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Insomnia moderates the association between recurrent seizures and emotional instability in persons with epilepsy

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ABSTRACT

Purpose: We investigated the moderating effect of sleep disturbance on the association between seizure recurrence and emotional instability in patients with epilepsy, independent of psychological distress.
Methods: This was a cross-sectional study. Patients completed the short form of the Affective Lability Scale (ALS-18), Insomnia Severity Index (ISI), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder-7 (GAD-7). A stepwise linear regression analysis and an analysis of covariance with an interaction term were performed.
Results: A total of 171 subjects (63.2% men) were included. The mean ALS-18 score was 15.6 ± 11.3. An ISI ≥ 15, PHQ-9 ≥ 10, and GAD-7 ≥ 7 were noted in 20.5%, 18.1%, and 23.4% of subjects, respectively. A stepwise linear regression analysis found that recurrent seizures in the last year, an ISI ≥ 15, a GAD-7 ≥ 7, and use of levetiracetam were significant and independent factors that were positively associated with higher ALS-18 scores. The coefficient of determination for the model was 0.331. The interaction between recurrent seizures and an ISI ≥ 15 had a significant effect on the ALS-18 scores ($F = 6.812$, $p = 0.010$, partial eta$^2 = 0.040$). An ISI ≥ 15 was associated with ALS-18 scores in patients without seizure recurrence ($p < 0.001$). This association almost reached significance ($p = 0.084$) in those with recurrent seizures. In contrast, the presence of recurrent seizures was associated with ALS-18 scores in patients with an ISI < 15 ($p < 0.001$), but not in those with an ISI ≥ 15 ($p = 0.360$).
Conclusions: The significant interaction between insomnia and seizure status may have an effect on emotional instability. These findings have clinical implications in the development of potential interventions for emotional instability in patients with epilepsy.

1. Introduction

Emotional instability is defined as the tendency to experience rapid oscillations of intense affect that are difficult to control [1]. The term is used interchangeably with affective instability, affective lability, mood instability, and emotional dysregulation. Emotional instability is described in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) as a "marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety)" [2]. Emotional instability is a feature found in various psychiatric disorders [3], and is related to substantial morbidities, including suicide attempts, aggressive behaviors, and disrupted interpersonal relationships [4]. Emotional instability can be identified as a personality trait, particularly in borderline personality disorder, or as a symptom profile for various psychopathologies [1]. The distinction between affective states as a trait and affective disturbances as a symptom is unclear [1,5].

Emotional instability is common in patients with epilepsy, but has received relatively little attention compared with depression and anxiety. Indeed, only a few studies have specifically focused on emotional instability in the field of epilepsy [6,7]. In one community-based study, bipolar symptoms were found in 12.2%

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of patients with epilepsy, a higher rate than those found in other chronic conditions [7]. Prevalence rates of interictal dysphoric disorder (IDD), which is characterized by symptoms of emotional instability, have been reported to be around 17–33% in an outpatient population of those with epilepsy [8–11]. Although the existence of IDD as an independent nosological entity is still a matter of debate [12], core features such as paroxysmal affects that range from irritability to anger and rage have long been described in patients with epilepsy [8–11].

Despite the paucity of studies regarding emotional instability in patients with epilepsy, emotional instability has been proposed to have a multifactorial background involving psychological, epilepsy-related, and anti-seizure medication (ASM)-related factors [13]. This assumption is largely based on research about IDD in patients with epilepsy [8–11]. Most studies have reported there to be a significant association between IDD and psychiatric disorders, such as depression and anxiety [8–11,14]. Although previous data on epilepsy-related factors have conflicted [9–11], some studies have found a significant association between IDD and epilepsy-related variables, such as seizure recurrence and age at seizure onset [9]. Some new ASMs, particularly perampanel, levetiracetam, and topiramate, have behavioral adverse effects, including irritability and aggression [15].

Sleep disturbance is twofold to threefold more common in patients with epilepsy than in the general population [16]. Insomnia is the most common sleep-related symptom, affecting up to two-thirds of adults with epilepsy [17]. There is a bidirectional relationship between disturbed sleep and emotional instability. Sleep deprivation strongly increases negative emotion [18]. High levels of emotional arousal can also disturb sleep, which suggests that there may be a vicious cycle between disturbed sleep and emotional instability [19]. Little attention has been paid to the relationship between emotional instability and sleep disturbance in patients with epilepsy. Furthermore, it is possible that emotional instability is influenced by recurrent seizures to varying degrees, according to the presence or absence of sleep disturbance in patients with epilepsy. Thus, the aims of this study were (1) to determine whether recurrent seizures and insomnia symptoms are associated with emotional instability in patients with epilepsy, independent of depressive symptoms or anxiety, and (2) to examine the moderating effect of insomnia symptoms on association between recurrent seizures and emotional instability.

2. Materials and methods

2.1. Subjects

Adults with epilepsy aged 19 years and over were recruited from six university hospitals between November 2020 and May 2021 throughout South Korea. The new classifications of seizures and epilepsy of the International League Against Epilepsy [20,21] were used. Patients with epilepsy were excluded if they had experienced generalized or focal to bilateral tonic-clonic seizures within 72 h before enrollment in the study, or they were unable to read or understand the questionnaire.

Seizure outcome after ASM therapy was assessed whenever patients visited outpatient clinic with an interval of one to six months. Seizure recurrence was defined by the presence of one or more seizures during the last one year of follow-up. Myoclonic jerks in patients with juvenile myoclonic epilepsy and aura in those with focal epilepsy were not counted as seizures. Written informed consent was received from all subjects. The study was reviewed and approved by the Institutional Review Board of Asan Medical Center.

2.2. Assessment tools

The short form of the Affective Lability Scale (ALS-18) is an 18-item self-reported measure used to evaluate emotional instability [22–24]. The ALS-18 comprises the three following subscales: anxiety/depression (7 items), depression/elation (7 items), and anger (4 items). Each item is scored on a 0 to 3 range so that the total score ranges from 0 and 54. A higher score represents greater self-reported emotional instability.

The Insomnia Severity Index (ISI) is a brief 7-item instrument designed to measure severity of nighttime and daytime symptoms of insomnia in the past month [25,26]. Each item is scored on a 0 to 4 range so that the total score ranges from 0 to 28. An ISI score $\geq$ 15 is indicative of clinically significant insomnia.

The Patient Health Questionnaire-9 (PHQ-9) is composed of 9 items and is designed around the nine diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) for major depressive disorders [27,28]. Each item is scored on a 0 to 3 range so that the total score ranges from 0 and 27. A higher score represents a more severe degree of depression, and a PHQ-9 score $\geq$ 10 is considered to indicate depression.

The Generalized Anxiety Disorders Scale (GAD-7) is composed of 7 items to measure worry and anxiety symptoms over the last 2 weeks [29,30]. Each item is scored on a 0 to 3 range so that the total score ranges from 0 and 21. A higher score represents greater severity of anxiety, and a GAD-7 score $\geq$ 7 is considered to indicate an anxiety disorder.

2.3. Statistical analyses

Data are shown as the number and percentage for categorical variables, and as the mean and standard deviation for continuous variables. For the univariate analyses, Chi-square test, Spearman correlation test, analyses of variance, or Student *t* test were conducted. To identify significant and independent variables associated with emotional instability, we used stepwise linear regression analyses with the ALS-18 total and subscale scores as the dependent variables. The initial regression model included variables showing $p < 0.1$ in the univariate analysis as the independent variables, which are shown in Table 1. Relative contribution of variables found to be significant in stepwise linear regression was evaluated using the hierarchical linear regression analyses. Multicollinearity was determined using the variance inflation factor (<3) and condition index (<10). The assumptions of the linear regression after fitting the model was checked using a normal probability plot.

To evaluate the effect of the interaction between insomnia symptoms and recurrent seizures on emotional instability, an analysis of covariance with an interaction term was used and was adjusted by the independent variables related to emotional instability in a linear regression model. Partial eta^2 = 0.01 is considered a small effect size, 0.06 represents a medium effect size and 0.14 a large effect size. A two-tailed p-value < 0.05 was considered significant. Statistical analyses were conducted with the Statistical Package for the Social Sciences, version 21.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Subjects

Descriptive statistics from the included 171 patients are shown in Table 1. Treatment with one, two, and three or more ASMs was found in 102 (59.6%), 32 (18.7%), and 21 (14.4%) subjects,

Table 1
Subject characteristics (n = 171).

Age, years, mean (SD)	39.7 (15.4)
Men, *n* (%)	108 (63.2)
Body mass index, kg/m^2, mean (SD)	23.4 (3.7)
Education, *n* (%)	
University or higher	97 (56.7)
High school	52 (30.4)
Middle school or lower	22 (12.9)
Unemployed, *n* (%)	42 (24.6)
Age at seizure onset, years, mean (SD)	29.7 (17.2)
Epilepsy type, *n* (%)	
Generalized, idiopathic	30 (17.5)
Focal	128 (74.9)
Unknown	13 (7.6)
Predominant seizure type, *n* (%)	
Focal aware	11 (6.4)
Focal impaired awareness	66 (38.6)
Generalized or focal to bilateral TCS	94 (55.0)
Seizure frequency in the last year, *n* (%)	
Seizure free	48 (28.1)
1–11 per year	82 (48.0)
1 or more per month	41 (24.0)
Generalized or focal to bilateral TCS in the last year, *n* (%)	68 (39.8)
ASM polytherapy, *n* (%)	54 (31.6)
Individual ASM prescribed	
Levetiracetam, *n* (%)	84 (49.1)
Dose, mg per day, mean (SD)	1556.6 (707.5)
Valproic acid, *n* (%)	44 (25.7)
Dose, mg per day, mean (SD)	985.2 (419.6)
Lamotrigine, *n* (%)	30 (17.5)
Dose, mg per day, mean (SD)	220.8 (86.6)
Oxcarbazepine, *n* (%)	27 (15.8)
Dose, mg per day, mean (SD)	1161.1 (415.2)
Others*, *n* (%)	44 (25.7)
Psychiatric history, *n* (%)	26 (15.2)
Past	11 (6.4)
Current	15 (8.8)
Medical comorbidities, *n* (%)	28 (16.4)
PHQ-9 score $\geq$ 10, *n* (%)	31 (18.1)
GAD-7 score $\geq$ 7, *n* (%)	40 (23.4)
ISI score $\geq$ 15, *n* (%)	35 (20.5)
ALS-18 score (range: 0–54), mean (SD)	15.6 (11.3)
Anxiety/Depression (range: 0–21)	6.2 (5.4)
Depression/Elation (range: 0–21)	5.5 (4.2)
Anger (range: 0–12)	3.9 (3.14)

ASM, anti-seizure medication; ALS-18, a 18-item short form of Affective Lability Scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; n, number; SD, standard deviation; TCS, tonic-clonic seizure.
*Carbamazepine, topiramate, zonisamide, clobazam, clonazepam, perampanel, phenobarbital, pregabalin, phenytoin, vigabatrin, gabapentin, and lacosamide were prescribed individually less than 10%.

respectively. Sixteen subjects were currently not taking ASMs. Twenty six patients had past (n = 11) and current (n = 15) histories of psychiatric disorders including major depression (n = 19), bipolar disorder (n = 3), panic disorder (n = 2), and obsessive compulsive disorder (n = 2). Patients with a current psychiatric disorder were being treated with antidepressants, anxiolytics, and/or antipsychotics by their psychiatrists. Among the medical comorbidities noted were hypertension (n = 7), diabetes (n = 5), thyroid diseases (n = 5), systemic lupus erythematosus (n = 3), heart diseases (n = 3), liver diseases (n = 3), hyperlipidemia (n = 2), cerebral infarction (n = 2), benign prostatic hypertrophy (n = 2), asthma (n = 1), osteoporosis (n = 1), and gastritis (n = 1). The mean ALS-18 score was 15.6 ± 11.3. An ISI score $\geq$ 15, GAD-7 score $\geq$ 7, and PHQ-9 score $\geq$ 10 were noted in 20.5%, 23.4%, and 18.1% of subjects, respectively.

3.2. Variables related to total ALS-18 scores

Univariate analyses showed that total ALS-18 scores were positively associated with an ISI score $\geq$ 15, a GAD-7 score $\geq$ 7, a PHQ-9 score $\geq$ 10, seizure recurrence, higher seizure frequency, ASM polytherapy, use of levetiracetam or lamotrigine, a history of psychiatric disorder, and a high school or lower educational level (Table 2). Age, sex, body mass index, unemployed status, age at seizure onset, and the presence of generalized or focal to bilateral tonic-clonic seizures in the last year were not associated with total ALS-18 scores. A stepwise linear regression analysis found that recurrent seizures in the last year, an ISI score $\geq$ 15, a GAD-7 score $\geq$ 7, and use of levetiracetam were significant and independent variables positively associated with higher ALS-18 scores (Table 3). The coefficient of determination for the model was 0.331. There was no multicollinearity in the model.

When each of the variables was entered in the first step in the hierarchical linear regression analyses (Table 4), all variables accounted for a significant percentage (4.9–21.3%) of the variance in the ALS-18 scores (all p values < 0.01). The GAD-7 score $\geq$ 7 accounted for the largest amount (21.3%) of the variance, which was followed by the ISI score $\geq$ 15 (10.8%) and seizure recurrence (6.1%). The variance explained by use of levetiracetam (4.9%) was the smallest among the variables.

3.3. Variables related to individual ALS-18 subscale scores

The stepwise linear regression analyses showed that recurrent seizures and a GAD-7 score $\geq$ 7 were significantly associated with

Table 2
Univariate analyses showing variables with p < 0.1 in association with emotional instability in patients with epilepsy (n = 171).

	ALS-18 score, mean (SD) or correlation coefficients			
	Total (range: 0–54)	Anxiety/depression (range: 0–21)	Depression/elation (range: 0–21)	Anger (range: 0–12)
Age, years	0.131†	0.108	0.084	0.202**
Female vs. male	17.7 (11.6) vs 14.4 (10.9)†	7.8 (5.9) vs 5.2 (4.9)**	5.9 (4.2) vs 5.3 (4.2)**	4.0 (3.1) vs 3.9 (3.1)
PHQ-9 score $\geq$ 10 vs. <10	23.0 (11.2) vs 14.0 (10.6)***	11.0 (5.6) vs 5.1 (4.8)***	7.5 (4.0) vs 5.1 (4.1)**	4.6 (3.2) vs 3.8 (3.1)
GAD-7 score $\geq$ 7 vs. <7	25.0 (10.8) vs 12.7 (9.8)***	11.5 (4.8) vs 4.5 (4.5)***	8.3 (4.5) vs 4.7 (3.7)***	5.2 (3.2) vs 3.5 (2.9)**
ISI score $\geq$ 15 vs. <15	22.9 (9.7) vs 13.7 (10.9)***	10.0 (5.5) vs 5.2 (5.0)***	8.0 (3.8) vs 4.9 (4.1)***	4.9 (2.9) vs 3.7 (3.1)*
Seizures $\geq$ 1/month vs. 1–11/year vs. seizure free	20.4 (10.1) vs 15.8 (11.1) vs 11.2 (10.7)***	8.4 (4.8) vs 6.1 (5.3) vs 4.4 (5.5)**	7.0 (3.7) vs 5.7 (4.3) vs 4.1 (4.0)**	5.0 (3.0) vs 4.1 (3.1) vs 2.7 (2.7)**
Seizure recurrence vs. seizure freedom	17.3 (11.1) vs 11.2 (10.7)**	6.9 (5.3) vs 4.4 (5.5)**	6.1 (4.1) vs 4.1 (4.0)**	4.4 (3.1) vs 2.7 (2.7)**
ASM polytherapy vs. monotherapy	19.3 (11.6) vs 13.9 (10.7)**	7.9 (5.6) vs 5.4 (5.2)**	6.8 (4.1) vs 5.0 (4.1)**	4.6 (3.1) vs 3.6 (3.1)*
Use of levetiracetam vs. not	18.1 (11.3) vs 13.1 (10.7)**	7.4 (5.4) vs 5.0 (5.2)**	6.4 (4.2) vs 4.7 (4.0)**	4.4 (3.0) vs 3.5 (3.1)*
Use of lamotrigine vs. not	20.1 (12.4) vs 14.5 (10.8)*	9.2 (6.4) vs 5.5 (5.0)**	6.7 (4.6) vs 5.3 (4.1)	4.2 (3.0) vs 3.9 (3.1)
High school or lower education vs. not	17.6 (11.5) vs 14.1 (10.9)*	6.6 (5.3) vs 5.8 (5.6)	6.1 (4.2) vs 5.1 (4.1)	4.9 (3.4) vs 3.2 (2.6)***
Psychiatric history: yes vs. no	22.5 (12.0) vs 14.4 (10.7)**	10.1 (6.2) vs 5.5 (5.0)***	7.8 (4.6) vs 5.1 (4.0)**	4.6 (3.2) vs 3.8 (3.1)

ASM, antiepileptic drug; ALS-18, the 18-item short form of the Affective Lability Scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation.
†p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001.

Table 3
A stepwise linear regression model for factors associated with emotional instability in patients with epilepsy ($n = 171$).

	Scores of the ALS-18 (range: 0–54)		
	B	SE	*p* value
GAD-7 score ≥ 7	10.140***	1.770	<0.001
ISI score ≥ 15	5.960**	1.840	0.001
Seizure recurrence[a]	5.380**	1.602	0.001
Use of levetiracetam	3.151*	1.455	0.032

B, non-standardized coefficient; ALS-18, a 18-item short form of Affective Lability Scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; SE, standard error.
[a]Reference: seizure freedom in the last year.

all individual subscale scores, an ISI score ≥ 15 and use of levetiracetam were associated with the anxiety/depression and depression/elation subscale scores, use of lamotrigine and female sex were only associated with the anxiety/depression subscale score, and high school or lower educational level was only associated with the anger subscale score (Table 5). These models for anxiety/depression, depression/elation, and anger subscales explained 43.3%, 23.7%, and 17.5% of the variance in the individual ALS-18 subscales, respectively. There was no multicollinearity in these models.

3.4. Interaction between insomnia symptoms and seizure recurrence

The interaction between recurrent seizures and an ISI score ≥ 15 had a significant effect on the ALS-18 total scores ($F = 6.812$, $p = 0.010$, partial eta$^2 = 0.040$) (Table 6). Specifically, an ISI score ≥ 15 was positively associated with ALS-18 scores in both patients with and without seizure recurrence in the last year. However, this association reached significance in patients without seizure recurrence ($B = 14.227$, $p < 0.001$), but not in those with recurrent seizures ($B = 3.531$, $p = 0.084$). Conversely, the presence of recurrent seizures was positively associated with ALS-18 scores in patients with an ISI score < 15 ($B = 7.283$, $p < 0.001$), but not in those with an ISI score ≥ 15.

Table 4
Hierarchical linear regression analyses showing the relative contribution of each variable to emotional instability in patients with epilepsy ($n = 171$).

Variables	Scores of the ALS-18 (range: 0–54)			
	Entered first		Entered last	
	ΔR^2	*p* value	ΔR^2	*p* value
GAD-7 score ≥ 7	0.213	<0.001	0.132	<0.001
ISI score ≥ 15	0.108	<0.001	0.042	0.001
Seizure recurrence[a]	0.061	0.001	0.045	0.001
Use of levetiracetam	0.049	0.004	0.019	0.032

ALS-18, a 18-item short form of Affective Lability Scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; ΔR^2, R^2 change.
[a]Reference: seizure freedom in the last year.

Table 5
Stepwise linear regression models for factors associated with ALS-18 subscale scores in patients with epilepsy ($n = 171$).

	ALS-18 scores								
	Anxiety/depression (range: 0–21)			Depression/elation (range: 0–21)			Anger (range: 0–12)		
	B	SE	*β*	*B*	SE	*B*	*B*	SE	*β*
GAD-7 score ≥ 7	5.473***	0.802	0.427	2.829***	0.702	0.287	1.631**	0.513	0.224
Seizure recurrence[a]	1.954**	0.720	0.162	1.697**	0.635	0.183	1.471**	0.489	0.215
ISI score ≥ 15	2.482**	0.839	0.185	2.241**	0.730	0.217	–	–	–
Use of levetiracetam	1.667*	0.657	0.154	1.142*	0.577	0.137	–	–	–
Use of lamotrigine	2.100*	0.880	0.147	–	–	–	–	–	–
Female	1.528*	0.674	0.136	–	–	–	–	–	–
High school or lower education	–	–	–	–	–	–	1.445**	0.444	0.233

B, non-standardized coefficient; β, standardized coefficient; ALS-18, the 18-item short form of the Affective Lability Scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; SE, standard error.
[a]Reference: seizure freedom in the last year.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 6
Analysis of covariance showing insomnia-by-seizure recurrence interaction effects on emotional instability in patients with epilepsy ($n = 171$).

Effects	Groups	Interaction *p*-value	Total ALS-18 scores			
			B	SE	*p*-value	Partial eta^2
ISI score ≥ 15	No seizure recurrence[a]	0.025	14.227	3.648	<0.001	0.084
	Seizure recurrence[a]		3.531	2.034	0.084	0.018
Seizure recurrence	ISI score < 15		7.283	1.735	<0.001	0.096
	ISI score ≥ 15		−3.413	3.718	0.360	0.005

B, non-standardized coefficient; ALS-18, the 18-item short form of the Affective Lability Scale; ISI, Insomnia Severity Index; SE, standard error.
Note: The model was adjusted by a General Anxiety Disorder-7 score ≥ 7 and the use of levetiracetam.
[a]Reference: seizure status in the last year.

4. Discussion

We identified significant and independent factors that were positively associated with emotional instability in patients with epilepsy. These included anxiety symptoms, the presence of recurrent seizures in the last year, regardless of seizure frequency, the presence of insomnia symptoms, and use of levetiracetam. Among these, anxiety symptoms were most strongly associated with overall emotional instability and all of its subscales, except the anger subscale, measured by the ALS-18. An association between depressive symptoms and emotional instability was also significant in the univariate analysis, but not in the stepwise linear regression model. This loss of significance was likely due to the strong correlation between depressive and anxiety symptoms ($p < 0.001$). Our findings are consistent with previous results of a significant relationship between emotional instability and comorbid psychiatric disorders in patients with epilepsy. For example, a recent Italian study showed that depressive symptoms were correlated with emotional instability, as measured using the Difficulties in Emotion Regulation Scale, after controlling for felt stigma of epilepsy [6]. In a study on bipolar symptoms in patients with epilepsy, 10 (10.1%) out of 99 patients met the criteria for bipolar disorder according to the Mood Disorder Questionnaire; of the seven patients interviewed, only one received a formal diagnosis of bipolar disorder, but all met the criteria for some depressive disorders [31]. The association between IDD and psychiatric disorders such as depression and anxiety has also been significant in most related studies [8–10,14].

Among epilepsy-related factors, seizure recurrence, seizure frequency, and ASM polytherapy were positively associated with emotional instability in our univariate analyses, but only the presence or absence of seizure recurrence in the last year, regardless of seizure frequency, remained significant after controlling for anxiety and insomnia symptoms. Studies on IDD and its association with epilepsy-related variables have revealed conflicting results [9–11,32]. Some studies found that IDD was associated with a younger age at seizure onset [9], refractory complex partial seizures [9], and ASM polytherapy [10], but others have found no associations of IDD with seizure frequency [11,32], a longer disease duration [9–11,32], or ASM polytherapy [9,11,32]. In a recent Italian study, the number of ASMs used was positively correlated with scores of the Difficulties in Emotion Regulation Scale in a univariate analysis, but not in a stepwise regression analysis [6]. In addition, Yang et al. showed that ASM polytherapy was one of the significant variables for moderate-to-severe insomnia in patients with epilepsy [33]. However, in the present study, ASM polytherapy was not found to be associated with emotional instability after controlling for anxiety and insomnia symptoms.

We found that the significant interaction between sleep disturbance and recurrent seizures had an effect on emotional instability. However, unexpectedly, the presence of recurrent seizures in the last year was positively associated with emotional instability in patients without insomnia symptoms, but not in those with insomnia symptoms. These findings suggest that there are no additive effects of seizure recurrence on emotional instability in patients with insomnia. In contrast, insomnia symptoms were positively associated with emotional instability in both patients with and without seizure recurrence although this association did not reach statistical significance in those with seizure recurrence ($p = 0.084$). The effect size was considerably larger in those without seizure recurrence than those with seizure recurrence. These differential effects of insomnia symptoms and seizure recurrence on emotional instability could be explained in part by that insomnia symptoms accounted for larger amount of the variance of the ALS-18 than seizure recurrence, shown in the hierarchical linear regression. Similarly, the effects of insomnia symptoms on emotional instability in patients without seizure recurrence were two times higher than in those with recurrent seizures in patients without insomnia symptoms.

In the present study, levetiracetam use was significantly and independently associated with emotional instability. Levetiracetam has a unique action mechanism that involves binding to the synaptic vesicle protein 2A, which is thought to affect neurotransmitter release from presynaptic vesicles [34]. Levetiracetam is known to have psychiatric and behavioral adverse effects, including depression, irritability, agitation, aggression, and emotional instability [35,36]. These adverse events occur more often in children and adolescents than in adults [35]. One randomized controlled trial found that the total number of behavioral adverse events, including hostility, nervousness, emotional instability, and agitation, significantly differed between pediatric patients receiving levetiracetam versus those receiving a placebo [37]. In addition, the positive association between lamotrigine use and the ALS-18 anxiety/depression subscale scores in our study is likely to have resulted from selection bias rather than a negative behavioral effect of lamotrigine. Lamotrigine is a well-known mood stabilizing agent [38]. Therefore, lamotrigine is more likely to have been prescribed in patients with mood problems such as depression or anxiety.

Some caution should be noted when interpreting our findings. First, our data do not provide evidence for causal or temporal relationships because the study was cross-sectional. Second, there were some overlap between the questionnaires we used. For example, item 3 (trouble falling or staying asleep, or sleeping too much), item 4 (feeling tired or having little energy), and item 7 (trouble concentrating on things) of the PHQ-9 assess insomnia and daytime functioning [27], which were also measured by item 1a (difficulty falling asleep), item 1b (difficulty staying asleep), and item 3 (to interfere with your daily functioning) of the ISI [25]. Although the ALS-18 focuses on measuring emotional fluctuation [23] rather than the stationary level of depression and anxiety assessed by the PHQ-9 and GAD-7, respectively [27,29], all of them are considerably related each other. Third, it was possible that unexpected findings of interaction between insomnia and seizures on emotional instability might result from uncontrolled confounding factors such as seizure severity and inadequate management of current mental illnesses. We measured seizure frequency but not seizure severity. A previous study showed that, if psychological variables were removed from analysis, seizure severity, but not seizure frequency, was the most significant predictor of self-esteem, locus of control, and anxiety [39]. Information about the specific medication for the treatment of current psychiatric disorders were not collected from subjects with epilepsy. They might bias the findings in the present study. Finally, the study subjects enrolled from tertiary hospitals were likely to have more severe seizures than those recruited from primary healthcare clinics, and the majority (87.1%) of patients had a formal education of 12 or more years. Despite the biased study sample, our main findings concerning the relationships between seizure recurrence, insomnia symptoms, and emotional instability could be applicable to a wider population of patients with epilepsy.

In summary, seizure recurrence and insomnia symptoms were positively associated with emotional instability, independent of anxiety symptoms, in patients with epilepsy. The association between seizure recurrence and emotional instability was significantly modulated by sleep in patients without insomnia symptoms only. Conversely, the association between insomnia symptoms and emotional instability was significantly modulated by seizure status in patients without seizure recurrence only. Overall, these findings enhance our understanding of emotional instability in patients

with epilepsy, and may have clinical implications in the development of interventions for emotional instability in these patients.

Conflicts of interest

The authors declare no conflicts of interest in relation to this study.

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