



Obstructive sleep apnea risk in patients with focal versus generalized epilepsy

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is common in patients with epilepsy (PWE), and treatment may improve seizure control. However, OSA is often undiagnosed in PWE, and understanding of the risk profile for OSA is important. In this study, we sought to determine if OSA risk is similar in patients with generalized versus focal epilepsy.

Methods: We recruited 115 patients presenting to the Rutgers-Robert Wood Johnson Epilepsy Clinic with focal or generalized epilepsy. Obstructive sleep apnea risk was assessed using the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ). Sleepiness was assessed using the Epworth Sleepiness Scale (ESS). Demographic and clinical information was gathered from the electronic medical record. Unadjusted and adjusted analyses were carried out to assess differences in the SA-SDQ between patients with generalized versus focal epilepsy. Further analyses were done to assess the relationship between seizure frequency, epilepsy type, and the SA-SDQ. **Results:** Unadjusted mean SA-SDQ scores, as well as scores high enough to represent likely OSA, were similar in patients with generalized versus focal epilepsy. However, in adjusted analyses, patients with generalized epilepsy had a significantly higher mean SA-SDQ score. Older age, higher body mass index (BMI), and a history of hypertension (HTN) were also associated with higher SA-SDQ scores. Sleep Apnea Scale of the Sleep Disorders Questionnaire scores were not significantly affected by the presence of a seizure within the prior one month or six months. Average ESS scores and the percentage of scores consistent with an abnormal degree of sleepiness were statistically similar in patients with generalized versus focal epilepsy.

Significance: Our study suggests that patients with generalized epilepsy have a higher risk of OSA. Further studies measuring OSA directly as well as assessing potential benefits of treatment are needed.

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1. Introduction

Obstructive sleep apnea (OSA) is a common disease in the United States and worldwide [1]. It is due to intermittent collapse of the upper airway during sleep, which can lead to respiratory pauses, oxygen desaturation, and sleep disruption among other problems. There are a number of impairments associated with OSA including excessive daytime sleepiness [2], worsened cognition [3], and increased likelihood

of motor vehicle accidents [4]. Furthermore, OSA is associated with hypertension (HTN) [5], diabetes [6], cardiovascular disease [7], cerebrovascular disease [8], and mortality [9,10]. Despite the greater awareness of OSA, many patients are not diagnosed, and identification of groups at high risk for OSA is important.

The prevalence of OSA varies substantially in different populations. Male gender, older age, and increasing body mass index (BMI) are risk factors for OSA across ethnicities [1]. The obesity epidemic in the United States and worldwide has increased the prevalence of OSA and has limited the utility of older OSA prevalence estimates. Furthermore, differences in diagnostic methods and definitions of disease have also contributed to variability in OSA prevalence estimates [1]. Therefore, differences in OSA prevalence estimates in different studies may be due, at least in part, to these factors.

There have been a number of studies that have examined the issue of OSA prevalence in patients with epilepsy (PWE). Depending on the tools used and population studied, OSA prevalence estimates in adults with epilepsy vary widely between 10 and 75% [11,12]. In studies that

Abbreviations: OSA, obstructive sleep apnea; PWE, patients with epilepsy; SA-SDQ, Sleep Apnea Scale of the Sleep Disorders Questionnaire; ESS, Epworth Sleepiness Scale; BMI, body mass index; HTN, hypertension; AED, antiepileptic medications; SUDEP, sudden unexplained death in epilepsy; DM, diabetes mellitus.

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have utilized the gold standard for assessing OSA, in-laboratory polysomnography, and avoided the selection bias of not solely evaluating patients specifically referred for a sleep complaint, the prevalence of OSA in adults with epilepsy was between 13 and 64% [13–16]. Similar to the observations in the general population, older age, male gender, and higher BMI were identified as risk factors for OSA in PWE [14,15] and for a higher apnea–hypopnea index [16]. These studies suggest that OSA is common in PWE, but determining a specific prevalence and whether OSA is more prevalent in PWE compared with the general population is difficult.

Obstructive sleep apnea risk could be higher in PWE because of altered control of muscles of the upper airway, use of antiepileptic medications (AED), or weight gain associated with chronic use of AEDs. Additionally, OSA could potentially lower the seizure threshold and worsen control of epilepsy due to sleep fragmentation, intermittent hypoxia, and activation of the sympathetic nervous system that can occur with OSA. In fact, OSA treatment in PWE has been shown to decrease epileptiform discharges both during wake and sleep [17]. Although the data are confounded by methodologic considerations, a number of studies have shown a reduction in seizure frequency among those receiving OSA treatment [18–22]. These observations suggest that OSA can potentiate seizures and that OSA treatment can improve seizure control. This is especially poignant because the risk of sudden unexplained death in epilepsy (SUDEP) is associated with OSA risk [23], and it is possible that OSA treatment may be particularly important in patients with poorly controlled epilepsy who are at the highest risk for SUDEP.

Epilepsy is not a homogenous disease, but rather, results from a number of different structural, metabolic, and physiologic processes resulting in the abnormal electrical synchronization in the brain that is the sine qua non of epilepsy. We hypothesize that OSA risk may be different in PWE that arises from different etiologies, and the vast majority of studies on this topic have not directly addressed this. Differences in OSA risk in patients with different types of epilepsy may be due to some of the well-characterized risk factors such as age, gender, and BMI, but there could also be other contributing factors. It is in this context that the present study was undertaken.

In this study, OSA risk was assessed in patients with generalized or focal epilepsy with the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ), which has been validated for use in PWE [15,24,25]. Differentiation of epilepsy into generalized or focal types is a well-established classification scheme, and it is likely that these categories of epilepsy have different underlying pathophysiology [26]. Although sleepiness is not always present in patients with OSA and assessment of sleepiness is not the same as assessment of OSA, since sleepiness is a common complaint in PWE, we also assessed sleepiness with the Epworth Sleepiness Scale (ESS). In this study, we sought to determine if a) OSA risk is similar in patients with generalized or focal epilepsy, b) what factors affect OSA risk, and c) if OSA risk is associated with seizure control similarly in these groups.

2. Methods

2.1. Design and study population

This was a cross-sectional study that focused on the population served by the Epilepsy Center at Rutgers–Robert Wood Johnson Medical School. All PWE who presented to the epilepsy center were screened for eligibility for this study using the following inclusion criteria: patients had to be ≥ 18 years old, be able to speak and write in English, and had to be able to independently fill out the SA-SDQ and ESS forms correctly. Patients were given instructions and had to verbalize an understanding of the instructions. If the patient could not fill out the forms with an appropriate number at each point of the survey or not circling the correct area, the patient was not included. The English requirement was used because the SA-SDQ has not been validated in languages other than

English. Eligible patients who signed an informed consent and filled out the questionnaires were included in the study. We aimed to recruit 100–130 patients similar to other studies using the SA-SDQ in PWE [16,24,25]. The institutional review board at Rutgers–Robert Wood Johnson Medical School approved this study, and ethical standards were observed during the study.

2.2. Epilepsy classification

Patients with epilepsy were classified into either focal or generalized epilepsy according to criteria of the International League Against Epilepsy (ILAE) [26]. Classification was based on clinical history, electroencephalogram (EEG), brain imaging, and genetic testing where available. Most patients with generalized epilepsy were likely genetic generalized epilepsy rather than symptomatic generalized epilepsy because of the requirement to fill out questionnaires. Patients for whom the diagnosis of epilepsy or the type of epilepsy was unclear were excluded. Final determination was made by a board-certified epileptologist blinded to the patient's SA-SDQ results.

2.3. Obstructive sleep apnea assessment

The SA-SDQ is a validated questionnaire used to assess for OSA risk in adults [27] including PWE [15,24,25]. The SA-SDQ questionnaire is shown in Table 1. Total scores were calculated and recorded as a continuous measure. Additionally, based on a previous study in which a score of ≥ 29 in males or ≥ 26 in females showed a high risk of OSA in PWE [24], the percentage of patients with high risk of OSA (based on these score cut-points) were compared between patients with focal or generalized epilepsy. For the adjusted analyses, the SA-SDQ scores were used as a continuous measure without the use of a cut-point. Although not a measure of OSA risk, the well-validated ESS was also used to measure sleepiness. Total scores were again calculated and compared as continuous, as well as further classified into whether or not they were considered “abnormally sleepy” with an ESS ≥ 11 cut-point [2] and were compared as categorical.

2.4. Data acquisition

Scores of SA-SDQ and ESS were taken directly from the forms filled out by the patients upon enrollment in the study. Other study variables were retrieved from the electronic medical record system including age, gender, BMI, history of diabetes mellitus (DM), history of HTN, history of OSA, epilepsy type, presence of a seizure within the last month, presence of a seizure within the last six months, and the number of AEDs. For presence of a seizure within the prior month or 6 months, data were available on 90% and 93% of patients, respectively. Missing data were excluded. As number of AEDs may not adequately represent AED treatment, a standardized AED dose was calculated according to World Health Organization (WHO) criteria [16,28]. This is calculated by dividing the dose of the AED by the defined daily dose for each AED and then adding up the total. Since there was no difference between patients with generalized versus focal epilepsy in either total number of AEDs or in standardized AED dose (Table 2), only standardized AED dose was used in adjusted analyses. Only one patient had a vagal nerve stimulator.

2.5. Statistical methods

Patient baseline characteristics were first analyzed using summary statistics (mean \pm SD, or frequency and percentage). Using the Shapiro–Wilk test of normality and visual inspection on quantile–quantile plots, it was determined that a number of the continuous variables were skewed; therefore, bivariate analyses were carried out to compare the SA-SDQ and ESS scores between the two groups using Wilcoxon tests for continuous covariates, and Pearson's Chi-squared or Fisher's

Table 1
Sleep Apnea Scale of Sleep Disorders Questionnaire (SA-SDQ).

1 = never, 2 = rarely, 3 = sometimes, 4 = usually, 5 = always						
Question						Score
1	"I am told I snore loudly and bother others" (raw score from above responses)					
2	"I am told I stop breathing in sleep" (raw score from above responses)					
3	"I awake suddenly gasping for breath, unable to breathe" (raw score from above responses)					
4	"I sweat a great deal at night" (raw score from above responses)					
5	"I have high blood pressure (or once had it)" (raw score from above responses)					
6	"I have a problem with my nose blocking up when I am trying to sleep" (raw score from above responses)					
7	"My Snoring/breathing problem is much worse if I sleep on my back" (raw score from above responses)					
8	"My Snoring/breathing problem is much worse if I fall asleep right after drinking alcohol" (raw score from above responses)					
9	Current weight (pounds) is:					
	1. <135	2. 135–159	3. 160–183	4. 184–209	5. ≥210	
10	Number of years as a smoker:					
	1. None	2. 1 year	3. 2–12 years	4. 13–25 years	5. ≥26 years	
11	Age:					
	1. <26 years	2. 26–35 years	3. 36–44 years	4. 45–50 years	5. ≥51 years	
12	Body mass index (BMI):					
	1. <22.2	2. 22.2–25.6	3. 25.7–27.4	4. 27.5–30.9	5. ≥31.0	

exact tests for categorical measures. Missing data were excluded from analysis. To further examine the relationship between the SA-SDQ score and type of epilepsy, a multiple linear regression model was fit with the SA-SDQ score regressed against the epilepsy type adjusting for the following covariates: age, male gender, standardized AED dose, reported history of OSA, BMI, history of DM, history of HTN, seizure within 1 month, and seizure within 6 months. To assess if the presence of a seizure within 1 month or 6 months was associated with type of epilepsy, separate multiple logistic regression models were fit adjusting for age, standardized AED dose, SA-SDQ, and ESS score. A *p*-value of <0.05 was considered statistically significant, and a *p* value of <0.10 was considered a trend. Analyses were performed using SAS (SAS System for Windows, Version 9.4. Cary, NC: SAS Institute Inc.; 2014) and the "lrm" package in R [29,30].

3. Results

A total of 115 patients, 27 with generalized epilepsy and 88 patients with focal epilepsy met the inclusion criteria for this study. Five patients had epilepsy that was unclassified and were excluded from further analysis. Among the demographic and clinical characteristics assessed, only

age was found to be statistically different between the two groups with the patients who were diagnosed with generalized epilepsy having a mean age of 32.1 ± 13.2 and patients with focal epilepsy having a mean age of 46.2 ± 15.8 ($p < 0.001$). Complete patient demographic and comorbidity data are presented in Table 2.

The number of AEDs, the standardized AED dose, and the number of patients with ≥ 2 AEDs were similar in patients with generalized and focal epilepsy (Table 2). Antiepileptic medications that are approved or supported by society guidelines [31] for use for either generalized or focal epilepsy (valproic acid, levetiracetam, lamotrigine, topiramate, zonisamide) comprised 82% of the AEDs for patients with generalized epilepsy and 62% of the AEDs for the patients with focal epilepsy. Levetiracetam was the most commonly used AED comprising 34% of prescriptions in each group. Valproic acid comprised 21% of AEDs used for patient with generalized epilepsy versus only 4% for patients with focal epilepsy. For patients with focal epilepsy, 22% of the AEDs were either oxcarbazepine or carbamazepine versus 5% in patients with generalized epilepsy. Lacosamide comprised 5% of the AEDs in each group. Several other AEDs, each of which comprised <5% of the total AEDs, made up the remaining 11–13% of prescriptions.

3.1. OSA risk

Mean SA-SDQ scores were similar in patients with generalized and focal epilepsy with scores of 24.4 ± 7.0 and 24.8 ± 7.2 ($p = 0.81$), respectively. Using a cut-point of ≥ 29 for males and ≥ 26 for females [24], the percentage of patients with an abnormal score was also assessed. Among patients with generalized epilepsy, 33.3% had an abnormal SA-SDQ score, whereas among patients with focal epilepsy, 35.2% had an abnormal SA-SDQ score ($p = 0.86$). To further explore whether these scores were similar once demographic and other clinical factors were taken into account, a multiple linear regression model was fit, which showed that on average, patients with focal epilepsy had an adjusted SA-SDQ score that was 3.52 points lower than patients with generalized epilepsy ($p = 0.01$). Older age, higher BMI, and a history of HTN were also associated with higher SA-SDQ scores ($p < 0.01$), and there was a trend towards significance for those with a history of OSA ($p = 0.07$) having significantly higher SA-SDQ scores. The model estimates information is presented in Table 3.

Table 2
Demographic and clinical characteristics.

N	Generalized	Focal
	n = 27	n = 88
Age	32.1 ± 13.2	46.2 ± 15.8
BMI	28.0 ± 5.7	28.2 ± 6.9
Male gender	59.3%	54.5%
HTN	14.8%	28.4%
DM	3.7%	4.5%
Diagnosis of OSA	11.1%	14.8%
Seizure – last month	16.0%	24.1%
Seizure – last 6 months	30.8%	40.7%
AEDs	1.4 ± 0.5	1.5 ± 0.7
Standardized AED	1.6 ± 1.1	1.9 ± 1.5
% with ≥ 2 AEDs	40.7%	42.0%

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; OSA, obstructive sleep apnea; AED, antiepileptic drug.

Table 3
Linear regression for the SA-SDQ by patient characteristics.

Variable	β estimate w/ 95% CI	p-Value
(Intercept)	5.95 [0.35, 11.55]	NA
Epilepsy type: focal	-3.52 [-6.04, -1.00]	0.01
Age	0.17 [0.09, 0.24]	<0.001
Gender: male	0.77 [-1.39, 2.93]	0.49
Standardized AED dose	0.14 [-0.66, 0.95]	0.73
Diagnosis of OSA: yes	2.94 [-0.18, 6.05]	0.07
BMI	0.40 [0.24, 0.57]	<0.001
DM: yes	1.23 [-3.74, 6.21]	0.63
HTN: yes	4.43 [1.80, 7.07]	0.001
Seizure @ 1 month: yes	0.50 [-3.36, 4.35]	0.80
Seizure @ 6 months: yes	1.27 [-1.70, 4.23]	0.40

Higher SA-SDQ scores were associated with generalized epilepsy, older age, higher BMI, and history of HTN. SA-SDQ, Sleep Apnea Scale of the Sleep Disorders Questionnaire; AED, antiepileptic drug; OSA, obstructive sleep apnea; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension.

3.2. Seizure frequency

As seen in Table 2, the proportion of patients who experienced a seizure within the prior month ($p = 0.58$) or 6 months ($p = 0.36$) was not significantly different between patients with generalized or focal epilepsy. Multiple logistic regression further showed that the type of epilepsy was not significantly associated with the presence of a seizure within 1 ($p = 0.21$) or 6 months ($p = 0.11$). However, younger age ($p = 0.04$) and higher standardized AED doses ($p = 0.01$) were associated with the occurrence of a seizure within 1 month. For the occurrence of a seizure within the prior 6 months, only younger age was significantly associated ($p = 0.02$), but there was a trend towards significance for those with higher standardized AED doses ($p = 0.07$) and higher SA-SDQ scores ($p = 0.08$) being associated with the presence of a seizure (Table 4).

3.3. Sleepiness

Average ESS scores were 7.8 ± 4.0 and 6.4 ± 4.3 in patients with generalized and focal epilepsy, respectively. While not significantly different, there was a trend towards a higher score in patients with generalized epilepsy ($p = 0.07$). Further, when assessing whether or not the percentage of patients with abnormal scores was different in the two groups, using a cut-point of ≥ 11 [2], there was no significant difference found ($p = 0.26$). Among patients with generalized epilepsy, 25.9% had

Table 4
Logistic regression of seizure control, stratified by presence of a seizure in the last 1 month or 6 months, by patient characteristics.

Variable	Seizure within 1 month		
	β estimate w/ 95% CI	p-Value	Odds ratio w/ 95% CI
(Intercept)	-2.36 [-4.70, -0.02]	NA	0.09 [0.01, 0.88]
Epilepsy type: focal	0.90 [-0.49, 2.29]	0.21	2.45 [0.65, 11.03]
Age	-0.05 [-0.09, -0.002]	0.04	0.96 [0.91, 0.99]
Standardized AED dose	0.60 [0.18, 1.02]	0.01	1.82 [1.23, 2.85]
SA-SDQ total	0.06 [-0.04, 0.15]	0.24	1.06 [0.96, 1.17]
ESS total	-0.05 [-0.20, 0.10]	0.49	0.95 [0.81, 1.10]
Variable	Seizure within 6 months		
	β estimate w/ 95% CI	p-Value	Odds ratio w/ 95% CI
(Intercept)	-1.41 [-3.22, 0.40]	NA	0.24 [0.04, 1.43]
Epilepsy type: focal	0.92 [-0.20, 2.04]	0.11	2.52 [0.85, 8.09]
Age	-0.04 [-0.08, -0.01]	0.02	0.96 [0.92, 0.99]
Standardized AED dose	0.32 [-0.02, 0.66]	0.07	1.38 [1.00, 1.98]
SA-SDQ total	0.07 [-0.01, 0.15]	0.08	1.07 [0.99, 1.16]
ESS	-0.05 [-0.16, 0.07]	0.43	0.96 [0.85, 1.07]

Presence of a seizure within 1 month was associated with younger age and higher standardized AED dose. Presence of a seizure within 6 months was associated with younger age. AED, antiepileptic drug; SA-SDQ, Sleep Apnea Scale of the Sleep Disorders Questionnaire; ESS, Epworth Sleepiness Scale.

an abnormal ESS, and among patients with focal epilepsy, 15.9% had an abnormal ESS.

4. Discussion

In this study, we found similar average SA-SDQ scores in patients with focal or generalized epilepsy. However, generalized epilepsy was significantly associated with higher SA-SDQ scores after adjusting for the confounders age, gender, standardized AED dose, prior diagnosis of OSA, BMI, DM, HTN, and seizure within the prior 1 or 6 months. Since the SA-SDQ has been validated to assess for OSA risk in adults [27] including in PWE [15,24,25], this suggests that patients with generalized epilepsy have a higher OSA risk compared with patients with focal epilepsy. Possible reasons for higher OSA risk in patients with generalized epilepsy include altered control of the muscles of the upper airway, ventilatory control instability, or differences in upper airway anatomy. Generalized epilepsy is most often characterized by epileptiform activity involving bilateral thalamocortical circuits. This may cause worse brainstem dysfunction than abnormal activity in focal epilepsy, which may lead to decreased brainstem-mediated respiratory control. Although the number of AEDs was similar between the two groups, patients with generalized epilepsy may have had longer-term use of AEDs and the use of AEDs at younger ages, which could differentially alter these factors. Furthermore, the higher use of valproic acid and the lower use of oxcarbazepine and carbamazepine in patients with generalized epilepsy could also be a contributing factor.

To the best of our knowledge, there are only two studies that directly compared OSA prevalence in patients with focal or generalized epilepsy [14,16]. Both studies showed a similar prevalence of OSA in patients with focal or generalized epilepsy. However, one study was done in an epilepsy monitoring unit where the prevalence of OSA in the study was more than 60%. This is substantially higher than the prevalence seen in a population of patients seen at an epilepsy clinic [16] and in populations with medically refractory epilepsy [15,32]. Furthermore, although OSA prevalence was similar in patients with generalized versus focal epilepsy, this study did not adjust for confounders. The other study that also showed no difference in OSA prevalence in patients with focal versus generalized epilepsy also did not adjust for confounders [16]. This is notable because in our study, raw SA-SDQ scores were similar between groups, but a difference between patients with generalized versus focal epilepsy was observed only on adjusted analysis. Therefore, our study is the first to evaluate OSA risk in patients with generalized versus focal epilepsy in a manner that takes into account known confounders. We are the first to report, to the best of our knowledge, that OSA risk is higher in patients with generalized versus focal epilepsy.

Older age, male gender, and higher BMI are well-characterized risk factors for OSA in the general population [1] and in PWE [14,15]. In our study, risk factors for a higher SA-SDQ score were age, BMI, and a prior history of HTN. These results are not surprising since age, BMI, and the presence of HTN, in addition to being known risk factors for OSA [1,5], are directly assessed on the SA-SDQ. However, it should be noted that on the SA-SDQ, age and BMI are classified into one of 5 categories and, on our model, are assessed as continuous variables. Furthermore, HTN in the SA-SDQ is self-reported, while in our model, it was based on the electronic medical record. This analysis was done this way because the SA-SDQ is taken as a composite score [24,25], and the contribution of these common OSA risk factors to aggregate OSA risk is often assessed. Interestingly, male gender has been identified as a risk factor for OSA but was not associated with a higher SA-SDQ score in this study. This study may have been underpowered to detect that relationship.

We did not find an association between SA-SDQ score and a seizure within the prior one month or 6 months. To understand this relationship better, we assessed for factors that were associated with a greater likelihood of a seizure within the prior one month

or prior 6 months using logistic regression models. We found that older age was associated with a lower likelihood of a seizure within either the prior one month or 6 months. A higher standardized AED dose was associated with a higher risk of seizure within one month, and there was a trend for 6 months. In these models, SA-SDQ score was not associated with a greater likelihood of a seizure within 1 month, but there was a trend for the SA-SDQ score associated with a greater likelihood of a seizure within 6 months. One limitation with our analysis was that we had to retrospectively collect seizure frequency data from the electronic medical record. In order to be able to include data on over 90% of patients, we assessed simply for the presence of a seizure within the prior one or 6 months. It is possible that this was too crude a measure of seizure control. It is also possible that our study was underpowered to detect a relationship with SA-SDQ score and poor seizure control. However, other studies have also not demonstrated a clear association between OSA and seizure frequency. In one small study of patients with medically refractory epilepsy, patients with OSA were more likely to have a seizure during sleep [15]. However, in larger studies, OSA was not associated with higher seizure frequency [14,16]. Similarly, the number of AEDs, which can be used as a measure of more difficult to control epilepsy, was associated with OSA in one study [16] but not in others [14,15]. Similar to other studies, our data are not generally supportive of an association between OSA risk and worse seizure control.

Since excessive daytime sleepiness is a relatively common symptom of patients with OSA [33] and of PWE [34], we assessed whether excessive daytime sleepiness was different in patients with generalized versus focal epilepsy. There was no significant difference in average ESS scores between patients with generalized versus focal epilepsy. Interestingly, other studies have not shown an association between the ESS score and OSA [14–16], but one study did show an association between moderate to severe OSA and higher ESS [14]. It should be noted that excessive daytime sleepiness is not present in many patients with OSA [35]. Furthermore, there are often differences observed between subjective and objective measures of sleepiness. For example, when looking at how quickly patients fall asleep during scheduled naps, i.e., a multiple sleep latency test, one study showed no correlation between how quickly patients fell asleep and the ESS score [36]. To further illustrate this point, other studies have shown that simple attentional tasks are impaired with sleep deprivation, but the performance on these tasks often does not correlate well with subjective sleepiness scales [37–39]. Subjective sleepiness, although very important, can be hard to characterize and define. It is likely that each sleepiness assessment tool may measure something different and this may even be affected by which groups of patients are being assessed. Interestingly, in one study in PWE, being employed, subjective sleep disturbances, and AED polytherapy were all predictive of excessive daytime sleepiness as determined by the ESS [40]. These results suggest that the ESS is not a reliable indicator of OSA risk in PWE but may be more common in patients with OSA of higher severity. Whether other measures of sleepiness are predictors of OSA in PWE, and if they are similarly predictive in patients with generalized versus focal epilepsy, remains to be determined.

Our cross-sectional study recruited patients presenting to an epilepsy clinic and is likely representative of this population. The primary tool of this study, the SA-SDQ, was collected at the time of enrollment, so there was no missing data and reliance on the electronic medical record for this measurement. The major limitation of this study was the use of a validated OSA screening tool rather than direct testing for OSA. This was also a relatively small, single-center study. Larger studies with the use of objective testing may reveal additional insights.

Our study showed that unadjusted SA-SDQ scores were similar in patients with generalized and focal epilepsy, but when adjusted for

confounders, the SA-SDQ scores were higher in patients with generalized epilepsy. Using the cut-points from a prior study [24], approximately a third of patients in this study are likely to have OSA. Since this study did not have a matched control group of patients without epilepsy, this study cannot specifically assess whether the prevalence of OSA is higher in PWE. However, it should be noted that only approximately 10–15% of patients in our study had a diagnosis of OSA, but our data suggest that approximately one-third are likely to have OSA. This disparity between diagnosed prevalence and estimated prevalence suggests that many PWE have OSA that is undiagnosed. It is likely that diagnosis and treatment of OSA in PWE is an insufficiently met healthcare need at this time. Further studies using formal diagnostic testing for OSA as well as studies assessing the benefits of OSA treatment in these patients are clearly needed. Treatment of OSA may be an important part of treatment of epilepsy, and identification of which PWE are most at risk for OSA and which are most likely to benefit from OSA treatment is important.

Declaration of competing interest

None.

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References

- [1] Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev.* 2017;34:70–81.
- [2] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14:540–5.
- [3] Stranks EK, Crowe SF. The cognitive effects of obstructive sleep apnea: an updated meta-analysis. *Arch Clin Neuropsychol.* 2016;31:186–93.
- [4] Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep.* 1997;20:608–13.
- [5] Konecny T, Kara T, Somers VK. Obstructive sleep apnea and hypertension: an update. *Hypertension.* 2014;63:203–9.
- [6] Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol.* 2004;160:521–30.
- [7] Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005;365:1046–53.
- [8] Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea–hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med.* 2010;182:269–77.
- [9] Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep.* 2008;31:1071–8.
- [10] Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busseton Health Study. *Sleep.* 2008;31:1079–85.
- [11] 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.
- [12] Vendrame M, Jackson S, Syed S, Kothare SV, Auerbach SH. Central sleep apnea and central sleep apnea in patients with epilepsy. *Sleep Breath.* 2014;18:119–24.
- [13] Marzec M, Edwards J, Sagher O, Fromes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. *Epilepsia.* 2003;44:930–5.
- [14] Sivathamboo S, Farrand S, Chen Z, White EJ, Pattichis AA, Hollis C, et al. Sleep-disordered breathing among patients admitted for inpatient video-EEG monitoring. *Neurology.* 2019;92:e194–204.
- [15] Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology.* 2000;55:1002–7.

- [16] 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.
- [17] Pornsriniyom D, Shinlapawittayatorn K, Fong J, Andrews ND, Foldvary-Schaefer N. Continuous positive airway pressure therapy for obstructive sleep apnea reduces interictal epileptiform discharges in adults with epilepsy. *Epilepsy Behav.* 2014;37:171–4.
- [18] Pornsriniyom D, Kim H, Bena J, Andrews ND, Moul D, Foldvary-Schaefer N. Effect of positive airway pressure therapy on seizure control in patients with epilepsy and obstructive sleep apnea. *Epilepsy Behav.* 2014;37:270–5.
- [19] Vendrame M, Auerbach S, Loddenkemper T, Kothare S, Montouris G. Effect of continuous positive airway pressure treatment on seizure control in patients with obstructive sleep apnea and epilepsy. *Epilepsia.* 2011;52:e168–71.
- [20] Devinsky O, Ehrenberg B, Barthlen GM, Abramson HS, Luciano D. Epilepsy and sleep apnea syndrome. *Neurology.* 1994;44:2060–4.
- [21] Malow BA, Weatherwax KJ, Chervin RD, Hoban TF, Marzec ML, Martin C, et al. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. *Sleep Med.* 2003;4:509–15.
- [22] Segal E, Vendrame M, Gregas M, Loddenkemper T, Kothare SV. Effect of treatment of obstructive sleep apnea on seizure outcomes in children with epilepsy. *Pediatr Neurol.* 2012;46:359–62.
- [23] McCarter AR, Timm PC, Shepard PW, Sandness DJ, Luu T, McCarter SJ, et al. Obstructive sleep apnea in refractory epilepsy: a pilot study investigating frequency, clinical features, and association with risk of sudden unexpected death in epilepsy. *Epilepsia.* 2018;59:1973–81.
- [24] Weatherwax KJ, Lin X, Marzec ML, Malow BA. Obstructive sleep apnea in epilepsy patients: the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) is a useful screening instrument for obstructive sleep apnea in a disease-specific population. *Sleep Med.* 2003;4:517–21.
- [25] Economou NT, Dikeos D, Andrews N, Foldvary-Schaefer N. Use of the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) in adults with epilepsy. *Epilepsy Behav.* 2014;31:123–6.
- [26] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58:512–21.
- [27] Douglass AB, Bornstein R, Nino-Murcia G, Keenan S, Miles L, Zarcone Jr VP, et al. The Sleep Disorders Questionnaire. I: creation and multivariate structure of SDQ. *Sleep.* 1994;17:160–7.
- [28] World Health Organization ATC/DDD Index. In . https://www.whocc.no/atc_ddd_index/
- [29] Team RC. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
- [30] Rizopoulos D. ltm: an R package for latent variable modeling and item response theory analyses. *J Stat Softw.* 2006:17.
- [31] Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology.* 2018;91:74–81.
- [32] Zanzmer P, Shukla G, Gupta A, Singh H, Goyal V, Srivastava A, et al. Markedly disturbed sleep in medically refractory compared to controlled epilepsy — a clinical and polysomnography study. *Seizure.* 2012;21:487–90.
- [33] Myers KA, Mirkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: the rational clinical examination systematic review. *JAMA.* 2013;310:731–41.
- [34] Maestri M, Romigi A, Schirru A, Fabbrini M, Gori S, Bonuccelli U, et al. Excessive daytime sleepiness and fatigue in neurological disorders. *Sleep Breath.* 2019. <https://doi.org/10.1007/s11325-019-01921-4>.
- [35] Ye L, Pien GW, Ratcliffe SJ, Bjornsdottir E, Amardottir ES, Pack AI, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J.* 2014;44:1600–7.
- [36] Benbadis SR, Mascha E, Perry MC, Wolgamuth BR, Smolley LA, Dinner DS. Association between the Epworth sleepiness scale and the multiple sleep latency test in a clinical population. *Ann Intern Med.* 1999;130:289–92.
- [37] Van Dongen HP, Baynard MD, Maislin G, Dinges DF. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep.* 2004;27:423–33.
- [38] Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose–response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep.* 2003;26:117–26.
- [39] Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, et al. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose–response study. *J Sleep Res.* 2003;12:1–12.
- [40] Lee SA, No YJ, Jo KD, Kwon JH, Kim JY, Shin DJ. Factors contributing to excessive daytime sleepiness in Korean adults with epilepsy: a sleep questionnaire-based study. *Epilepsy Behav.* 2019;90:61–5.