SLEEP APNEA AND EPILEPSY: WHO'S AT RISK?

by

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Prevalence and Predictors of Sleep Apnea in People with Epilepsy

Abstract

by

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Epilepsy is the second most common chronic neurological disorder, affecting over 50 million people worldwide. Nearly 40% of cases are drug resistant. The prevalence of obstructive sleep apnea (OSA) is reportedly higher in epilepsy patients than the general population. Treatment has been shown to reduce seizures in some cases. We performed a cross-sectional study to assess the prevalence and predictors of OSA in adults with epilepsy. We hypothesized an association between OSA and seizure control such that more drug resistant patients were more likely to be affected. The prevalence of OSA was found to be 41.7%, markedly exceeding general population estimates. Multivariate modeling found age and body mass index to be OSA predictors. Measures of epilepsy severity were not associated with presence of OSA or OSA severity. Despite limitations, these observations raise questions regarding the impact of OSA on seizure control, alertness and quality of life in people with epilepsy.

Hypotheses:

1. We hypothesized that the prevalence of OSA in adults with epilepsy should exceed that of the general population.
2. We hypothesized that there should be an association between OSA and seizure control such that subjects with more active epilepsy (higher seizure frequency) are more likely to have OSA and a higher apnea-hypopnea index (AHI) than subjects with rare or infrequent seizures.
3. We hypothesized that subjects with OSA should be more likely to be older, male and have a higher body mass index (BMI) than subjects without OSA as observed in the general population.

Specific Aims:*Primary aim*

To estimate the prevalence of OSA in adults with epilepsy

Secondary aim

To examine predictors of OSA and AHI, with the primary focus on age, gender, BMI and measures of epilepsy severity in adults with epilepsy

Background

Epilepsy is the second most common chronic neurological disorder, affecting over 50 million people worldwide, with 2 million new cases each year (1). The prevalence of epilepsy is 8.0/1000 in the U.S. (2) and may be twice as high in developing countries. Although the majority of patients can be treated successfully with antiepileptic drugs (AEDs), an estimated 30% to 40% of people with epilepsy are drug resistant (3). Thus, in the U.S., the number of patients with drug resistant epilepsy, approximately 700,000, is higher than those affected with Parkinson's disease (349,000) and multiple sclerosis (266,000) combined (2). Epilepsy has substantial morbidity including an increased risk of accidents and injuries, poor academic and occupational performance sudden unexplained death in epilepsy (SUDEP). The incidence of SUDEP ranges from 0.09 to 9.3 per 1000, 24-fold higher than in the general population (4, 5). Therefore, identification of management strategies beyond traditional medical and surgical therapy is of interest to the epilepsy community.

Excessive daytime sleepiness (EDS) is the most common sleep/wake complaint among people with epilepsy, typically attributed to the effects of AEDs and seizures. Several studies have found that one-third to one-half of adults with epilepsy report EDS (6, 7). Epworth Sleepiness Scale (ESS) scores of 10 or greater are observed up to one-quarter of cases (8, 9). In a recent study, only 39% of 148 adults with epilepsy rated their sleep as always good compared to 79% of 100 healthy controls (10). People with epilepsy were significantly more likely to report nocturnal and early morning awakenings even though their total hours slept was comparable to those of the controls. Among 486

adults with epilepsy, a 2-fold higher prevalence of sleep disturbances was found in patients compared with age-matched controls (39% vs.18%) and the presence of a sleep disturbance adversely affected quality of life (11).

In recent years, primary sleep disorders, specifically OSA, has been identified as another potential contributor to EDS in this population (12-14). In a study involved 39 adults with drug resistant epilepsy unselected for sleep disorder symptoms, 33% were found to have OSA (AHI ≥ 10 on polysomnography [PSG]), substantially greater than large epidemiologic studies (12, 15). Those with OSA were more likely to be male, have a higher BMI, and a history of snoring, witnessed apnea or nocturnal seizures. Treatment of OSA has been shown to reduce seizures in over 50% of patients in small series (16-18). No study has explored the prevalence and predictors of OSA in a larger group of adults with epilepsy having a broader range of seizure control.

Methods

This is a cross-sectional study involving adults with epilepsy treated at a tertiary care center. The study was approved by the Cleveland Clinic Institutional Review Board. Subjects provided informed consent prior to the participating in any study-related activities.

Subject Selection

Subjects with epilepsy who presented to a weekly clinic attended by the principal investigator were invited to participate. Subjects met the following criteria:

- Ability to provide written informed consent and willing to comply with study procedures
- At least 18 years of age
- Diagnosed with epilepsy with classifiable and quantifiable seizures
- No prior history of PSG or sleep disorder including sleep apnea, insomnia, restless legs syndrome or narcolepsy
- Absence of medical or psychiatric condition that would compromise participation.
- Absence of vagus nerve stimulation (VNS) therapy (subjects with stimulators in place but device deactivated were eligible for enrollment)

Subjects were able to withdraw from the study at any time. Possible reasons for early withdrawal included:

- A two-fold or greater increase in seizures, new onset generalized tonic-clonic seizures, or status epilepticus
- Development of a clinically relevant change in medical condition
- Pregnancy
- Consent withdrawal

Study Procedures

Subjects underwent the following procedures:

Sleep History and Medical Record Review

Subjects underwent a structured interview ascertaining sleep and wake patterns, nighttime behaviors and sleep disorder symptoms. Excessive daytime sleepiness was assessed by asking the question “In the last six months, have you felt excessively sleepy during the day at least a few days per week?”. Epilepsy type and management, seizure type(s) and frequency in the previous six months, demographic data, pertinent medical history and medications were determined through subject interview and electronic medical record review. Variables included are shown in Table 1.

Subjective Assessments

Epworth Sleepiness Scale (ESS): The ESS is a self-administered eight-item questionnaire that measures a subject’s subjective daytime sleep propensity. Subjects are asked how likely they are to doze off or fall asleep in 8 specific situations such as watching television or riding a car (never, slight, moderate, high: 0-3), with total scores ranging from 0-24. It has high test-retest reliability and a high level of internal consistency. An ESS score of 10 and greater is considered indicative of EDS (19).

Insomnia Severity Index (ISI): The ISI is a validated self-reported measure to evaluate perceived sleep difficulties. It is composed of seven items that evaluate sleep-onset, sleep maintenance and early morning awakening problems, satisfaction with current sleep pattern, interference with daily functioning and awareness of the impairment and level of distress caused in the last two weeks. Each item is rated on a 5-point scale with total scores ranging from 0 to 28. A score greater than 7 indicates insomnia with higher scores indicating greater insomnia (20).

Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA/SDQ): The SA/SDQ is a validated instrument that assesses the likelihood of having OSA based on variables including loud snoring, age, body mass index, tobacco use and hypertension. In the original validation, cutoffs of 32 or higher for women and 36 or higher for men correlated well with having a diagnosis of OSA by PSG (20). Cutoffs of 26 or higher for women and 29 or higher for men were found to correlate better with PSG in epilepsy patients (22).

Beck Depression Inventory (BDI): The BDI is a validated 21-item self-administered questionnaire. It is widely used as a screening tool for depression and many patients with depression report EDS and/or fatigue. Each item assesses a specific symptom or attitude consistent with description of the depression contained in the psychiatric literature. A 0-3 point scale is assigned for each statement to indicate degree of severity. It has good test-retest reliability and there is consistent relationship between BDI scores and clinical state. A score of greater than 9 is considered suggestive of depression (23).

Sleep Diary: Subjects completed a sleep diary for one week prior to sleep laboratory testing. Subjects were asked to record sleep and wake times, nightly awakenings lasting at least 30 minutes and seizures. Total sleep duration (TSD) was determined by averaging the duration of the major sleep period over the period of data entry.

Sleep Laboratory Testing

Polysomnography: Subjects underwent PSG in the Cleveland Clinic Sleep Disorders Center attended by a registered technologist recording electroencephalography (EEG; 21 electrode placement), electro-oculography (EOG; 2 channels), chin electromyography (EMG; 3 channels), leg EMG (4 channels), airflow (nasal thermistor and nasal pressure transducer), thoracic and abdominal effort (piezo electric belts), snoring, EKG, pulse oximetry, body position and video. Sleep staging and event scoring was performed according to standard criteria (24). Apneas and hypopneas were tallied to derive the AHI (number of respiratory events per sleep hour).

Multiple Sleep Latency Test (MSLT): Subjects underwent the MSLT, the gold standard objective measurement of daytime sleepiness, on the day following PSG. The results will be reported separately.

Analytic Approach

Patients having an $AHI \geq 5$ were identified as having OSA. Summary statistics were computed for each variable. A standardized variable of the amount of AED taken daily was determined for each subject based on the Defined Daily Dose (DDD; 25). The DDD is a measure of the average maintenance dose needed for adults and was obtained from the World Health Organization website (26). For each subject, the ratio of the total AED daily dose to the DDD was determined and then summed over all drugs in the subject's regimen. Standardized AED values greater than 1 indicated dose regimens that are higher than the average.

The percent of subjects having OSA was determined along with a corresponding 95% confidence interval. Predictors of OSA were individually examined first followed by a multivariate analysis. Because of non-normality concerns in many of the continuous measures, a Mann-Whitney U-test was used to identify differences in continuous variables between those with and without OSA. Categorical variables were evaluated through chi-square tests or, for extremely small samples, through Fisher's exact test. Age was evaluated as a continuous variable and as a categorical variable defined as <30, 30-50 and >50 years. Similarly, BMI was treated as a continuous and categorical variable <30 (non-obese) and ≥ 30 kg/m² (obese). A multivariate analysis was conducted to examine the relationship of the traditional population predictors with OSA (age, gender and BMI). A logistic regression model was built having OSA as the dependent variable and age, gender and BMI as independent variables. All interactions were considered.

Predictors of AHI were examined through Spearman correlations for continuous variables, and Mann-Whitney U-tests/Kruskal-Wallis tests for categorical variables. A multivariate regression model was built having AHI as the dependent variable and age, gender and BMI as independent variables. All interactions were investigated. An additional model was created that controlled for other variables of interest (number of AEDs, mean monthly seizure frequency, epilepsy type). For both models, a log transformation was applied, $\ln(\text{AHI}+1)$, to induce normality. Analyses were conducted in R 2.10.1 and SAS[®] v9.2.

Results

There were 132 subjects available for analysis. This represents approximately 10% of the outpatient epilepsy clinic population that likely would have met enrollment criteria. The most common reason for declining was lack of transportation, as participation required an overnight stay in the sleep laboratory. Table 2 contains summary statistics.

The prevalence of OSA was found to be 41.7% (55 out of 132) with a 95% confidence interval (33.2%, 49.8%). Significant predictors of OSA based on univariate results (Table 3), were age ($p<.0001$), BMI ($p=.0002$) and SA/SDQ ($p=.0002$). Age category ($p<.0001$) and BMI category ($p=.0010$) were also significant. No other variables were found to be significantly associated with OSA. Patients with OSA were more likely to be older and have a higher BMI. Additionally, SA/SDQ was greater for OSA patients as expected.

Logistic model results for OSA are shown in Table 4. The analysis was limited to looking at the traditional predictors of OSA in the general population: age, BMI and gender. BMI was found to be significant ($OR=1.081$, $p=.0065$). For every 1 unit increase in BMI, the odds of having OSA increased by 8.1%. For example, a change in BMI from 30 to 35, an increase of 5 units, would increase of the odds of having OSA by 47.6%, all other factors held constant. Age was also significant ($OR=1.064$, $p=0.0002$). Females were less likely to have OSA than males, but this was not found to be significant. No interactions were found to be significant. Figures 1 and 2 show gender and BMI-specific OSA prevalence by age.

The correlations between AHI and variables of interest are shown in Table 5. Correlations between AHI and age ($r_s=.405$, $p<.0001$), BMI ($r_s=.314$, $p=.0002$), and SA/SDQ ($r_s=.435$, $p<.0001$) were mild-to-moderately strong. All were positive indicating that AHI tended to increase as these variables also increased. After categorization, age ($p=.0001$) and BMI ($p=.0056$) remained significant. Older subjects were found to have higher AHI values as did obese subjects. Dental problems and AHI were also significantly associated ($p=.0231$). Subjects with dental problems had higher AHI values.

Examination of the effect of traditional OSA predictors on AHI found age, BMI and gender to be significant (Table 6). The effect of age on AHI varied by gender ($p=.0473$). AHI values increased as age increased, but at a faster rate for females than males (transformed AHI values increased 4.6% for females and 1.8% for males for every 1 unit increase in age). The effect of BMI ($p=.0046$) on AHI was the same for both genders. Age ($p=.0095$) and BMI ($p=.0009$) remained significant after adjusting for other covariates of interest (EDS, ESS, alcohol use, presence of hypertension, tobacco use, number of AEDs, total number of seizures per month, number of GTCs per 6 months and standardized AED dose) as shown in Table 7. The interaction between age and gender, however, was no longer significant.

Discussion

Obstructive sleep apnea is the most common sleep related breathing disorder, characterized by a narrow and floppy upper airway that causes no problems when awake, but recurrent episodes of partial (hypopnea) or complete (apnea) collapse in sleep. The disorder is exceptionally common, with 24% of men and 9% of women in large epidemiologic studies having an AHI ≥ 5 on PSG (15). Established OSA risk factors include male gender, age, BMI, large neck girth, snoring and witnessed apnea, menopause, alcohol and sedative hypnotic use, allergies and tobacco use (26). The American Academy of Sleep Medicine estimates that 80-90% of affected individuals in the U.S. are undiagnosed or untreated. Obstructive sleep apnea is associated with diverse systemic abnormalities, although evidence for causal relationships is lacking. A maladaptive autonomic response of chemoreceptors, reacting to hypoxia, hypercapnia and acidosis is the proposed mechanism leading to sympathetic nervous system activation that triggers an inflammatory response cascading in a variety of downstream consequences including hypertension, diabetes mellitus and hyperlipidemia (27).

Recent reports suggest that OSA may be particularly common in people with epilepsy. One-third of 33% of 39 patients (50% of males and 19% of females) with drug resistant focal epilepsy without sleep complaints were found to have OSA (10). Those with OSA were more likely to be male, have a higher BMI and a history of snoring, witnessed apnea and nocturnal seizures. The severity of OSA was moderate or worse in nearly 50% of cases. While 9 of 13 OSA patients were on multiple AEDs, epilepsy-related variables including seizure frequency, specific AED and epilepsy type (temporal vs. extratemporal epilepsy) were not predictive of OSA.

In the only other study investigating OSA prevalence in epilepsy, 283 adults were prospectively screened using a structured interview and referred for ambulatory PSG when the history was positive for snoring, witnessed apnea or gasping/choking in sleep (11). Unlike the prior study that was limited to refractory focal epilepsy, 23% of subjects had idiopathic generalized epilepsy and seizures were controlled (less than one per month) in 56% of cases. Forty (14%) subjects screened positive for OSA and underwent PSG and of these, 73% (72% male) had OSA. Subjects with OSA were older, had a higher BMI, were more likely to be male and have experienced the first seizure at a later age. No other epilepsy-related variable was associated with the presence of OSA.

Older age is a risk factor for epilepsy presumably due to the increased prevalence of stroke, brain tumors and degenerative disorders. A recent cross sectional study of 21 adults with epilepsy ≥ 50 years examined whether OSA was more common in those with poor seizure control (12). Overall 52% of subjects had an AHI of > 5 (73% of men, 30% of women) including 82% of those with seizure onset or worsening at or over the age of 50 years versus only 20% of those with earlier onset and seizure free or improving after age 50. While the groups were comparable in age, BMI, neck girth, number of AEDs and frequency of nocturnal seizures, males predominated in the late-onset/worsening group. Nevertheless, this study suggests that OSA may be a contributing factor to worsening seizure control or new onset seizures in older adults.

Our observational study revealed a high prevalence of OSA in a group of adults with epilepsy, with traditional OSA risk factors of age and BMI increasing the risk of OSA in epilepsy patients. In contrast to the general population, the rate of increase in AHI with age was greater for women than for men. However, we failed to confirm an association between OSA and poor seizure control in people with epilepsy. A cross-sectional design was chosen as the primary goal of this pilot study was to determine the prevalence of OSA in a timely and cost-effective manner, avoiding losing subjects to follow-up. A prospective cohort study would have required substantial time, in this case, years, for OSA to develop, and substantial cost as sleep laboratory testing would have been required at multiple points in time. Furthermore, epilepsy is a dynamic disorder that can spontaneously remit or evolve to an intractable state or status epilepticus associated with substantial morbidity and mortality. Dramatic changes in management strategies are not uncommon, particularly in epilepsy surgical centers where the current study was conducted. Alternative study designs requiring follow-up over time in our patient population would likely have been compromised by an unacceptable drop-out rate and/or marked changes in disease status due to standard of care therapeutic modalities.

Several factors could explain the observed increased prevalence of OSA in people with epilepsy. Central nervous system depressants, such as barbiturates and benzodiazepines, and possibly phenytoin, through smooth muscle relaxation, can adversely affect upper airway tone, rendering the airway more collapsible (28). Weight gain is a significant adverse effect of some AEDs, most notably valproate, gabapentin, carbamazepine, pregabalin and vigabatrin (29). Relatively modest weight gain may lead

to clinically significant OSA, particularly in predisposed individuals. In a prospective trial including nearly 700 adults, weight change positively correlated with an increase in AHI, when adjusting for sex, age and smoking habits (30). At the lower range of AHI, each 1% change in weight was associated with a 3% increase in AHI, such that a 10% increase in body weight resulted in a 30% increase in AHI. People with epilepsy are also less physically fit than age-matched control subjects, demonstrated by significant differences in aerobic endurance, muscle strength endurance and flexibility resulting in higher BMI (31, 32). Endocrinopathies associated with OSA including polycystic ovarian syndrome and hypothyroidism are also common in people with epilepsy (33).

Treatment of OSA reduces obesity, blood pressure, insulin resistance and the risk of cardiovascular disease, normalizes lipid levels, and improves cognition, mood and daytime sleepiness (27). Further, positive airway pressure, positional therapy or upper airway surgery reduces seizures in 40-86% of people with epilepsy and OSA (16-18). Resolution of sleep fragmentation, sleep deprivation, cerebral hypoxemia, decreased cardiac output and cardiac arrhythmias associated with untreated OSA may underlie these observations.

This study has several limitations related to the observational design. Firstly, the prevalence of OSA may not be generalizable to the adult epilepsy population. The sample population is a convenience sample recruited from a single physician's tertiary care surgical center practice. While there are no obvious reasons why this sample would differ from other epilepsy practices at the same institution, it is expected to have had

more active epilepsy than subjects treated in a community neurology setting. In addition, subjects with sleep disorder symptoms or knowledge about the relationship between sleep and epilepsy may have been more likely to participate. This may have been off-set in part by the exclusion of potentially recruitable subjects who had previously been diagnosed and/or treated for OSA. These limitations aside, drug resistant epilepsy, defined as persistent monthly seizures despite appropriate medical therapy, is the subject of virtually all research exploring potential therapeutic modalities and innovative treatments as this subset of patients accounts for nearly 80% of the global cost of epilepsy and nearly all its morbidity and mortality. To further explore the associations reported herein, we hope to identify a control group within our tertiary care center of epilepsy patients referred to the sleep laboratory for PSG.

Other study limitations related to epilepsy parameters may have affected the results. Seizure frequency was quantified retrospectively using self-report and EMR review and may have been inaccurately estimated. Furthermore, the number of AEDs was presumed to be a surrogate for seizure control (more drugs implying more active epilepsy), but this is not always the case. AED doses were standardized to estimate the burden of drug therapy and this did not correlate with the presence of OSA or AHI either. To further explore associations between OSA and epilepsy severity parameters, the analyses presented will be repeated using an $AHI \geq 5$ with self-reported EDS and an $AHI \geq 15$ (moderate to severe OSA cases). Given the potential impact of unrecognized OSA in the epileptic population, further elucidation of the predictors of OSA may lead to

earlier recognition, improved treatment options, and ultimately, better seizure control and quality of life.

Future plans are to utilize this dataset to explore a variety of other research questions related to the impact of OSA and EDS on epilepsy.

Impact of PAP therapy on seizure control and spike rate in adults with epilepsy and OSA: Treatment of OSA with CPAP reduces seizures in approximately 50% of cases. In addition, a study involving 8 adults with focal epilepsy and OSA or hypoxia in sleep found that CPAP not only normalized the AHI, but markedly reduced spike rate (number of interictal discharges per unit time in sleep; 34). Most subjects diagnosed with OSA in the present study were offered PAP therapy and continue to be followed in the Cleveland Clinic Epilepsy Center where seizure frequency is documented in a standardized manner. For those who had follow up care in the Sleep Disorders Center, PAP compliance data and ESS scores are also available. A smaller number of subjects underwent PSG-EEG on therapeutic CPAP subsequent to obtaining a diagnosis of OSA. A retrospective study comparing seizure frequency and ESS scores pre- and post-CPAP therapy will be completed. This study is expected to include more subjects and employ standardized methodology not detailed in prior reports. Finding that treatment of OSA reduces seizures would reinforce the importance of this research despite the lack of an association between epilepsy severity parameters and OSA. Similarly, a comparison of pre- and post- CPAP EEG spike rate would provide further support that OSA treatment reduces excitability in the epileptic brain. To date, spike quantification has been performed in 5 subjects who participated in the present study.

Relationship between habitual sleep duration and epilepsy: In recent years, short habitual sleep duration (< 6 hrs/night) has been linked to adverse outcomes in a variety of chronic diseases. We previously tested this hypothesis in 40 adults with drug resistant focal epilepsy admitted to the Epilepsy Monitoring Unit for presurgical evaluation. A significant, inverse relationship between seizure control and self-reported habitual sleep duration was found (35). Subjects sleeping less than 6 hrs per night had a higher mean monthly seizure frequency (25.5 seizures/mo.) compared with those sleeping 6 to 8 and more than 8 hrs (8.4 and 9.4, respectively). This finding can be confirmed using linear regression analysis to measure the association between mean monthly seizure frequency and habitual sleep duration obtained from sleep diaries completed prospectively in the current study controlling for important covariates, including presence of OSA and AHI. A positive finding will underscore the importance of good sleep hygiene in the comprehensive care of people with epilepsy.

Predictors of mean sleep latency (MSL) on the MSLT in adults with epilepsy: Results of the MSLT were not included in the current study. Daytime sleepiness is the most common complaint of people with epilepsy. In a preliminary analysis involving 92 subjects from the current dataset, the MSL was less than 8 minutes in 62% of cases, suggesting a high prevalence of sleepiness (36). The MSL was less than 5 minutes, comparable to that of narcolepsy patients, in 36% of cases. Further analysis of the predictors of a short MSL will be performed using regression analysis. An

analysis of the predictive value of the ESS total score and individual items on MSL will be performed as an initial effort to develop a reliable assessment of subjective sleepiness in the epilepsy population.

Table 1. Study Variables

Variable	Coding
<i>Demographics</i> Age Gender Body Mass Index (BMI) Marital Status Employment Status Tobacco Use Alcohol Caffeine Recreational Drugs	years male/female kilogram/meter ² married/single/divorced/other employed/retired/disabled/homemaker /student current or last 6 month/never no. beverages per week no. ounces per day yes/no
<i>Epilepsy-Related</i> Epilepsy Type Focal Epilepsy Type No. Antiepileptic Drugs (AEDs) AED Std AED Type AED Group Focal Seizures (Sz)/mo Generalized Seizures (Sz)/mo Total Seizures (Sz)/mo Generalized Tonic-Clonic Seizures (GTCs) GTCs/6 mo	focal/generalized/unclassified temporal (TLE)/extratemporal (ExTLE) no. used currently standardized dose of AED regimen first/second generation/combination monoRx/polyRx mean focal seizures per month mean generalized seizures per month mean total seizures per month history of generalized motor seizures no. GTCs in last 6 months
<i>Sleep-Related</i> Total Sleep Duration (TSD) Apnea-Hypopnea Index (AHI) Obstructive Sleep Apnea (OSA) Sleep Apnea/Sleep Disorders Quest (SA/SDQ) Insomnia Severity Index (ISI) Beck Depression Index (BDI) Epworth Sleepiness Scale (ESS) Excessive Daytime Sleepiness (EDS)	mean hours habitual sleep per night respiratory events per sleep hour yes/no total score total score total score total score yes/no
<i>Medical</i> Hypertension Pulmonary Disease Thyroid Disease Heart Disease Mood Disorder	yes/no

Other Psychiatric Disorder Head Trauma Brain Surgery Nasal Surgery Dental Problems	
<i>Medications</i> Antidepressant Other Psychotropic Stimulant Sedative-Hypnotic	yes/no

Table 2: Sample Characteristics

Variable	N	Mean $\pm$ SD or N (%)
<i>Demographics</i>		
Age, yr	132	39 $\pm$ 13.2
Male	132	58 (43.9)
BMI, kg/m ²	132	28.9 $\pm$ 7.3
Tobacco use	132	45 (34.9)
Alcohol, beverages/wk	130	0.67 $\pm$ 2.0
Caffeine, oz/d	129	2.4 $\pm$ 2.9
Recreational Drugs	130	5 (3.9)
<i>Epilepsy-Related</i>		
Focal Epilepsy	132	97 (73.5)
TLE	97	58 (59.8)
No. AEDs	132	1.6 $\pm$ 0.7
1 st Gen AED	132	33 (25)
AED Std	132	1.9 $\pm$ 1.2
AED MonoRx	132	64 (48.5)
Focal Sz/mo	132	3.4 $\pm$ 7.9
Generalized Sz/mo	129	1.9 $\pm$ 5.7
Total Sz/mo	132	5.2 $\pm$ 9.3
GTCs	132	72 (54.6)
GTCs/6 mo	132	0.43 $\pm$ 0.6
<i>Sleep-Related</i>		
TSD, hr	120	7.5 $\pm$ 1.9
AHI	132	8.4 $\pm$ 15.5
OSA	132	55 (41.7)
SA/SDQ	94	25 $\pm$ 7
ISI	91	11 $\pm$ 7
BDI	102	10 $\pm$ 8
ESS	111	8 $\pm$ 4
EDS	132	95 (77.9)
<i>Medical</i>		
Hypertension	132	13 (9.9)
Pulmonary Disease	132	27 (20.5)
Thyroid Disease	132	10 (7.6)
Heart Disease	132	2 (1.5)
Mood Disorder	132	38 (28.8)
Other Psychiatric Disorder	132	19 (14.4)

Head Trauma	132	23 (17.4)
Nasal Surgery	132	35 (26.5)
Brain Surgery	132	17 (12.9)
Dental Problems	132	20 (15.2)
<i>Medications</i>		
Antidepressant	100	27 (27)
Other Psychotropic	98	2 (2)
Stimulant	106	5 (4.7)
Sedative-Hypnotic	108	20 (18.5)

Table 3: Univariate Analysis of Potential Predictors of OSA

Variable	No OSA		OSA		P-value*
	N	Mean (SD)	N	Mean (SD)	
Age	77	34.4 (11.55)	55	44.8 (13.04)	<.0001
BMI	77	27.0 (6.71)	55	31.5 (7.35)	0.0002
No. AEDs	77	1.6 (0.71)	55	1.7 (0.72)	0.49
AED Std	77	1.9 (1.22)	55	2.0 (1.30)	0.81
Focal Sz/mo	77	3.3 (7.79)	55	3.5 (8.04)	0.89
Generalized Sz/mo	75	2.1 (5.68)	54	1.7 (5.83)	0.83
Total Sz/mo	77	5.1 (9.36)	55	5.4 (9.18)	0.20
GTCs/ 6 mo	77	0.4 (0.60)	55	0.4 (0.63)	0.70
TSD	72	7.6 (1.96)	48	7.4 (1.92)	0.42
SA/SDQ	51	22.6 (6.61)	43	28.0 (7.10)	0.0002
ISI	50	10.5 (6.72)	41	10.5 (6.80)	0.98
BDI	57	9.6 (7.72)	45	11.2 (8.23)	0.33
ESS	63	8.0 (4.43)	48	7.9 (4.30)	0.97
	N (%)				
Gender, Male	32 (41.6)		26 (47.3)		0.51
Tobacco use	23 (30.7)		22 (40.7)		0.24
Focal Epilepsy	53 (68.8)		44 (80.0)		0.67
TLE	33 (62.3)		25 (56.8)		0.90
AED MonoRx	39 (50.7)		25 (45.5)		0.56
1st Gen AED	21 (27.3)		12 (21.8)		0.65
GTCs	43 (55.8)		29 (52.7)		0.72
EDS	56 (77.8)		39 (78.0)		0.97
Hypertension	6 (7.8)		7 (12.7)		0.35
Thyroid Disease	3 (3.9)		7 (12.7)		0.09
Mood disorder	23 (29.9)		15 (27.3)		0.75
Nasal Surgery	18 (23.4)		17 (30.9)		0.33
Dental Problems	8 (10.4)		12 (21.8)		0.07

*Continuous variables - Mann-Whitney U-tests; Categorical variables - Chi-square or Fisher's exact test.

Table 4: Multivariate Logistic Model Assessing Traditional OSA Risk Factors for Predicting OSA in Adults with Epilepsy

Variable	Coefficient	Odds Ratio	95% CI	P-value
Age	0.0624	1.064	1.030, 1.099	0.0002
BMI	0.0780	1.081	1.022, 1.144	0.0065
Gender (female)	-0.3649	0.694	0.317, 1.521	0.3619

CI – confidence interval

Table 5: Univariate Analysis of Potential Predictors of AHI

Variable	N	Correlation	P-value*
Age	132	0.405	<.0001
BMI	132	0.314	0.0002
No. AEDs	132	0.123	0.1589
AED Std	132	0.107	0.2240
Focal Sz/mo	132	0.006	0.9460
Generalized Sz/mo	129	-0.042	0.6383
Total Sz/mo	132	0.014	0.8751
GTCs/6 mo	132	-0.054	0.5409
TSD	120	-0.144	0.1164
SA/SDQ	94	0.435	<.0001
ISI	91	0.009	0.9293
BDI	102	0.124	0.2139
ESS	111	0.167	0.0793
	N (%)		
Gender, Female	74	8.4	0.9434
Tobacco use	45	9.9	0.3232
Focal Epilepsy	97	9.8	0.3009
TLE	58	9.9	0.5469
AED MonoRx	64	7.1	0.2026
1st Gen AED	33	5.1	0.1155
GTCs	72	8.3	0.7015
EDS	95	7.2	0.6981
Hypertension	13	19.2	0.0661
Thyroid Disease	10	19.7	0.0907
Mood disorder	38	8.2	0.9400
Nasal Surgery	35	14.9	0.3250
Dental Problems	20	14.2	0.0231

*Continuous variables - Spearman correlations; Categorical variables - Mann-Whitney U-tests or Kruskal-Wallis tests.

Table 6: Multivariate Regression Model Assessing Traditional OSA Risk Factors for Predicting AHI in Adults with Epilepsy

Variable	Coefficient	P-value
Age	0.0180	<.0001
BMI	0.0363	0.0046
Gender (Female)	-1.1444	0.0465
Age*Gender (Female)	0.0280	0.0473

* Results based on $\ln(\text{AHI}+1)$ transformation

Table 7: Multivariate Model Assessing Predictors of AHI in Adults with Epilepsy*

Variable	Coefficient	P-value
Age	0.0096	0.0095
BMI	0.0587	0.0009
Gender (Female)	-0.9484	0.1621
Age*Gender(Female)	0.0266	0.1156
No. AEDs	0.0953	0.6522
AED Std	0.0973	0.4092
Total Sz/mo	-0.0035	0.7881
GTCs/6 mo	0.1063	0.5784
ESS	-0.0131	0.5968
EDS (No)	0.2184	0.3873
Hypertension (No)	0.0020	0.9958
Tobacco use (No)	-0.1380	0.5476

*Model results for $\ln(\text{AHI}+1)$ transformation

Figure 1: Age and Gender Specific Prevalence of OSA

Figure 2: Age and BMI Specific Prevalence of OSA

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