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Insomnia and Epilepsy: A Questionnaire-Based Study

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SCIENTIFIC INVESTIGATIONS

Study Objectives: Although disturbed sleep has been frequently reported in patients with seizures, little is known about insomnia and epilepsy. The aims of this study were (1) to analyze the prevalence and degree of insomnia in patients with epilepsy, (2) to examine the clinical features and correlates of insomnia in these patients, and (3) to evaluate the impact of poor sleep on their quality of life.

Methods: One hundred-fifty-two patients with epilepsy (mean age 46 years) completed the following questionnaires: Insomnia Severity Index, Pittsburgh Sleep Quality Index, Beck Depression Inventory-II, Quality of Life in Epilepsy Inventory-31. Patients with other known sleep disorders, including obstructive sleep apnea, were excluded from the study. Regression analysis was conducted for adjusting for age, years since epilepsy onset, number of antiepileptic drugs, comorbidities, and depression scores.

Results: More than half of the participants (55%) suffered from insomnia and more than 70% were "poor sleepers." Insomnia and poor sleep quality were significantly correlated with the number of antiepileptic medications and scores of depressive symptoms. After controlling for covariates, insomnia and poor sleep quality were significant predictors of lower quality of life.

Conclusion: These results suggest that insomnia and poor sleep are common in patients with epilepsy and may adversely impact quality of life. Further studies should examine whether improvements in sleep can improve seizure control and quality of life of these patients.

Keywords: Insomnia, sleeplessness, dyssomnias, seizures, convulsions, epilepsy, depression, anticonvulsants, antiepileptics.

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Disturbed sleep and sleep breathing disturbances are common in patients with epilepsy.[1-5] Polysomnogram studies of patients with epilepsy have shown disrupted sleep with increased sleep onset latency, increased number of nocturnal awakenings, and altered sleep architecture.[6-9]

Despite the increasing recognition of sleep disturbances as predictors of quality of life in these patients,[1,10-12] insomnia in epilepsy has been poorly investigated. Some studies have focused on the impact of antiepileptic drugs (AEDs) on sleep quality.[13-15] Overall, the available information on the prevalence and the predictors of insomnia in this patient population is limited.[16-18]

The aims of this study were (1) to analyze the prevalence and degree of insomnia in patients with epilepsy, (2) to examine the clinical features and predictors of insomnia in these patients, and (3) to evaluate the impact of poor sleep on their quality of life.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Despite significant research on the prevalence and health impact of sleep disorders in patients with seizures, there is a relative paucity of data on insomnia among these patients. This study describes the prevalence and clinical features of insomnia in epilepsy patients and its impact of their quality of life.

Study Impact: Our study increases the awareness that insomnia and poor sleep quality are common in a clinical cohort of patients with epilepsy, and these may adversely impact their quality of life. These findings highlight the need for increased screening by healthcare providers, and for further research exploring whether treatment of insomnia may improve seizure control in these patients.

METHODS

Study Population

This retrospective study presents an analysis of descriptive data collected at the baseline assessment of adult epilepsy patients seen at the Boston University Neurology outpatient clinic. Data were collected consecutively between July 2010 and October 2011. Assessment of sleep and depressive symptoms with questionnaires was part of standard clinical practice in the epilepsy clinic, and institutional review board approval from Boston University was obtained to review these data retrospectively. Patients older than 18 years of age with a physician-confirmed diagnosis of epilepsy were included in the study. In addition, patients with non-epileptic spells and pregnant patients were excluded from the analysis. Patient with history of cardiovascular accidents and history of mental retardation were not excluded, as none of these conditions involved language disability or mental disability of the degree to preclude reliable survey response. Of 195 patients eligible for entry in the study, 14 were excluded because of incomplete questionnaire data. Another 29 patients were excluded because of known history of sleep disorders fulfilling diagnostic criteria of the International Classification of Sleep Disorders and confirmed by a sleep specialist.[19,20] Comorbid sleep disorders included obstructive sleep apnea, circadian rhythm disorders, narcolepsy, REM behavior disorder, periodic limb movement disorder, and restless legs syndrome. Patients with preexisting diagnosis of insomnia were not excluded from the study.

Specifically, when diagnosis had to be supported by polysomnogram findings, obstructive sleep apnea was defined as apnea-hypopnea index ≥ 5 events per hour, and periodic limb

movement disorder was defined as a periodic limb movement index ≥ 15 events per hour.[19]

Demographic and clinical data were collected using a structured data collection instrument. For each patient, we recorded age, gender, and clinical characteristics, including seizure types, seizure frequency, relationship of seizure to sleep, number of years from epilepsy diagnosis, medications, current number and types of AEDs, electroencephalography (EEG) results, Epworth Sleepiness Scale (ESS), and comorbidities.

Measures

Insomnia and Sleep Quality

Insomnia and sleep quality were measured with the Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality Index (PSQI). The ISI is a self-report questionnaire measuring the patient's perception of his or her insomnia. The ISI consist of 7 items assessing the severity of sleep onset and sleep maintenance difficulties, satisfaction with current sleep, interference with daily functioning, degree of impairment attributed to the sleep issue, and degree of concern caused by the sleep problem.

The PSQI measures self-reported sleep quality and disturbances over the last 1 month time period.[21] The scale includes 19 items and measures 7 components of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The global PSQI score is obtained by the sum the 7 component scores (range = 0-21). The PSQI global score differentiates "good sleepers" (PSQI total score ≤ 5) from "poor sleepers" (PSQI > 5) with sensitivity of 89.6% and specificity of 86.5%.[21] The PSQI has validated psychometric properties such as internal consistency and test-retest reliability.

Depression

We used the Beck Depression Inventory-II (BDI-II) to measure depressive symptoms. The BDI-II is a validated 21-item measure designed to assess depressive symptoms.[22] The total score is obtained by summing the scores for the 21 questions (each item range 0-3; total range = 0-63). A total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe. As the BDI-II contains one item referring to sleep patterns, these were omitted from the analysis to avoid false associations with PSQI scores. The BDI-II is known to have high internal consistency and high test-retest reliability.[22]

Quality of Life

The Quality of Life in Epilepsy Inventory-31 (QOLIE-31) is a widely used epilepsy-specific self-administered instrument.[23] The 31-item questionnaire contains 7 subscales (emotional well-being, social function, energy/fatigue, cognitive function, seizure worry, medication effects, and overall quality of life) and one question about overall health status. Raw scores are converted to 0-100 range scores, with higher scores indicating better quality of life. Total and subscale scores were calculated according to the QOLIE-31 scoring manual.

Statistical Analysis

Data analyses were conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL). Summary statistics were presented as mean (standard deviation) for continuous variables and as frequencies for the categorical data. Independent-sample *t*-test was used to examine differences between values of normally distributed variables, and the Mann-Whitney U test was used for variables which were not normally distributed. The χ^2 test was used to analyze differences between categorical variables. Correction for multiple comparisons was not performed. Bivariate relations between continuous variables were examined with Pearson product-moment correlation. Hierarchical regression analysis was used to examine the relationship between ISI and PSQI scores and quality of life, while controlling for covariates. The following covariates were entered in the first step of the regression analysis: Age, Years since epilepsy onset, Number of comorbidities, Number of AEDs, Depression scores (BDI-II). ISI and PSQI scores were independently entered in the second step of the regression analysis. The total QOLIE-31 score was used as outcome variable.

RESULTS

A total of 152 patients with epilepsy were included into the analysis. Demographic and clinical characteristics of the participants are presented in **Table 1**. The mean age of the group was 46 years, ranging from 20 to 88. Comorbid mood disorders were found in 48%, although the majority of the patients (81%) had a BDI-II score representing minimal level of depression (0-13). Of the 74 patients (48%) with mood disorders, major depression was the most common (n = 50), followed by bipolar disorder (n = 11), generalized anxiety disorder (n = 7), dysthymia (n = 2), posttraumatic stress disorder (n = 2), panic disorder (n = 1), and obsessive compulsive disorder (n = 1). Neurological conditions included headaches (25), cardiovascular accidents (15), neuropathies and chronic pain conditions (20), mental retardation (9), neoplasm (6), and head trauma (6). The whole sample had an average QOLIE of 70.3.

Overall, the ISI scores indicated that 78 (51%) participants suffered from insomnia (moderate severity and severe insomnia). According to the PSQI data, the whole sample included 72% "poor sleepers" (with PSQI > 5). ISI and PSQI scores in respect to their demographic and epilepsy-related clinical characteristics are presented in **Table 2**. In both groups of insomniacs and poor sleepers the female gender predominated (58% in both groups, p = 0.03 and 0.02, respectively). There were higher numbers of participants on AED polytherapy among the insomniacs and poor sleepers than the non-insomniacs (p = 0.03 and p = 0.04, respectively). The most commonly used AED in monotherapy and polytherapy was levetiracetam (n = 25 in both monotherapy and polytherapy). Data on prevalence of insomnia complaints per specific AED, when used in monotherapy or polytherapy, are shown in **Table 3**. No differences between prevalence of sleep complaints among different AED types were found. Poorer sleep quality and higher degree of insomnia were associated with higher number of AEDs and higher degree of depressive symptoms (BDI-II) (**Table 4**). The ISI score and the PSQI global score were significantly correlated with the QOLIE total score and all 7 domains of the QOLIE (significance for all p < 0.01).

Multivariate analysis adjusting for covariates was performed in order to examine the associations between sleep quality

and insomnia complaints and quality of life (QOLIE score) (**Table 5**). Depressive symptoms were significantly associated with QOLIE ($\beta = -0.88$, $p < 0.01$). After controlling for age, years since epilepsy onset, number of comorbidities, number of AEDs, and depression symptoms, insomnia was a significant predictor of QOLIE ($\beta = -0.43$, $p < 0.01$). After adjusting for the same above covariates, sleep quality was also a significant predictor of QOLIE ($\beta = -0.40$, $p < 0.01$).

DISCUSSION

This hypothesis-generating study suggests that insomnia by ISI and poor sleep quality by PSQI correlate with number of antiepileptic medications, and higher scores of depressive symptoms. After controlling for covariates, insomnia and poor sleep quality were significant predictors of lower quality of life.

In epilepsy, AED polytherapy is generally needed in pharmaco-resistant cases, and the higher the number of AEDs needed, the higher is the degree of severity of pharmaco-resistance. Therefore the tight relation between insomnia scores and AED polypharmacy suggests that insomnia may occur as a consequence of the disease itself, or it may be secondary to the effects of medications. Although some studies have suggested that specific AEDs may have detrimental effects on sleep,[24] in the present study we did not find any correlation between specific AEDs and insomnia scores. These results may have been confounded by differences in dosages of AEDs and differences in length of therapies.[14]

Contrary to what may be suggested by other investigations,[16,18] we did not find that insomnia correlated with poor seizure control. It is accepted that prolonged awakening is related to increased cortical excitability and susceptibility to seizures,[25] and that regulatory mechanisms of sleep-wake cycle can affect the expression of epilepsy.[26-28] For example, epileptiform discharges are activated during SWS, while seizures are promoted during lighter NREM sleep stages.[29] Given this intrinsic relationship between sleep and epileptogenesis, we could hypothesize a relation between insomnia and seizures at the clinical level. In the present study there were no polysomnographic data taken into account, and the small sample size may have limited the analysis. Larger prospective studies should evaluate the impact of insomnia and poor sleep on seizure control.

More than half of the participants (55%) suffered from insomnia and more than 70% were "poor sleepers." These prevalences of insomnia in our sample are higher than those of the general population.[30,31] Khatami and colleagues examined 100 clinic patients with epilepsy and found sleep onset insomnia in 33 of 98 subjects (34%) and sleep maintenance insomnia in 50 of 97 subjects (52%).[17] Lower prevalence of insomnia in epilepsy patients has been reported by Piperidou and colleagues, who found that only 24% of their cohort of 122 subjects suffered from insomnia, as measured with the Athens Insomnia Scale (AIS).[32] We may relate this discrepancy to different assessment instruments. Both ISI and AIS are brief self-report instruments comprising 7 items assessing the severity of sleep-onset and sleep maintenance difficulties and their impact in daily functioning. In conjunction with the ISI, we used also the PSQI which contains 19 items measuring sleep quality and disturbance over the last month.[21] We could also attribute differences in prevalence of insomnia to differences between the studies populations, as the study by Piperidou examined the a population from three University Hospitals of Greece, while our study included patients from a major inner city hospital of the United States.

About 48% of our sample had history of a mood disorder, and depressive scores strongly correlated with both ISI and PSQI.

Table 1—Clinical characteristics of all patients (n = 152)

Gender (males/females)	79/73
Age (years, mean ± SD)	46 ± 16 (range 20-88)
Epilepsy etiology (unknown/known)	107/45
EEG findings (normal/abnormal)	98/54
Epworth Sleepiness Scale (mean ± SD)	3 ± 3
Years of epilepsy (mean ± SD)	6 ± 6
Comorbid Psychiatric Disorders and Symptoms	
Mood disorders	74 (48%)
Psychotic disorders	9 (6%)
Disorders usually seen in childhood and adolescence	2 (1%)
Other disorders and symptoms	8 (5%)
Comorbid Medical Disorders, Conditions, and Symptoms	
Neurological	56 (37%)
Cardiovascular	48 (32%)
Pulmonary	36 (24%)
Digestive	14 (9%)
Genitourinary and reproductive	15 (10%)
Endocrine	21 (14%)
Musculoskeletal	22 (14%)
Contributing Medications and Substances	
Antidepressants	50 (33%)
Stimulants	4 (3%)
Decongestants	1 (1%)
Narcotic analgesics	21 (14%)
Cardiovascular	48 (31%)
Pulmonary	36 (24%)
Alcohol	18 (12%)
Mean AEDs per patient	
No AEDs	27 (17%)
One AED	80 (53%)
Two or more AEDs	45 (30%)
Insomnia Severity Index	
No clinically significant insomnia (0-7)	23 (15%)
Subthreshold insomnia (8-14)	51 (33%)
Clinical insomnia (moderate severity) (15-21)	63 (41%)
Clinical insomnia (severe) (22-28)	15 (10%)
Pittsburgh Sleep Quality Index	
"good sleepers" (PSQI ≤ 5)	43 (28%)
"poor sleepers" (PSQI > 5)	109 (72%)
Quality of Life in Epilepsy Inventory-31	70.22 ± 19.3
Beck Depression Inventory-II	
Minimal (0-13)	123 (81%)
Mild (14-19)	25 (16%)
Moderate (20-28)	3 (2%)
Severe (29-63)	1 (1%)

EEG, electroencephalogram; mo, month; SD, standard deviation; AED, antiepileptic drug.

Table 2

Insomnia Severity Index	Non-Insomnia group (n = 74)	Insomnia group (n = 78)	p-value
Age	47.3 ± 15.2	44.3 ± 13.4	0.44
Gender (females)	28 (38%)	45 (58%)	0.03
Known epilepsy etiology	20 (27%)	25 (16%)	0.71
Years of epilepsy	4 ± 4	5 ± 4	0.08
Abnormal EEG	25 (34%)	29 (37%)	0.9
Seizure frequency (/mo)	1 ± 1	0.9 ± 0.9	0.9
Focal seizures	18 (24%)	22 (28%)	0.8
Nocturnal seizures	6 (8%)	10 (13%)	0.7
AED monotherapy	37 (50%)	43 (55%)	0.9
AED polytherapy	10 (13%)	35 (45%)	0.03
Pittsburgh Sleep Quality Index	**Good sleepers (n = 43)**	**Poor sleepers (n = 109)**	**p-value**
Age	41.3 ± 11	48.9 ± 9.9	0.2
Gender (females)	10 (23%)	63 (58%)	0.02
Known epilepsy etiology	12 (28%)	33 (30%)	0.8
Years of epilepsy	5 ± 5	6 ± 6	0.09
Abnormal EEG	13 (30%)	41 (38%)	0.7
Seizure frequency (/mo)	1.3 ± 1	1.5 ± 1.5	0.8
Focal seizures	12 (28%)	28 (26%)	0.7
Nocturnal seizures	4 (9%)	12 (11%)	0.8
AED monotherapy	21 (48%)	59 (54%)	0.9
AED polytherapy	5 (12%)	40 (37%)	0.04

EEG, electroencephalogram; mo, month; AED, antiepileptic drug. Student t-test (normally distributed) and Mann-Whitney U test (not normally distributed). Chi-square test was used to analyze differences between categorical variables.

Table 3—Insomnia (ISI ≥ 15) and poor sleep (PSQI > 5) for each AED therapy

AED Monotherapy	Patients on AED (N = 80)	Patients with Insomnia (N = 43)	Poor Sleepers (N = 59)
Levetiracetam	25	12 (48%)	20 (80%)
Phenytoin	16	10 (63%)	14 (88%)
Oxcarbazepine	13	6 (46%)	6 (46%)
Lamotrigine	6	4 (67%)	5 (83%)
Valproic Acid	7	3 (43%)	5 (71%)
Topiramate	5	2 (40%)	3 (60%)
Gabapentin	1	1 (100%)	1 (100%)
Carbamazepine	7	5 (71%)	5 (71%)
AED Polytherapy	**Patients on AEDs (N = 45)***	**Patients with Insomnia (N = 35)***	**Poor Sleepers (N = 40)***
Levetiracetam	25	18 (72%)	22 (88%)
Phenytoin	9	6 (67%)	7 (78%)
Oxcarbazepine	20	11 (55%)	15 (75%)
Lamotrigine	12	6 (50%)	5 (42%)
Valproic Acid	8	4 (50%)	4 (50%)
Topiramate	6	4 (67%)	5 (83%)
Gabapentin	7	4 (57%)	6 (86%)
Carbamazepine	9	5 (57%)	7 (78%)

AED, antiepileptic drug; *Each patient is included in more than one category.

Table 4—Correlations between ISI/PSQI scores and continuous variables

	ISI	PSQI
Age	0.12	0.03
ESS	0.03	0.01
Years since epilepsy onset	0.06	0.08
Number of comorbidities	0.09	0.08
Number of AEDs	0.36*	0.30*
BDI-II	0.42*	0.44*
QOLIE-31		
Total score	-0.47*	-0.42*
Emotional well-being	-0.33*	-0.29*
Social function	-0.30*	-0.41*
Energy/fatigue	-0.48*	-0.31*
Cognitive function	-0.28*	-0.33*
Seizure worry	-0.34*	-0.32*
Medication effects	-0.45*	-0.42*
Overall quality of life	-0.49*	-0.43*

AED, antiepileptic drug; BDI-II, Beck depression inventory-II; QOLIE-31, Quality of life in epilepsy-31. *Significant for p < 0.01.

Most patients were found to have low depressive scores, and this may be secondary to partial and/or successful treatment. Depression represents one of the most common comorbidities of epilepsy and has profound negative impact on the quality of life of patients.[33-35] It has been hypothesized that in patients with seizures dysregulation of the hypothalamus-pituitary-adrenal axis may cause deficit in the raphe-hippocampal serotonergic transmission and predispose to depression.[36] Similar mechanisms involving the alteration of serotoninergic transmission may explain the apparent clinical link between epilepsy and insomnia.

Insomnia correlated negatively with all the seven subscales of QOLIE-31. After adjusting for covariates poor sleep quality was a significant predictor of quality of life. Our results are similar to those of Piperidou and colleagues in a sample of epilepsy patients[16] and other studies showing a negative impact of insomnia on quality of life in the general population.[37,38]

Table 5—Regression analysis for insomnia and sleep quality predicting quality of life (QOLIE)

Step	Variables	ΔR^2	Total R^2	F	β	T
1	Age	0.33	0.33	31.2*	0.09	1.55
	Years since epilepsy onset				0.02	0.32
	Number of comorbidities				0.05	0.65
	Number of AEDs				0.05	0.71
	Depression (BDI-II)				-0.42*	-9.9
2	Insomnia (ISI)	0.02	0.32	26.9*	-0.16*	-2.60
2	Sleep quality (PSQI)	0.03	0.4	27.1*	-0.19*	-3.10

QOLIE-31, Quality of life in epilepsy-31; AED, antiepileptic drug; BDI-II, Beck depression inventory-II; ISI, Insomnia severity index; PSQI, Pittsburgh sleep quality index. *Significant for $p < 0.001$. R^2, R-squared (coefficient of determination); ΔR^2, R-squared change; F, F-value of the F statistic; β, standardized coefficient beta; t, t-value of the t statistic.

The present study has several limitations. Given that sleep apnea is common and often unrecognized in patients with epilepsy,[2,3] results may have been confounded by excluding only patients with a known diagnosis of sleep apnea. Given that sleep apnea *per se* may present with insomnia symptoms,[20] results may have been confounded by including patients with undiagnosed sleep apnea. We only assessed insomnia with subjective measures consisting in questionnaires on self-reported sleep disturbances and insomnia symptoms. The collection of sleep logs and objective measures such as actigraphy would yield a more global assessment of insomnia[39] and enable further exploration between sleep features and epilepsy variables. Additionally, our evaluation of insomnia and sleep quality consisted in a one-time only assessment. Longitudinal collection of data and information on outcomes of insomnia treatment will allow gathering further knowledge on the impact of insomnia on seizure control and quality of life for these patients.

Taken together, these results suggest that insomnia and poor sleep are common in patients with epilepsy and may adversely impact quality of life. Insomnia may occur as a direct consequence of the disease itself or may be secondary to associated factors, such as depression or the effects of medications. Interventions to improve sleep hygiene can be suggested to patients as part of more comprehensive epilepsy education programs.[40,41] Management of insomnia in patients with seizures should be individualized to each patient's needs. The type of insomnia and any underlying causes of disturbed sleep must first be determined, paying particular attention to underlying mood dysfunctions and polypharmacy.

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