<3) and the condition index (<10). In a logistic regression analysis, the goodness of fit of the statistical model was measured by the Hosmer–Lemeshow test, with $p > 0.05$ indicating a well-calibrated model. We further calculated the c-statistics, which assess the discriminatory ability of the model. Significance was determined at p-values < 0.05 (two-tailed). Statistical analyses were performed using Statistical Package for the Social Sciences version 21.0 (IBM Corp., located in Armonk, NY, USA).

3. Results

3.1. Subject characteristics

The characteristics of the 282 patients with epilepsy who participated in this study are summarized in Table 1. Men accounted for 57.8 % of the study population, and the mean age was 40.4 ± 13.9 years. Focal epilepsy was the most common type, found in 77.7 % of the participants. Uncontrolled seizures were noted in 24.5 % of the participants. Symptoms of insomnia (defined as an ISI score ≥ 15), daytime sleepiness (an ESS score ≥ 11), depression (a PHQ-9 score ≥ 10), and anxiety (a GAD-7 score ≥ 7) were noted in 20.2 % (n = 57), 12.8 % (n = 36), 23.4 % (n = 66), and 25.9 % (n = 73) of participants, respectively. More participants with depressive symptoms had an ISI score of ≥ 15 (56.1 % vs. 9.3 %; p < 0.001) than those without.

3.2. Factors associated with an ISI score ≥ 15 in participants with epilepsy

Univariate analyses showed several variables with $p < 0.05$ that were associated with an ISI score ≥ 15 (Table 2). Stepwise logistic regression demonstrated that sex ($p = 0.029$), PHQ-9 score ≥ 10 ($p < 0.001$), history of psychiatric disorders ($p = 0.017$), uncontrolled seizures ($p = 0.009$), and the use of perampanel ($p = 0.025$) were all associated with an ISI score ≥ 15 in the total cohort (Table 3). This model had a c-statistic of 0.844, suggesting good discrimination ability.

3.3. Different associations with an ISI score ≥ 15 based on depressive symptoms

In the stepwise logistic regression analysis (Table 3), an ESS score ≥ 11 ($p = 0.019$), uncontrolled seizures ($p = 0.003$), and a history of psychiatric disorders ($p = 0.029$) were found to be associated with an ISI score ≥ 15 in participants with a PHQ-9 score < 10, but this was not true in those with a PHQ-9 score ≥ 10. In contrast, female sex ($p = 0.035$) and no use of perampanel ($p = 0.047$) were associated with an ISI score ≥ 15 in all with a PHQ-9 score ≥ 10, but not in participants with an ISI score ≥ 15 in those with a PHQ-9 score < 10. Based on a logistic regression using interaction terms (Table 4), interactions of a PHQ-9 score ≥ 10

Table 2
Univariate analyses showing age, sex, and variables with $p < 0.05$ in associations with a presence of insomnia symptoms in subjects with epilepsy.

	Total subjects (n = 282)		PHQ-9 < 10 (n = 216)		PHQ-9 ≥ 10 (n = 66)	
	ISI score < 15	ISI score ≥ 15	ISI score < 15	ISI score ≥ 15	ISI score < 15	ISI score ≥ 15
N (%)	225 (79.8)	57 (20.2)	196 (90.7)	20 (9.3)	29 (43.9)	37 (56.1)
PHQ-9 score of ≥ 10, n (%)	29 (12.9)	37 (64.9)***	–	–	–	–
Age, years, mean (SD)	40.0 (13.9)	42.0 (14.0)	39.8 (14.3)	39.2 (14.3)	41.5 (10.9)	43.5 (13.8)
Women, n (%)	88 (39.1)	31 (54.4)*	80 (40.8)	10 (50.0)	8 (27.6)	21 (56.8)*
GAD-7 score of ≥ 7, n (%)	40 (17.8)	33 (57.9)***	20 (10.2)	4 (20.0)	20 (69.0)	29 (78.4)
ESS score of ≥ 11, n (%)	22 (9.8)	14 (24.6)**	11 (5.6)	4 (20.0)*	11 (37.9)	10 (27.0)
Uncontrolled seizures, n (%)	43 (19.1)	26 (45.6)***	30 (15.3)	10 (50.0)**	13 (44.8)	16 (43.2)
ASM polytherapy, n (%)	104 (46.2)	37 (64.9)*	81 (41.3)	10 (50.0)	23 (79.3)	27 (73.0)
Use of lamotrigine, n (%)	34 (15.1)	16 (28.1)*	27 (13.8)	3 (15.0)	7 (24.1)	13 (35.1)
Use of perampanel, n (%)	34 (15.1)	7 (12.3)	23 (11.7)	2 (10.0)	11 (37.9)	5 (13.5)*
Medical comorbidities, n (%)	31 (13.8)	15 (26.3)*	25 (12.8)	5 (25.0)	6 (20.7)	10 (27.0)
History of psychiatric disorders, n (%)	20 (8.93)	19 (33.3)***	12 (6.1)	6 (30.0)**	8 (27.6)	13 (35.1)

ASM, antiseizure medication; ESS, Epworth Sleepiness Scale; GAD-7, Generalized Anxiety Disorder-7; ISI, Insomnia Severity Index; n, number; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation.
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Table 3
Stepwise logistic regression showing variables significantly associated with the presence of insomnia symptoms in subjects with epilepsy.

	ISI score ≥ 15					
	Total (n = 282)		PHQ-9 < 10 (n = 216)		PHQ-9 ≥ 10 (n = 66)	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
PHQ-9 score of ≥ 10	11.248***	5.348–23.659	–	–	–	–
History of psychiatric disorders	2.845*	1.206–6.711	3.971*	1.150–13.719	–	–
Uncontrolled seizures	2.765**	1.288–5.935	4.896**	1.701–14.095	–	–
Use of perampanel	0.291*	0.099–0.856			0.282*	0.081–0.981
Female sex	2.226*	1.087–4.560	–	–	3.178*	1.083–9.321
ESS score of ≥ 11	–	–	5.369*	1.321–21.818	–	–

ASM, antiseizure medication; CI, confidence interval; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; n, number; OR, odds ratio; PHQ-9, Patient Health Questionnaire-9.
Notes. The initial models included age, sex, PHQ-9 ≥ 10, GAD-7 ≥ 7, ESS ≥ 11, duration of epilepsy, refractory seizures, ASM polytherapy, use of lamotrigine, use of perampanel, medical comorbidity, and history of psychiatric disorders.

Table 4
Multivariate logistic regression showing interactions of depressive symptoms with daytime sleepiness and refractory seizures and their effects on the presence of insomnia symptoms in subjects with epilepsy (n = 282).

Independent variable	Model	Subgroups	Interaction p value	ISI score ≥ 15		
				OR	95 % CI	p value
ESS score ≥ 11	Crude	PHQ-9 < 10	0.020	4.205	1.201–14.722	0.025
		PHQ-9 ≥ 10		0.606	0.213–1.721	0.347
	Adjusted[a]	PHQ-9 < 10	0.049	4.374	1.141–16.765	0.031
		PHQ-9 ≥ 10		0.748	0.239–2.344	0.618
Uncontrolled seizures	Crude	PHQ-9 < 10	0.011	5.533	2.121–14.435	<0.001
		PHQ-9 ≥ 10		0.938	0.352–2.496	0.898
	Adjusted[a]	PHQ-9 < 10	0.049	5.593	2.051–15.252	0.001
		PHQ-9 ≥ 10		1.285	0.436–3.785	0.649

CI, confidence interval; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; n, number; OR, odds ratio; PHQ-9, Patient Health Questionnaire-9.
[a] The adjusted models were adjusted by sex, PHQ-9 score ≥ 10, ESS score ≥ 11, history of psychiatric disorder, refractory seizures, and use of perampanel.

with an ESS score ≥ 11 and uncontrolled seizures were found to be significant for an ISI score ≥ 15 in both the crude and adjusted models (all interactions $p < 0.05$); however, interactions between sex and the use of perampanel were not significant. In particular, an ESS score ≥ 11 and uncontrolled seizures were more likely to be associated with an ISI score ≥ 15 in those with a PHQ-9 score < 10, but this was not true in those with a PHQ-9 score ≥ 10.

4. Discussion

Herein, we investigated the prevalence of insomnia symptoms, as measured using an ISI score ≥ 15, in patients with epilepsy. The overall prevalence of insomnia symptoms was 20.2 %, and we found significant differences in sex, daytime sleepiness, uncontrolled seizures, a history of psychiatric disorders, and the use of perampanel in association with insomnia symptoms between patients with and without depressive symptoms. In particular, daytime sleepiness, uncontrolled seizures, and a history of psychiatric disorders were identified as significant factors that were more likely associated with insomnia symptoms; however, this was only true in patients without depressive symptoms. In contrast, the use of perampanel and male sex was less likely to be associated with insomnia symptoms only in patients with depressive symptoms.

In the present study, among the cohort of patients without depressive symptoms, those with uncontrolled seizures showed a significantly a higher prevalence of insomnia symptoms than those without. It was unclear why this difference was dependent on the presence of depressive symptoms. However, these differences could be partially explained by the considerable impact of psychological distress on insomnia. Further, it is well known that psychological distress, such as depression and anxiety, is a major determinant of insomnia in patients with epilepsy [8,10,15]. In the present study, the odds of insomnia symptoms were the highest with the presence of depressive symptoms. The considerable impact of depression could mask the potential association between uncontrolled seizures and insomnia symptoms in patients with depressive symptoms. However, we did not find any published studies presenting data comparable to our current findings. Indeed, prior reports on the associations between seizure control and insomnia have reported inconsistent results [8,10,12–14]. For example, one study of adults with epilepsy found a significant association between uncontrolled seizures (defined as seizures recurring more than once per month) and the severity of insomnia, even after controlling for depression and anxiety [8]. However, in recent studies, such statistical significance of uncontrolled seizures was lost after controlling for depression and anxiety [10,15].

Prior research has shown that ASMs may affect sleep, although the effects on sleep architecture vary depending on the individual ASM [22]. In our study, we found that, among patients with depressive symptoms, those who were taking perampanel had a significantly lower prevalence of insomnia symptoms. This decrease in the insomnia symptoms in patients treated with perampanel was consistent with the findings of previous studies, which demonstrated a significant improvement in sleep quality in patients receiving perampanel [23–26]. Further, one multicenter prospective study investigated the effect of adjunctive perampanel on quality of sleep and daytime sleepiness in patients with uncontrolled focal epilepsy [23], finding that sleep quality, but not daytime sleepiness, was significantly improved at 3-month. In another study, adjunctive treatment with perampanel for three or more months in adults with epilepsy was associated with significant improvements in sleep latency, sleep efficiency, wake after sleep onset, duration of deep sleep, and total sleep time [24]. However, there was no effect on rapid eye movement sleep. The improvements in these sleep parameters were reported without any worsening in daytime sleepiness [24]. A recent study using the ISI evaluated the effect of adjunctive perampanel treatment for at least one month in adults with epilepsy, revealing that insomnia was less prevalent and less severe in patients with epilepsy receiving perampanel, independent of the presence of affective

symptoms [25]. Overall, the existing evidence indicates that the beneficial effects of perampanel on sleep do not seem to occur indirectly via effects on affective symptoms or seizures. In recent longitudinal studies, treatment with adjunctive perampanel had no influence on the levels of depression and anxiety after six months in patients with epilepsy [27,28]. Another prospective study found improvements in sleep quality in patients taking perampanel, but the reduced seizure frequency was not correlated with improved sleep quality [23]. In the present study, these beneficial effects of perampanel were not identified in patients without depressive symptoms. This finding could be explained in part by the lack of sleeping problems experienced by patients without depression. As expected, we found that the prevalence of insomnia symptoms was significantly decreased in patients without depressive symptoms compared to those with depressive symptoms. In contrast to perampanel, lamotrigine has been reported to be an independent risk factor for insomnia in patients with epilepsy [8,29,30]. In support of this, we found that patients taking lamotrigine had a significantly higher prevalence of insomnia symptoms, but the statistical significance of this association was lost in the multivariate analyses.

In the present study, daytime sleepiness was identified as one of the significant factors that was more likely associated with insomnia symptoms in patients without depressive symptoms. However, in patients with depression, the prevalence of insomnia symptoms did not differ depending on excessive daytime sleepiness. These differences in the relationships between daytime sleepiness and insomnia symptoms suggest different underlying mechanisms of insomnia symptoms in patients with epilepsy with and without depression. In general, patients with insomnia disorders generally do not complain of daytime sleepiness, even though they experience an insufficient sleep duration during nighttime sleep. This is usually explained by hyperarousal in cognitive/emotional, cortical, and/or physiological domains [31]. Indeed, signs of increased daytime arousal in patients with insomnia have been found in many studies [31–33]. For example, in one study using simultaneous functional magnetic resonance imaging and electroencephalography, patients with insomnia showed increases in absolute alpha power and alpha attenuation, potentially indicating increased levels of wakefulness during the day [32]. Therefore, the theory of hyperarousal in insomnia could explain our findings of a negative association between daytime sleepiness and insomnia symptoms in patients with depressive symptoms. Conversely, the positive association between daytime sleepiness and insomnia symptoms in patients without depressive symptoms could be explained by a homeostatic sleep drive, a biological process that makes up part of the two-process model controlling sleep [34]. Increased daytime sleepiness and associated daytime naps could be linked to a decreased sleep propensity, resulting in difficulty in initiating and/or maintaining sleep at night. Similar to our findings in patients without depressive symptoms, some studies have found a positive correlation between the severities of daytime sleepiness and insomnia symptoms [6,14]; however, they did not consider its interaction with depressive symptoms.

The current study has several limitations. First, causal or temporal relationships could not be determined because of the cross-sectional study design. Second, we did not enroll a control group; therefore, the characteristics of insomnia between epileptic and non-epileptic populations could not be compared. Third, our data were subject to referral bias because of enrollment of the study participants from tertiary hospitals. As such, the severities of symptoms of insomnia, depression, and anxiety reported here might not be applicable to other epileptic populations, particularly to patients visiting primary care clinics. In contrast, excluding patients with recent changes in ASMs regimen may result in a selection bias, as it is likely that some patients with difficult-to-control epilepsy would have been excluded from the analysis. However, our main findings, including the identification of factors associated with insomnia symptoms in patients with epilepsy with and without depressive symptoms, should be generally applicable. Fourth, this study utilized convenience sampling to recruit participants with epilepsy; however, we did not apply a random sampling method. Fifth, data on nocturnal seizure frequency was collected through reporting by the patient, a bed partner, or both, but it was not assessed using the specific device. Finally, polysomnography or multiple sleep latency testing was not utilized in the present study; therefore, objective sleep parameters for insomnia and daytime sleepiness could not be analyzed. Further, subjective reports of sleep may not be in agreement with assessments of objective sleep measures, particularly in patients with insomnia [35].

5. Conclusions

In conclusion, the results of the present study indicate that insomnia-related factors may significantly differ between epilepsy patients with and without depression. Further, we found that daytime sleepiness and uncontrolled seizures were more likely to be associated with insomnia in patients without depression. In contrast, use of perampanel was less likely to be associated with insomnia in patients with depression. Although the significant relationship between depression and insomnia has been well-established, few studies have taken into consideration the potential impact of depression on insomnia when investigating the potential factors associated with insomnia in patients with epilepsy. Therefore, our findings of different insomnia-related factors based on the presence of depression may fill this gap in the literature, and could facilitate the management of patients with epilepsy.

Funding

This study received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Sang-Ahm Lee: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Eun Ju Choi:** Data curation. **Hyun-Woo Kim:** Data curation. **Ji-Ye Jeon:** Data curation. **Su-Hyun Han:** Data curation. **Gha-Hyun Lee:** Data curation. **Han Uk Ryu:** Data curation. **Boyoung Kim:** Data curation. **Tae-Young Kim:** Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82. https://doi.org/10.1111/epi.12550.
[2] Macêdo PJOM, Oliveira PS, Foldvary-Schaefer N, Gomes MDM. Insomnia in people with epilepsy: a review of insomnia prevalence, risk factors and associations with epilepsy-related factors. Epilepsy Res 2017;135:158–67. https://doi.org/10.1016/j.eplepsyres.2017.05.014.
[3] Khatami R, Zutter D, Siegel A, Mathis J, Donati F, Bassetti CL. Sleep-wake habits and disorders in a series of 100 adult epilepsy patients: a prospective study. Seizure 2006;15:299–306. https://doi.org/10.1016/j.seizure.2006.02.018.
[4] de Weerd A, de Haas S, Otte A, Trenité DK, van Erp G, Cohen A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. Epilepsia 2004;45:1397–404. https://doi.org/10.1111/j.0013-9580.2004.46703.x.
[5] Bonilla-Jaime H, Zeleke H, Rojas A, Espinosa-Garcia C. Sleep dsruption worsens seizures: neuroinflammation as a potential mechanistic link. Int J Mol Sci 2021;22:12531. https://doi.org/10.3390/ijms222212531.
[6] Quigg M, Gharai S, Ruland J, Schroeder C, Hodges M, Ingersoll KS, et al. Insomnia in epilepsy is associated with continuing seizures and worse quality of life. Epilepsy Res 2016;122:91–6. https://doi.org/10.1016/j.eplepsyres.2016.02.014.
[7] Hoeppner JB, Garron DC, Cartwright RD. Self-reported sleep disorder symptoms in epilepsy. Epilepsia 1984;25:434–7. https://doi.org/10.1111/j.1528-1157.1984.tb03439.x.
[8] Shen Y, Zhang M, Wang Y, Wang L, Xu X, Xiao G, et al. Subjective sleep disturbance in chinese adults with epilepsy: associations with affective symptoms. Epilepsy Res 2017;135:150–7. https://doi.org/10.1016/j.eplepsyres.2017.06.014.

[9] Ismayilova V, Demir AU, Tezer FI. Subjective sleep disturbance in epilepsy patients at an outpatient clinic: a questionnaire-based study on prevalence. Epilepsy Res 2015;115:119–25. https://doi.org/10.1016/j.eplepsyres.2015.06.009.
[10] Tan B, Liu Q, Qin Y, Chen Q, Chen R, Jin Y, et al. Insomnia in epilepsy is associated with nocturnal seizures and anxiety. Epilepsy Behav 2024;150:109559. https://doi.org/10.1016/j.yebeh.2023.109559.
[11] Im HJ, Park SH, Baek SH, Chu MK, Yang KI, Kim WJ, et al. Associations of impaired sleep quality, insomnia, and sleepiness with epilepsy: a questionnaire-based case-control study. Epilepsy Behav 2016;57(Pt A):55–9. https://doi.org/10.1016/j.yebeh.2016.01.022.
[12] Piperidou C, Karlovasitou A, Triantafyllou N, Terzoudi A, Constantinidis T, Vadikolias K, et al. Influence of sleep disturbance on quality of life of patients with epilepsy. Seizure 2008;17:588–94. https://doi.org/10.1016/j.seizure.2008.02.005.
[13] Vendrame M, Yang B, Jackson S, Auerbach SH. Insomnia and epilepsy: a questionnaire-based study. J Clin Sleep Med 2013;9:141–6. https://doi.org/10.5664/jcsm.2410.
[14] Yang KI, Grigg-Damberger M, Andrews N, O'Rourke C, Bena J, Foldvary-Schaefer N. Severity of self-reported insomnia in adults with epilepsy is related to comorbid medical disorders and depressive symptoms. Epilepsy Behav 2016;60:27–32. https://doi.org/10.1016/j.yebeh.2016.03.023.
[15] Jo S, Kim HJ, Kim HW, Koo YS, Lee SA. Sex differences in factors associated with daytime sleepiness and insomnia symptoms in persons with epilepsy. Epilepsy Behav 2020;104(Pt A):106919. https://doi.org/10.1016/j.yebeh.2020.106919.
[16] Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. Neurology 2004;62:708–13. https://doi.org/10.1212/01.wnl.0000113763.11862.26.
[17] Bastien CH, Vallieres A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307. 10.1016/S1389-9457(00) 00065-4.
[18] Cho YW, Song ML, Morin CM. Validation of a Korean version of the insomnia severity index. J Clin Neurol 2014;10:210–5. https://doi.org/10.3988/jcn.2014.10.3.210.
[19] Cho YW, Lee JH, Son HK, Lee SH, Shin C, Johns MW. The reliability and validity of the Korean version of the Epworth sleepiness scale. Sleep Breath 2011;15:377–84. https://doi.org/10.1007/s11325-010-0343-6.
[20] Choi HS, Choi JH, Park KH, Joo KJ, Ga H, Ko HJ, et al. Standardization of the Korean version of patient health Questionnaire-9 as a screening instrument for major depressive disorder. J Korean Acad Farm Med 2007;28:114–9.
[21] Seo JG, Cho YW, Lee SJ, Lee JJ, Kim JE, Moon HJ, et al. Validation of the generalized anxiety disorder-7 in people with epilepsy: a MEPSY study. Epilepsy Behav 2014;35:59–63. https://doi.org/10.1016/j.yebeh.2014.04.005.
[22] Jain SV, Glauser TA. Effects of epilepsy treatments on sleep architecture and daytime sleepiness: an evidence-based review of objective sleep metrics. Epilepsia 2014;55:26–37. https://doi.org/10.1111/epi.12478.
[23] Toledo M, Gonzalez-Cuevas M, Miro-Llado J, Molins-Albanell A, Falip M, Martinez AB, et al. Sleep quality and daytime sleepiness in patients treated with adjunctive perampanel for focal seizures. Epilepsy Behav 2016;63:57–62. https://doi.org/10.1016/j.yebeh.2016.08.004.
[24] Rocamora R, Álvarez I, Chavarría B, Principe A. Perampanel effect on sleep architecture in patients with epilepsy. Seizure 2020;76:137–42. https://doi.org/10.1016/j.seizure.2020.01.021.
[25] Lee SA, Jung M, Kim SJ, Jo S, Kim HJ, Kim HW, et al. Insomnia is less prevalent and less severe, independent of depressive symptoms, in patients with epilepsy treated with perampanel as an adjuvant. Epilepsy Behav 2020;112:107384. https://doi.org/10.1016/j.yebeh.2020.107384.
[26] Gonzalez-Cuevas M, Romero O, Toledo M, Quintana M, Cambrodi R, Santamarina E, et al. Effect of adjunctive perampanel on the quality of sleep and daytime somnolence in patients with epilepsy. Epilepsy Behav Case Rep 2017;7:13–5. https://doi.org/10.1016/j.ebcr.2016.10.002.
[27] Deleo F, Quintas R, Turner K, Didato G, Zambrelli E, Pappalardo I, et al. The impact of perampanel treatment on quality of life and psychiatric symptoms in patients with drug-resistant focal epilepsy: an observational study in Italy. Epilepsy Behav 2019;99:106391. https://doi.org/10.1016/j.yebeh.2019.06.034.
[28] Lee SA, Jeon JY, Kim HW. Effect of perampanel on aggression in patients with refractory focal epilepsy: a 6-month longitudinal study. Epilepsy Behav 2020;102:106658. https://doi.org/10.1016/j.yebeh.2019.106658.
[29] Foldvary N, Perry M, Lee J, Dinner D, Morris HH. The effects of lamotrigine on sleep in patients with epilepsy. Epilepsia 2001;42:1569–73. https://doi.org/10.1046/j.1528-1157.2001.46100.x.
[30] Sadler M. Lamotrigine associated with insomnia. Epilepsia 1999;40:322–5. https://doi.org/10.1111/j.1528-1157.1999.tb00712.x.
[31] Dressle RJ, Riemann D. Hyperarousal in insomnia disorder: current evidence and potential mechanisms. J Sleep Res 2023;32:e13928.
[32] Feige B, Spiegelhalder K, Kiemen A, Bosch OG, Tebartz van Elst L, Hennig J, et al. Distinctive time-lagged resting-state networks revealed by simultaneous EEG-fMRI. Neuroimage 2017;145(A):1–10. https://doi.org/10.1016/j.neuroimage.2016.09.027.
[33] Kallestad H, Hansen B, Langsrud K, Hjemdal O, Stiles TC. Psychometric properties and the predictive validity of the insomnia daytime worry scale: a pilot study. Cogn Behav Ther 2010;39:150–7. https://doi.org/10.1080/16506070903115317.
[34] Deboer T. Sleep homeostasis and the circadian clock: do the circadian pacemaker and the sleep homeostat influence each other's functioning? Neurobiol Sleep Circadian Rhythms 2018;5:68–77. https://doi.org/10.1016/j.nbscr.2018.02.003.
[35] Bianchi MT, Williams KL, Mckinney S, Ellenbogen JM. The subjective-objective mismatch in sleep perception among those with insomnia and sleep apnea. J Sleep Res 2013;22:557–68. https://doi.org/10.1111/jsr.12046.