Epilepsy & Behavior 60 (2016) 27–32

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Severity of self-reported insomnia in adults with epilepsy is related to comorbid medical disorders and depressive symptoms

Kwang Ik Yang [a], Madeleine Grigg-Damberger [b], Noah Andrews [c], Colin O'Rourke [d], James Bena [d], Nancy Foldvary-Schaefer [c,*]

[a] Sleep Disorders Center, Department of Neurology, Soonchunhyang University College of Medicine, Cheonan Hospital, Cheonan, Republic of Korea
[b] Department of Neurology, University of New Mexico, Albuquerque, NM, USA
[c] Sleep Disorders and Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
[d] Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

ARTICLE INFO

Article history:
Received 17 February 2016
Revised 12 March 2016
Accepted 14 March 2016
Available online 10 May 2016

Keywords:
Epilepsy
Insomnia
Severity
Comorbidities
Insomnia Severity Index

ABSTRACT

Background: Few studies have systematically investigated insomnia in adults with epilepsy.
Methods: We performed a prospective cross-sectional investigation of the prevalence, severity, and comorbidities of insomnia in 90 adults with epilepsy using a battery of self-reported instruments and polysomnography. We quantified insomnia severity using the Insomnia Severity Index (ISI).
Results: Fifty-nine of 90 (65.5%) adults with epilepsy reported insomnia (ISI ≥ 8), moderate or severe (ISI ≥ 15) in 28.9%. Good agreement between standard clinical diagnostic criteria and ISI was found for patients with ISI scores <8 and ≥15. Scores on the modified Beck Depression Inventory (mBDI) ($r = 0.25$, $p = 0.021$), the original BDI ($r = 0.32$, $p = 0.002$), and self-reported total sleep duration (TSD) ($r = -0.3$, $p = 0.006$) were significantly related to ISI score. A multiple regression model found that decreased TSD (ß = −0.93, $p = 0.007$), head trauma (ß = 4.37, $p = 0.003$), sedative–hypnotic use (ß = 4.86, $p = 0.002$), AED polytherapy (ß = 3.52, $p = 0.005$), and asthma/COPD (ß = 3.75, $p = 0.014$) were predictors of a higher ISI score. For 63 patients with focal epilepsy, an increased mBDI (ß = 0.24, $p = 0.015$), decreased TSD (ß = −1.11, $p = 0.008$), asthma/COPD (ß = 4.19, $p = 0.02$), and epilepsy surgery (ß = 5.33, $p = 0.006$) were significant predictors of an increased ISI score. Patients with temporal lobe epilepsy (TLE) showed a trend for greater severity compared with those with extra-TLE (ß = −2.92, $p = 0.054$).
Conclusions: Our findings indicate that severity of insomnia in adults with epilepsy is more likely to be associated with comorbid medical and depressive symptoms and less likely to be directly related to epilepsy. Good agreement between standard clinical diagnostic criteria for insomnia and the ISI for subjects without insomnia symptoms and for those with moderate-to-severe symptoms supports the use of this instrument in epilepsy research.

1. Introduction

Sleep and epilepsy are common but often poor bedfellows. Sleep disorders are two to three times more common in adults with epilepsy compared with those in general age-matched populations [1–4]. The few prospective studies that have examined sleep complaints in adults with epilepsy have identified sleep maintenance insomnia (difficulty staying asleep) as the most common sleep/wake complaint in adults with epilepsy. The few prospective studies examining the complaint of insomnia in adults with epilepsy have been based primarily on self-reported sleep questionnaires [1,3,5–9].

To better understand the prevalence, severity, and comorbidities of insomnia in adults with epilepsy, we chose to systematically study it using structured interviews and a battery of validated self-reported questionnaires including the Insomnia Severity Index (ISI) [10] and performed in-laboratory video-polysomnography (PSG) with 18-channel EEG to identify undiagnosed obstructive sleep apnea (OSA).

2. Materials and methods

2.1. Study population

We prospectively enrolled consecutive adults (≥18 years) with epilepsy seen in the Cleveland Clinic Epilepsy Center in a cross-sectional study exploring the prevalence of sleep disorders and previously published the prevalence and risk factors of OSA [11]. Enrollment was completed in 2008. None had been specifically referred for sleep

* Corresponding author at: Cleveland Clinic, Neurological Institute, 9500 Euclid Avenue, FA20, Cleveland, OH 44195, USA. Tel.: +1 216 445 2990; fax: +1 216 445 6205.
E-mail address: foldvan@ccf.org (N. Foldvary-Schaefer).

http://dx.doi.org/10.1016/j.yebeh.2016.03.023

problems nor presented with sleep problems as their chief complaint. Patients who had: 1) prior history of PSG or known sleep disorder, 2) active medical or psychiatric conditions that would compromise one's ability to complete study procedures (recent psychiatric admission or suicide attempt) and newly diagnosed or progressive medical condition necessitating frequent follow-up, 3) inability to provide written informed consent and comply with study procedures, and/or 4) active vagal nerve stimulation therapy were excluded. The Institutional Review Board of the Cleveland Clinic approved this study, and participants gave informed consent before enrollment.

2.2. Structured interviews and completion of a battery of self-assessment measures

Participants underwent a structured interview to ascertain their sleep/wake patterns, nocturnal behaviors, sleep/wake disorder symptoms, epilepsy characteristics, medical history and medications, and other substances (alcohol and caffeine quantified in ounces per week). The interview was performed by one of the investigators (NFS) board-certified in both epilepsy and sleep medicine.

Participants completed a battery of self-reported validated questionnaires which included: 1) ISI to systematically grade presence and severity of insomnia, 2) Epworth Sleepiness Scale (ESS) measuring subjective daytime sleepiness, and 3) Beck Depression Inventory (BDI) gauging the likelihood of comorbid depression. Participants completed a one-week sleep/wake diary prior to PSG. Sleep and wake times, nightly awakenings of at least 30 min, and seizures were recorded. Total sleep duration (TSD) was the average duration of the major sleep period over the diary period.

2.3. Comprehensive in-laboratory video-PSG with 18-channel EEG

Participants underwent in-laboratory overnight-attended video-PSG–EEG to evaluate for OSA. We considered the apnea–hypopnea index (AHI), a measure of OSA severity, as a covariate in our analysis because OSA is a common comorbidity in patients with epilepsy [11,12].

Polysomnography recordings included 18 channels of EEG, electrooculography (two channels), chin electromyography (EMG; three channels), leg EMG (four channels), and single-channel modified lead II EKG. Airflow and respiration were monitored using nasal pressure transducers, oronasal thermal sensors and piezoelectric thoracic and abdominal belts, snore microphone, pulse oximetry, and body position.

Sleep/wake stages, arousals, respiratory events, and other events were scored using the American Academy of Sleep Medicine (AASM) scoring manual rules in place at the time of the analysis [13]. Hypopneas were defined as a reduction in nasal pressure excursions by ≥50% of baseline for at least 10 s and associated with a ≥3% oxygen desaturation or an arousal. Deidentified PSG studies were interpreted by a polysomnographer (NFS) blinded to the identity of the patient or other test results. Apneas and hypopneas were summed to derive the AHI (mean number of apneas and hypopneas per sleep hour).

2.4. Electronic medical record review

We reviewed data from the Cleveland Clinic electronic medical record (EMR) specifically collecting information on: 1) demographics (age, gender, body mass index [BMI], marital status, employment status, and tobacco use); 2) characteristics of the patients epilepsy (epilepsy syndrome, seizure types, mean monthly seizure frequency excluding auras, presence of generalized tonic–clonic (GTC) seizures in the previous 6 months); 3) medications prescribed at the time of enrollment including antiepileptic drugs (AEDs), sedative–hypnotics, psychotropic medications, central nervous system stimulants, and recreational drugs; 4) comorbid medical disorders; and 5) history of epilepsy surgery.

2.5. Calculation of seizure burden, seizure types, and standardized AED doses

To more systematically evaluate the impact of seizure type, seizure burden, and AEDs, we calculated for each patient their seizure burden, seizure type, and World Health Organization (WHO)-standardized variable of the amount of AED(s) taken daily to treat their epilepsy (STD dose) using the Defined Daily Dose, a measure based on the assumed average daily dose in its main indication for adults [14,15]. We classified AEDs as first generation, second generation, or combination.

Mean monthly frequency of disabling seizures (excluding auras) was determined through EMR review and seizure diaries when available over the 6-month period prior to enrollment and evaluated as a continuous measure and categorically (seizure-free, <1 seizure per month, or ≥1 seizures per month). Based upon the structured interview and EMR and, when available, routine EEG, video-EEG monitoring, and neuroimaging studies, we classified each study participant's epilepsy into generalized, focal temporal lobe epilepsy (TLE), focal extratemporal (XTLE), or unknown.

2.6. Insomnia Severity Index (ISI)

The *Insomnia Severity Index* (ISI) is a validated measure for identifying insomnia and grading its severity [10,16–19]. The ISI consists of seven items which evaluate for difficulty falling asleep, difficulty staying asleep, early morning awakenings, satisfaction with the current pattern of sleep, how it interferes with daily functioning when awake, subjective awareness of the daytime impairment, and level of distress caused by it within the past two weeks. Each item is rated on a 5-point scale with total scores ranging from 0 to 28. A cutoff score of ≥8 on the ISI has been shown to reliably identify insomnia in patients with cancer [20]. Another recent study found that the ISI reliably identified objective insomnia and showed good correlation with PSG findings of insomnia (prolonged sleep latency, lower sleep time, and lower percentage of REM sleep time) in 151 adults [16]. The ISI was graded as insignificant (0–7) or no insomnia, subthreshold/mild insomnia (8–14), or moderate or severe insomnia (≥15).

The *Epworth Sleepiness Scale* (ESS) measures a person's recent subjective perception of daytime sleep propensity [21]. Individuals rate on a 4-point scale (0–3) their chances of dozing off or falling asleep in eight different real-life common situations or activities. The total ESS score is the sum of 8-item scores and can range between 0 and 24 with a total score of ≥10 considered abnormal and indicative of excessive daytime sleepiness (EDS) [22]. The ESS has high test–retest reliability and internal consistency [22–25].

The *Beck Depression Inventory* (BDI) is a validated 21-item self-report questionnaire for depression. The BDI has good test–retest reliability with a consistent relationship between the scores and the clinical state. A score >9 is considered suggestive of depression [26]. A recent study found that the sensitivity and specificity of the BDI for the diagnosis of depression in 126 adults with epilepsy were around 90% [27]. In this study, we developed a modified BDI (mBDI) omitting two items (16 and 17) that ascertain sleep and wake complaints, in order to avoid colinearity. Specifically, item 16 addresses sleep quality, early morning awakening, and sleep maintenance, and item 17 addresses tiredness.

2.7. Statistical analysis

The ISI was treated as both a categorical (ISI < 8 for insignificant, 8 to <15 for subthreshold/mild, ≥15 for moderate or severe) and a continuous variable. The AHI was classified into three categories (AHI < 5, 5 to <10, and ≥10). The ESS (≥10 considered abnormal) was treated as a categorical variable.

The relationship between continuous variables and the ISI categorical variables was tested using Spearman's rank correlation. The

relationship between ISI score as a continuous variable and ESS was tested using Welch's two-sample t-test. Tests for difference between categorical ISI variables and ordinal categorical groups were performed using Wilcoxon rank–sum test for two categories or Kruskal–Wallis rank–sum test for greater than two categories.

We categorized study participants as having insomnia according to the International Classification of Sleep Disorders, 2nd Edition (ICSD-2) [28] based on the sleep interview and analyzed the agreement between significant insomnia as measured by the ISI (ISI ≥ 15) and the ICSD-2 using Cohen's kappa.

The correlations between ISI score and independent variables were tested using Pearson's product–moment correlation for continuous variables or Spearman's rank correlation for ordinal factors. Finally, the ISI score was modeled using multiple regressions. Variables included were chosen based on reaching a 10% level of significance in the univariate analyses.

Continuous variables are shown as means with standard deviation, and categorical variables are shown using counts (%). All analyses were performed using R software (version 2.15.1, Vienna, Austria). A significance level of $p < .05$ was the criterion for all tests.

3. Results

3.1. Patient demographics

Ninety subjects (mean age: 39.1 ± 12.4 years; 67% female; mean BMI: 28.9 ± 7 mm/kg^2) completed the study procedures. The epilepsy type was focal in 63 (70%). Mean seizure frequency (excluding auras) was 4 ± 7.6 seizures per month. Twenty-six (28.9%) were seizure-free for the 6-month period before enrollment. Subjects were prescribed a mean of 1.7 ± 0.8 AEDs. The mean standardized AED dose was 2.1 ± 1.6 per month suggesting a higher-than-average drug burden. Table 1 shows the demographic characteristics of the study population.

3.2. Apnea–Hypopnea Index and Epworth Sleep Scale scores

The AHI on overnight PSG was normal (<5) in 49 (54%), 5 to <10 in 15 (17%), and >10 in 26 (29%). Epworth Sleepiness Scale scores ≥10 endorsing EDS were reported in 31 (34.4%) patients.

3.3. Insomnia Severity Index

The mean Insomnia Severity Index (ISI) score for the group was 10.6 ± 6.7. Thirty-one patients (34.4%) had a score of <8 suggesting no significant insomnia symptoms, 33 (36.7%) had subthreshold/mild insomnia complaints, and 26 (28.9%) had ISI scores consistent with a diagnosis of moderate or severe insomnia. Table 2 shows results of the comparison between insomnia classification by the ICSD-2 and the ISI for clinically significant insomnia (ISI total ≥ 15). Of the patients classified as not having insomnia by the ICSD-2, all were classified as not having clinically significant insomnia by the ISI. For the 67 patients who were classified as having insomnia by the ICSD-2, only 26 (39%) had an ISI ≥ 15. The two classifications agreed fairly well on people with lower and higher levels of insomnia symptoms but disagreed on how to classify those with intermediate levels of insomnia symptoms. The proportion of agreement between the ISI and ICSD-2, adjusting for chance agreement, was 0.24, with 95% CI (0.13, 0.36).

Univariate analysis of the ISI and continuous variables found significant relationships only for the mBDI ($p = .005$), BDI ($p < .001$), and TSD based on sleep diaries ($p = .004$) (Supplementary Data Table 1). Significant univariate relationships were found between ISI severity categories and categorical variables for comorbid asthma/COPD ($p = .003$) and use of sedative–hypnotics ($p < .001$) (Supplementary Data Table 2). Comparisons of ISI severity categories on PSG measures found significant differences only for REM latency, with those with moderate or severe insomnia scores having greater REM latency (Supplementary Data Table 3). No significant correlations were found between total monthly seizure frequency and PSG variables.

Significant correlations between ISI and the BDI ($r = .32$, $p = .002$), mBDI ($r = .25$, $p = .021$), TSD ($r = -0.3$, $p = .006$), and ESS ($r = .25$, $p = .02$) were observed (Table 3). Higher scores on the mBDI, BDI, and ESS and shorter TSD were significantly associated with moderate or severe insomnia. No significant correlations were found for ISI score and age, BMI, alcohol/caffeine use, or epilepsy-related variables.

Using a final multiple regression model (Table 4), we found that moderate or severe insomnia scores were more likely to be reported in adults with epilepsy who had decreased TSD (ß = −0.93, $p = .007$), head trauma (ß = 4.37, $p = .003$), sedative–hypnotic use (ß = 4.86, $p = .002$), AED polytherapy (ß = 3.52, $p = .005$), and asthma/

Table 1
Sample characteristics (N = 90).

Demographics	
Age (years)	39.1 ± 12.4
Gender (male)	30 (33.3)
BMI	28.9 ± 7.1
Marital status (married)	39 (49.4)
Employment (employed)	53 (61.6)
Epilepsy type	
Focal epilepsy	63 (70)
Temporal	37 (41.1)
Extratemporal	20 (22.2)
Undetermined	6 (6.7)
Generalized epilepsy	22 (24.4)
Unknown	5 (5.6)
Antiepileptic drugs	
Number AEDs	1.7 ± 0.8
AED monotherapy	42 (46.7)
1st generation	20 (22.2)
2nd generation	43 (47.8)
Combination	27 (30)
Standardized Dose	2.1 ± 1.6
Seizure burden[a]	
Total seizures/mo	4 ± 7.6
Focal seizures/mo	2.9 ± 7.2
GTCs/mo	1.2 ± 2.9
Seizure-free	26 (28.9)
≥1 seizure/mo	41 (45.6)
History of GTCs	53 (58.9)
Comorbid conditions[b]	
Hypertension	11 (12.2)
Asthma/COPD	18 (20)
Mood disorder	28 (31.1)
Epilepsy surgery	11 (12.2)
Head trauma	20 (22.2)
Other medications and substances[b]	
Tobacco use	33 (36.7)
Sedative–hypnotics	17 (18.9)
Antidepressants	24 (22.2)
Psychotropics	23 (25.6)

Mean ± SD for continuous variables; otherwise N (%). AED: antiepileptic drug; GTCs: generalized tonic–clonic seizures; COPD: chronic obstructive pulmonary disease; mo: month.
[a] Over prior 6 months.
[b] Affecting at least 10% of subjects.

Table 2
Agreement between ICSD-2 and ISI for clinically significant insomnia.

	ISI category					
	No (<15)			Yes (≥15)		
ICSD-2	Count	Row %	Col %	Count	Row %	Col %
No	23	100	35.9	0	0	0
Yes	41	61.2	64.1	26	38.8	100

Kappa = 0.24 (0.13, 0.36). ICSD-2: International Classification of Sleep Disorders, 2nd Edition; ISI: Insomnia Severity Index.

Table 3
Correlations between ISI and variables of interest.

Variable	Correlation	95% CI	p-Value
Age (years)	0.07	−0.14, 0.27	0.51
Body mass index	0.19	−0.02, 0.38	0.076
Modified Beck Depression Inventory	0.25	0.04, 0.44	**0.021**
Beck Depression Inventory	0.32	0.12, 0.5	**0.002**
Epworth Sleepiness Scale	0.25	0.04, 0.43	**0.02**
Total sleep duration	−0.3	−0.48, −0.09	**0.006**
Alcohol amount (oz/week)	−0.1	−0.3, 0.11	0.34
Caffeine amount (oz/week)	−0.01	−0.22, 0.2	0.96
Total seizures/mo[a]	0.07	−0.14, 0.27	0.54
GTCs/mo[a]	−0.03	−0.24, 0.18	0.77
Number AEDs[b]	0.13	−0.08, 0.34	0.24
Standardized AED dose	0.13	−0.08, 0.33	0.23

Pearson's product moment correlation unless otherwise indicated. AED: antiepileptic drug; GTCs: generalized tonic–clonic seizures; mo: month.
[a] Over prior 6 months.
[b] Spearman's rank correlation.

COPD (ß = 3.75, p = .014). A subset analysis among the 63 patients with focal epilepsy identified a higher mBDI score (ß = 0.24, p = .015), decreased TSD (ß = −1.11, p = .008), asthma/COPD (ß = 4.19, p = 0.02), and epilepsy surgery (ß = 5.33, p = .006) as significant predictors of a higher ISI score. A statistically insignificant trend for more severe insomnia was identified in patients with TLE compared with those with XTLE (ß = −2.92, p = 0.054).

4. Discussion

Systematically employing a validated measure of insomnia [10], we found that 66% of 90 community-dwelling adults with epilepsy who were not referred to our epilepsy center for sleep/wake complaints had an abnormal ISI score consistent with some degree of insomnia, moderate or severe in 29%. This is a substantially higher prevalence of insomnia in adults with epilepsy compared with a 25% prevalence of ISI scores of 8 or more in general adult population studies [29]. In contrast to the general population, good agreement between the ICSD-2 diagnostic classification for insomnia and ISI scores ≥15 was found for patients without insomnia and high levels of insomnia complaints but not for low/intermediate levels of insomnia. Disagreement for low/intermediate levels of insomnia in our study may be due to the inherent sleep fragmentation and fatigue experienced by this population typically attributed to seizures and AED therapy. That we found good agreement at the ends of the spectrum supports the utility of the ISI for identifying significant insomnia in patients with epilepsy.

This high prevalence of insomnia is similar to the few other prospective studies reported in the medical literature. Vendrame et al. found a prevalence of moderate or severe insomnia in 55% of 152 adults with less refractory epilepsy referred to their sleep center [30]. They used the same criteria for moderate or severe insomnia (ISI ≥ 15) but did not exclude patients with preexisting insomnia as we did. They found that insomnia correlated with the number of AEDs and scores of depression on a modified version of the BDI-omitting item 16 only (sleep quality, early morning awakening, and sleep maintenance). Another prospective study using self-reported questionnaires found that sleep-maintenance insomnia was more likely to be reported among 100 consecutive adults with epilepsy than among 90 controls (52% vs. 34%), although similar percentages of patients with epilepsy and controls reported sleep-onset insomnia (34% vs. 28%, respectively) [2]. However, the control group was recruited from hospital staff, which may have led to bias in that study. Forty percent of 165 veterans with epilepsy (87% male; mean age 56) attending an epilepsy clinic reported insomnia, an older and predominantly male population, different from ours [31].

Table 4
Final regression model of ISI showing significant variables for moderate-to-severe insomnia.

Factor	Level	Beta	95% CI	p-Value
Total sleep duration		−0.93	−1.56, −0.27	0.007
Head trauma	Yes vs. No	4.37	1.38, 6.96	0.003
Sedative–hypnotic use	Yes vs. No	4.86	2.56, 8.65	0.002
AED therapy	Poly vs. Mono	3.52	0.14, 5.15	0.005
Asthma/COPD	Yes vs. No	3.75	0.24, 6.1	0.014

AED: antiepileptic drug; COPD: chronic obstructive pulmonary disease.

In the present study, we neither defined the type of insomnia nor compared it with a control group; instead, we investigated the severity of insomnia symptoms using the ISI and its related factors in patients with epilepsy. We found no significant correlations between ISI score and age, gender, BMI, alcohol/caffeine use, OSA severity, seizure burden, seizure type, AED type, or AED STD dose, a measure of drug burden. The only epilepsy variable which increased the likelihood for moderate or severe insomnia was AED polytherapy, typically considered a marker of pharmacoresistant epilepsy. Although total drug burden was not a predictor of moderate or severe insomnia, it is possible that specific drugs or drug combinations impact insomnia symptoms. Our sample was too small to explore the many drug regimens taken by our patients.

While we found significant correlations between ISI scores and BDI, mBDI, and ESS, depressive symptoms, daytime sleepiness, and presence of OSA were not predictive of moderate or severe insomnia in multivariate regression models. Rather, in our final model, only TSD, comorbid asthma/COPD, head trauma, sedative–hypnotic use, and AED polypharmacy predicted significant insomnia symptoms. As expected, reduced TSD based on sleep diaries and sedative–hypnotic use, consisting of nonbenzodiazepine sleep aids, were strongly associated with insomnia symptoms. Studies of insomnia in the general population have similarly found that insomnia is more prevalent in patients with other medical disorders including asthma, COPD, and neurological problems including epilepsy [32].

Depression is the most common comorbid psychiatric disorder among patients with epilepsy [33,34]. Patients with insomnia were shown to have significantly higher BDI scores than people without insomnia in a general population community-based sample [35]. Depression may be an independent risk factor for insomnia in people with epilepsy as in the general population. A recent study confirmed that depression and anxiety in people with epilepsy are associated with sleep quality, EDS, and increased risk of suicidal ideation and suicide [36]. Depression in persons with epilepsy also increases the likelihood of AED nonadherence and reduced quality of life [37]. In our sample, no association between ISI score and comorbid mood disorder was observed, and neither the BDI nor the mBDI was an independent predictor of insomnia symptoms in our final regression model. Given the high usage of antidepressant and psychotropic agents, it is possible that patients with depression in our sample were adequately treated, rendering insomnia symptoms less prevalent. This cross-sectional study was not designed to explore causal relationships between depression, its treatments, and sleep/wake complaints.

We further found that a third (34%) of adults with epilepsy in our study reported EDS based on the ESS. Other studies have found EDS the second most common sleep/wake complaint in adults with epilepsy [6]. These questionnaire-based studies similar to ours found that the prevalence of EDS was significantly higher in adults with epilepsy than in age- and gender-matched controls (18% and 28% of adults with epilepsy vs. 12% and 17% of controls, respectively) using an ESS cutoff as we did of ≥10 [6]. In addition to the high prevalence of EDS, we found a significant positive correlation between the ESS and ISI that is in striking contrast to general population cohorts with insomnia, where significant negative correlations are generally observed.

Our study is limited by a cross-sectional design and small sample size. Selection bias may have contributed to the findings. Study participants were recruited from a tertiary care epilepsy center and were more likely to have active epilepsy than patients treated in general neurology or primary care clinics. Hence, our findings may not be generalizable to patients with epilepsy in such clinical settings. Also, we did not investigate the severity of insomnia in relation to individual AEDs. Because of sample size constraints, we chose to categorize AEDs as either first or second generation and treatment with one or the other or combination therapy. We know that sleep/wake complaints are commonly attributed to AED therapy [38]. Detrimental and beneficial effects on sleep and wakefulness have been reported; however, prospective, randomized trials investigating these effects are lacking. Polytherapy with AEDs was associated with an increased ISI score in the present study, and this result is comparable with findings from another recent study [30]. Finally, with the exception of evaluating for OSA, we did not analyze whether other primary sleep disorders may have contributed to the insomnia complaint.

Among the few prior studies exploring insomnia symptoms in cohorts with epilepsy, our study is unique for several reasons. Firstly, because OSA is more common in adults with epilepsy than in the general population, we controlled for this comorbidity by recording PSG in all subjects [11,12]. Secondly, we controlled for AED burden by determining the standardized AED dose for each subject using methodology published by the WHO. Thirdly, we modified the BDI by eliminating two items that are pertinent in the evaluation of insomnia: sleep quality and daytime tiredness.

Our study adds to the growing body of literature exploring relationships between sleep and epilepsy. We found that the severity of insomnia was not associated with epilepsy itself (save AED polytherapy) but rather with comorbid conditions, particularly asthma/COPD, head trauma, and depressive symptoms. The lack of an association between ISI score and age or gender further suggests that insomnia in patients with epilepsy may be different than that observed in the general population, where affected women outnumber men by a factor of two or more and symptoms present with increasing age [39–41]. These findings should be considered in the diagnosis and management of insomnia in patients with epilepsy.

Acknowledgment

The authors would like to thank Douglas E. Moul, MD for his helpful review of this work.

Disclosure of conflict of interest

The authors have no conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.03.023.

References

[1] de Weerd A, de Haas S, Otte A, Trenite 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.
[2] 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.
[3] 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.
[4] Jenssen S, Gracely E, Mahmood T, Tracy JI, Sperling MR. Subjective somnolence relates mainly to depression among patients in a tertiary care epilepsy center. Epilepsy Behav 2006;9:632–5.
[5] Manni R, Politini L, Sartori I, Ratti MT, Galimberti CA, Tartara A. Daytime sleepiness in epilepsy patients: evaluation by means of the Epworth sleepiness scale. J Neurol 2000;247:716–7.
[6] Malow BA, Bowes RJ, Lin X. Predictors of sleepiness in epilepsy patients. Sleep 1997; 20:1105–10.
[7] Vignatelli L, Bisulli F, Naldi I, Ferioli S, Pittau F, Provini F, et al. Excessive daytime sleepiness and subjective sleep quality in patients with nocturnal frontal lobe epilepsy: a case–control study. Epilepsia 2006;47(Suppl. 5): 73–7.
[8] Pizzatto R, Lin K, Watanabe N, Campiolo G, Bicalho MAH, Guarnieri R, Claudino R, Walz R, Sukys-Claudino L. Excessive sleepiness and sleep patterns in patients with epilepsy: a case-control study. Epi Behav 2013;29:63–6.
[9] Haut SR, Katz M, Masur J, Lipton RB. Seizures in the elderly: impact on mental status, mood, and sleep. Epilepsy Behav 2009;14:540–4.
[10] 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.
[11] Foldvary-Schaefer N, Andrews ND, Pornsriniyom D, Moul DE, Sun Z, Bena J. Sleep apnea and epilepsy: who's at risk? Epilepsy Behav 2012;25:363–7.
[12] Manni R, Terzaghi M, Arbasino C, Sartori I, Galimberti CA, Tartara A. Obstructive sleep apnea in a clinical series of adult epilepsy patients: frequency and features of the comorbidity. Epilepsia 2003;44:836–40.
[13] Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, Illinois: American Academy of Sleep Medicine; 2007.
[14] Clarke KW, Gray D. The defined daily dose as a tool in pharmacoeconomics.Advantages and limitations. Pharmacoeconomics 1995;7:280–3.
[15] Wessling A, Boethius G. Measurement of drug use in a defined population. Evaluation of the defined daily dose (DDD) methodology. Eur J Clin Pharmacol 1990;39: 207–10.
[16] Sadeghniiat-Haghighi K, Yazdi Z, Firoozeh M. Comparison of two assessment tools that measure insomnia: the insomnia severity index and polysomnography. Indian J Psychol Med 2014;36:54–7.
[17] Gagnon C, Belanger L, Ivers H, Morin CM. Validation of the Insomnia Severity Index in primary care. J Am Board Fam Med 2013;26:701–10.
[18] Severson CA, Tsai WH, Ronksley PE, Pendharkar SR. Identification of insomnia in a sleep center population using electronic health data sources and the insomnia severity index. J Clin Sleep Med 2013;9:655–60.
[19] Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011; 34:601–8.
[20] Savard MH, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. Psychooncology 2005;14:429–41.
[21] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.
[22] Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376–81.
[23] Mondal P, Gjevre JA, Taylor-Gjevre RM, Lim HJ. Relationship between the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in a sleep laboratory referral population. Nat Sci Sleep 2013;5:15–21.
[24] Miletin MS, Hanly PJ. Measurement properties of the Epworth sleepiness scale. Sleep Med 2003;4:195–9.
[25] George PT. Sleepiness, troika of consciousness cycle, and the Epworth sleepiness scale. Sleep Breath 2001;5:181–91.
[26] Beck AT. Beck depression inventory. San Antonio: The Psychological Corporation; 1987.
[27] de Oliveira GN, Lessa JM, Goncalves AP, Portela EJ, Sander JW, Teixeira AL. Screening for depression in people with epileps: comparative study among neurological disorders depression inventory for epilepsy (NDDI-E), hospital anxiety and depression scale depression subscale (HADS-D), and Beck depression inventory (BDI). Epilepsy Behav 2014;34:50–4.
[28] International classification of sleep disorders. Diagnostic and coding manual. 2nd ed. Westchester, Illinois: American Academy of Sleep Medicine; 2005.
[29] Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. Sleep 1999;22(Suppl. 2): S347–53.
[30] Vendrame M, Yang B, Jackson S, Auerbach SH. Insomnia and epilepsy: a questionnaire-based study. J Clin Sleep Med 2013;9:141–6.
[31] Lopez MR, Cheng JY, Kanner AM, Carvalho DZ, Diamond JA, Wallace DM. Insomnia symptoms in South Florida military veterans with epilepsy. Epilepsy Behav 2013; 27:159–64.
[32] Budhiraja R, Roth T, Hudgel DW, Budhiraja P, Drake CL. Prevalence and polysomnographic correlates of insomnia comorbid with medical disorders. Sleep 2011;34: 859–67.
[33] Hermann BP, Seidenberg M, Bell B. Psychiatric comorbidity in chronic epilepsy: identification, consequences, and treatment of major depression. Epilepsia 2000; 41(Suppl. 2):S31–41.
[34] Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. Biol Psychiatry 2003;54:388–98.
[35] Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. Sleep 2005;28:1457–64.
[36] Wigg CM, Filgueiras A, Gomes Mda M. The relationship between sleep quality, depression, and anxiety in patients with epilepsy and suicidal ideation. Arq Neuropsiquiatr 2014;72:344–8.

[37] Ettinger AB, Good MB, Manjunath R, Edward Faught R, Bancroft T. The relationship of depression to antiepileptic drug adherence and quality of life in epilepsy. Epilepsy Behav 2014;36:138–43.
[38] Foldvary-Schaefer N, Neme-Mercante S. Sleep and epilepsy. In: Wyllie E, editor. The treatment of epilepsy: principles and practice of epilepsy. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2015. p. 467–73.
[39] Spencer PZ. Gender, age, and the risk of insomnia. CNS Spectr 2008;13:7–9.
[40] Yoshioka E, Saijo Y, Kita T, Satoh H, Kawaharada M, Fukui T, et al. Gender differences in insomnia and the role of paid work and family responsibilities. Soc Psychiatry Psychiatr Epidemiol 2012;47:651–62.
[41] Jaussent I, Dauvilliers Y, Ancelin ML, Dartigues JF, Tavernier B, Touchon J, et al. Insomnia symptoms in older adults: associated factors and gender differences. Am J Geriatr Psychiatry 2011;19:88–97.