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# *Evaluation of Treatment Effects on Patients with Sleep-Related Breathing Disorders and Epilepsy Comorbidity*

## *Uyku ile İlişkili Solunum Bozuklukları ve Epilepsi Komorbiditesi Olan Hastalarda Tedavi Etkilerinin Değerlendirilmesi*

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### Abstract

**Objective:** Epilepsy and sleep-related breathing disorders (SBD) are among the most prevalent conditions in neurology. This study aimed to compare sleep parameters in patients with primary snoring-epilepsy (PrS-E) and severe obstructive sleep apnea syndrome-epilepsy (OSAS-E). Additionally, the study sought to assess the mutual effects of treatments administered in each clinical area on the other.

**Materials and Methods:** Patients who were subjected to follow-up in the sleep laboratory and epilepsy outpatient clinic between 2006 and 2022 were analysed retrospectively, following approval from ethics committe. The demographic data, medical history, characteristics of epileptic seizures, electroencephalograms (EEGs) and antiseizure drugs (ASD) before and after SBD treatment were compared. The effect on sleep structure and respiratory issues of lowering the dose of ASD after SBD treatment was also assessed.

**Results:** The study included 28 patients with PrS-E and 28 patients with severe OSAS-E. Focal onset impaired awareness focal to bilateral tonic-clonic seizures were found to be more prevalent in both groups. Following treatment for SBD, there was a decline in seizure severity and frequency, a resolution of EEG pathologies, or a decrease ASDs in both groups. The reduction in ASDs and treatment for SBD resulted in an improvement in sleep structure, a reduction in body mass index, snoring, and Epworth Sleepiness Scale.

**Conclusion:** Treating SBDs can lead to a reduction in the dosage of ASD, improved sleep structure, and decreased snoring. This study demonstrated mutual benefits in the management of both epilepsy and SBDs. SBD symptoms should be investigated in epilepsy patients, and the presence of epileptic seizures should be considered in patients with SBD.

**Keywords:** Obstructive sleep apnea syndrome, primary snoring, epilepsy, antiepileptic drug, body mass index, Epworth Sleepiness Score

### Öz

**Amaç:** Nörolojide en çok görülen hastalıklar arasında epilepsi ve uyku ile ilişkili solunum bozuklukları (USB) yer almaktadır. Çalışmamızda primer horlama-epilepsi (PrH-E) ile ağır obstruktif uyku apne sendromu-epilepsi (OUAS-E) birlikteliği olan hastalarda uyku parametrelerinin karşılaştırmasının yanı sıra, her iki klinikte uygulanan tedavilerin birbirlerine olan etkisinin değerlendirilmesi amaçlandı.

**Gereç ve Yöntem:** 2006-2022 yılları arasında kurumumuz uyku laboratuvarı ve epilepsi polikliniğinde takip edilen hastalar etik kurul onayı sonrası retrospektif olarak incelendi. USB tedavisi öncesi ve sonrası demografik veriler, tıbbi öykü, epileptik nöbetlerin özellikleri, elektroensefalogramlar (EEG) ve antiepileptik ilaç (AEİ) tedavileri karşılaştırıldı. Ek olarak, USB tedavisi sonrası AEİ'nin doz ve sayısının azaltılmasının uyku yapısı ve solunum yolu üzerindeki etkileri değerlendirildi.

**Bulgular:** Çalışmaya 28 PrH-E hastası ve 28 ağır OUAS-E hastası dahil edildi. Farkındalığın bozulduğu fokal başlangıçlı bilateral tonik-klonik nöbetler her iki grupta daha sık bulundu. USB tedavisini takiben, her iki grupta da nöbet şiddeti ve sıklığında bir azalma, EEG patolojilerinde bir azalma veya AEİ'lerin sayısında ve dozlarında azalma vardı. AEİ'lerdeki azalma ve USB tedavisi, uyku yapısında iyileşme, vücut kitle indeksinde düşüş, horlama ve Epworth Uykululuk Skoru'nda bir azalma ile sonuçlandı.

**Sonuç:** Uykuda solunum bozukluklarının tedavisiyle AEİ'nin sayısı ve dozu azalmakta, uyku yapısı düzelmekte ve horlama yakınması azalmaktadır. Çalışmamızda tedavi ile hem epilepsi hem de USB kliniklerinde karşılıklı düzelmeler saptanmıştır. Epilepsili hastalarda USB ile ilişkili şikayetler ve USB'li hastalarda ise olası epileptik nöbet varlığı sorgulanmalıdır.

**Anahtar Kelimeler:** Obstruktif uyku apne sendromu, primer horlama, epilepsi, antiepileptik ilaç, vücut kitle indeksi, Epworth Uykululuk Skoru

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## Introduction

Epilepsy and sleep-related breathing disorders (SBD) are among the most common clinical conditions encountered in neurology.[1] SBD encompasses a range of disorders, from primary snoring (PrS) to severe obstructive sleep apnea syndrome (OSAS).[2] These conditions can occur independently or coexist, and early recognition of SBD is crucial, as it exacerbates the frequency and severity of epileptic seizures. In cases where both SBD and epileptic seizures are present, treatment management becomes more complex, leading to more frequent complications.[3,4]

OSAS is characterized by repetitive reductions or interruptions of airflow in the upper respiratory tract during sleep. Its hallmark symptoms include witnessed apneas, particularly snoring, and excessive daytime sleepiness.[5] Polysomnography (PSG) is the gold standard for diagnosing OSAS. The severity of OSAS is determined by the Apnea-Hypopnea Index (AHI), which measures the total number of apneas and hypopneas per hour of sleep. AHI values of 5-14 indicate mild OSAS, 15-29 indicate moderate OSAS, and AHI >30 indicates severe OSAS. PrS refers to respiratory noise during the inspiratory (and sometimes expiratory) phases of breathing during sleep, without associated sleep apnea.[6] Treatment for PrS includes conservative approaches, intraoral implants, and surgery,[7] while OSAS treatment involves positive airway pressure (PAP) therapy and/or upper airway surgery.[8-10]

Patients with epilepsy have a higher prevalence of OSAS compared to the general population. OSAS can lower the seizure threshold through mechanisms such as sleep fragmentation, oxygen desaturation, and chronic sleep deprivation.[9-11] Older age, and having sleep disorders are all associated with a higher risk of epilepsy.[11] Furthermore, it has been established that certain conditions, including the occurrence of refractory seizures, the utilisation of antiseizure medications, and the administration of antiseizure drugs (ASDs) in the form of polytherapy, render these patients more susceptible to OSAS. Although data on the efficacy of PAP therapy for controlling seizures are limited, retrospective studies suggest it can significantly reduce seizure frequency, excessive daytime sleepiness, and cognitive complaints.[12]

The relationship between sleep and epilepsy is complex, with each condition influencing the other in various ways. In epilepsy patients with SBD, seizures may become more resistant and harder to manage. OSAS increases seizure frequency and severity, as well as daytime sleepiness in these patients.[13] It also reduces oxygen levels in the brain, disrupts natural sleep patterns, and triggers spike discharges and paroxysmal activities on electroencephalography (EEG), further aggravating epileptic seizures. However, effective OSAS treatment can lead to better seizure control and a reduction in epileptiform activity on EEG.[14]

In our study, we aimed to compare the demographic data, disease duration, clinical findings, PSG data, seizure types, seizure frequency and EEG examination results between patients with primary snoring-epilepsy (PrS-E) and those with severe obstructive sleep apnea syndrome-epilepsy (OSAS-E).

## Materials and Methods

This study was conducted as a retrospective study following the approval of Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee (approval number: 307, date: 25.07.2022). The study population comprised 56 patients who were under follow-up in the Department of Neurology-Sleep Outpatient Clinic-Sleep Laboratory and Epilepsy Outpatient Clinic of Private Buca Hospital between January 2006 and June 2022. The study population was further subdivided into two groups: 28 patients with PrS-E and 28 patients with severe OSAS-E. It should be noted that the follow-up and treatment of these patients are ongoing.

### Inclusion Criteria

- The patient has been diagnosed with epilepsy [2017 International League Against Epilepsy (ILAE)] and PrS (American Academy of Sleep Medicine Guidelines).
- The diagnosis of epilepsy (2017 ILAE) is made, and the patient also exhibits severe OSAS (American Academy of Sleep Medicine Guidelines).
- Normal brain imaging results, including magnetic resonance imaging and/or other imaging methods such as cranial brain tomography.
- Age over 18 years.
- Voluntary consent form obtained.

Exclusion criteria encompassed epileptic seizures attributable to alternative etiologies, substance abuse, psychiatric diagnoses necessitating pharmacotherapy, mental retardation, other neurodegenerative diseases, syndromic seizures, irregular use of antiseizure medications and vagal nerve stimulators, and epilepsy surgery.

### Data Acquisition Tools

The parameters compared between the PrS-E and severe OSAS-E groups included included demographic data [age at presentation, gender, body mass index (BMI)], medical history, birth history, duration of epilepsy, duration of snoring, relationship of seizures with sleep, comorbidities (if present). Additional factors included epilepsy features, EEG findings and treatments for epilepsy. Pathological EEG findings were classified as paroxysmal activity disorders with non-specific or epileptiform potential, generalised epileptiform discharges, focal epileptiform discharges, paroxysmal lateralising epileptiform discharges and bilateral paroxysmal lateralising epileptiform discharges were considered pathological. Furthermore, a comparison of the features of epilepsy (clinical and electroencephalographic) after treatment for PrS or severe OSAS was performed. Metrics evaluated in patients diagnosed with PrS-E and severe OSAS-E included the AHI, sleep latency duration, N1, N2, N3, rapid eye movement (REM) latencies, percentages of N1, N2, N3, REM durations, fragmentations, respiratory arousal index, arousal index associated with leg movements (LM), spontaneous arousal index, and sleep efficiency [ratio of total sleep time (TST) to time in bed multiplied by 100 to yield a percentage].

In addition to the aforementioned data, the effects of the SBD treatment on epilepsy and secondary sleep structure were also investigated. The Epworth Sleepiness Scale (ESS) was performed on all patients both before and after SBD treatment in order to determine excessive sleepiness. The ASD used by all patients were recorded both before and after SBD treatment.

### Epworth Sleepiness Scale

To assess excessive sleepiness, questionnaire forms are used that vary in compatibility with objective sleepiness measurement methods. The most commonly used of these is the ESS. The ESS includes questions such as, "Do you feel drowsy, sleepy, or experience somnolence?" for each item, scoring is based on the following options: 0=never, 1=mildly, 2=moderately, and 3=severely. The total score ranges from 0 to 24, with sleepiness assessed by summing the scores from the patient's responses. A score of 10 or above is classified as hypersomnia. The Turkish validity and reliability of the ESS have been confirmed in our country.[15]

### Statistical Analysis

The data obtained from the study were entered into a database created using IBM SPSS 25 (SPSS Inc., Chicago, IL, USA), and statistical analyses were conducted using the same software. For continuous variables, the mean, standard deviation, median, minimum, and maximum values were calculated. The normality of the variables was assessed by using the Shapiro-Wilk test. Independent groups were compared using the Mann-Whitney U test, and pre- and post-treatment comparisons were analyzed with the Wilcoxon test. The chi-square test was employed to assess whether the relationship between two nominal variables was statistically significant. In all statistical tests, a "p" value of less than 0.05 was considered to indicate a statistically significant difference between groups.

## Results

Of the 56 patients included in our study, 28 were in the PrS-E group and 28 were in the severe OSAS-E group. The mean age of all patients was 46.54±15.68 years (range: 19-82). Of these, 17 patients (30.4%) were female and 39 (69.6%) were male (p=0.380).

Regarding birth histories, 50 patients (89.3%) were born via normal spontaneous vaginal delivery, while 6 patients (10.7%) were born by cesarean section. Childhood epilepsy was reported in 8 patients (14.3%), and childhood snoring in 37 patients (66.1%).

Physical examination revealed that, based on the Mallampati score (class 1, 2, 3), 30 patients (53%) were classified as Mallampati class 1, 12 patients (22%) as Mallampati class 2 and 14 patients (25%) Mallampati class 3. When considering jaw anatomy, 42 patients (75%) had normal anatomy, 12 patients (21%) had mandibular prognathism, and 2 patients (3%) had micrognathia. In terms of neck anatomy, 13 patients (23%) had a short neck, while 43 patients (77%) had a normal neck.

BMI assessments showed that 16 patients (28.5%) had a normal BMI (<25), 25 patients (44.6%) had a BMI between 25-35, and 15 patients (26.7%) were morbidly obese (BMI >35).

When all patients were evaluated according to seizure types, 30 (53%) patients exhibited focal onset impaired awareness focal to bilateral tonic-clonic seizures, 14 (25%) patients presented with generalised onset motor tonic-clonic seizures. Six (10%) patients had generalised onset motor myoclonic seizures, three (6%) patients had focal onset aware motor automatism seizures and 3 (6%) patients had focal onset aware motor clonic seizures.

In the PrS-E group, 14 patients (50%) exhibited focal onset impaired awareness seizures progressing to bilateral tonic-clonic seizures, 6 patients (21%) presented generalised onset motor tonic-clonic seizures, 4 patients (14%) had generalised onset motor myoclonic seizures, 2 patients (7.5%) experienced focal onset aware motor automatism seizures and 2 patients (7.5%) had focal onset aware motor clonic seizures.

In the severe OSAS-E group, 16 patients (58%) exhibited focal onset impaired awareness seizures progressing to bilateral tonic-clonic seizures, 8 patients (28%) demonstrated presented with generalized onset motor tonic-clonic seizures, 2 patients (7.5%) had generalised onset motor myoclonic seizures, 1 patient (3.25%) experienced focal onset aware motor automatism seizures, and 1 patient (3.25%) had focal onset aware motor clonic seizures.

The analysis revealed no significant disparities in seizure frequency between the two groups. The demographic data, childhood symptoms, physical examination findings and epilepsy-related characteristics of all patients and patient groups are outlined in Table 1.

Before treatment of sleep-related disorders, the ESS was 9.73±6.77 (1.00-24.00), whereas after treatment, the ESS was 4.66±2.89 (1.00-12.00) (p<0.001). The data obtained in the PSG examination of all patients and patient groups and ESS values were summarized in Table 2.

Before treatment for SBD, 30 patients (53.6%) were on monotherapy for epilepsy, while 26 patients (46.4%) were on polytherapy. The mean seizure frequency was 5.02±4.63 (range: 1-12) per year. Regarding EEG activity, 20 patients (35.7%) showed paroxysmal activity disorder, 10 patients (17.9%) had paroxysmal activity disorder with epileptiform potential, 5 patients (8.9%) had generalized epileptiform discharges, and 4 patients (7.1%) had focal epileptiform activity. EEG results were normal in 17 patients (31%).

After SBD treatment, 40 patients (71.4%) were on monotherapy, while 16 patients (28.6%) were on polytherapy. The mean seizure frequency decreased to 3.21±2.92 per year (range: 0-12). When post-treatment EEG results were evaluated as normal or pathological, 35 patients (62.5%) had normal EEGs, while 21 patients (37.5%) showed pathological EEG findings during their treatment for sleep-related disorders.

The results of the pre- and post-treatment evaluations of patients with PrS-E are displayed in Table 3, while those with severe OSAS-E are shown in Table 4.

In terms of seizure frequency prior to PrS treatment, the average frequency was 3.25±3.84 per year (range: 1.00-12.00). Four patients (14%) experienced seizures once a month, 6 patients (21%) had seizures once every 3 months, 8 patients (29%)

| Table 1. Demographic and examination data of all patients and both groups | | | | |
|---|---|---|---|---|
| | **All patients (n=56) mean ± SD (minimum-maximum)** | **PrS-E (n=28) mean ± SD (minimum-maximum)** | **Severe OSAS-E (n=28) mean ± SD (minimum-maximum)** | **p-value PH + E vs. severe OSAS-E** |
| Age | 46.54±15.68 (19-82) | 37.68±12.66 (19.00-66.00) | 55.39±13.32 (22.00-82.00) | <0.001¶ |
| Gender F/M | 17/39 | 7/21 | 10/18 | 0.380$^{\chi 2}$ |
| Age at admission | 38.45±15.39 (18-72) | 27.75±10.17 (18.00-56.00) | 49.14±11.89 (18.00-72.00) | <0.001¶ |
| Age of onset of epilepsy | 30.73±13.91(3-65) | 25.25±10.02 (8.00-46.00) | 36.21±15.21 (3.00-65.00) | 0.004¶ |
| Epilepsy duration (years) | 15.80±8.03 (2-40) | 12.53±5.16 (2.00-22.00) | 19.18±9.01 (8.00-40.00) | 0.005¶ |
| Duration of adult snoring (years) | 20.25±15.28 (1-62) | 17.2±7.7 (1.00-46.00) | 31.46±13.26 (5.00-62.00) | <0.001¶ |
| Type of birth (N/CS) | 50/6 | 23/5 | 27/1 | 0.083$^{\chi 2}$ |
| Childhood snoring (yes/no) | 37/19 | 22/6 | 15/13 | 0.048$^{\chi 2}$ |
| Childhood epilepsy (yes/no) | 8/48 | 5/23 | 3/25 | 0.445$^{\chi 2}$ |
| Mallampati score (n) | Class I: 30<br>Class II:12<br>Class III: 14 | Class I: 17<br>Class II: 9<br>Class III: 2 | Class I: 13<br>Class II: 3<br>Class III: 12 | 0.004$^{\chi 2}$ |
| Jaw anatomy (n) | Normal: 42<br>Mandibular prognathism: 12<br>Micrognathia: 2 | Normal: 19<br>Mandibular prognathism: 8<br>Micrognathia: 1 | Normal: 23<br>Mandibular prognathism: 4<br>Micrognathia: 1 | 0.424$^{\chi 2}$ |
| Neck anatomy (n) | Normal: 43<br>Short neck: 13 | Normal: 25<br>Short neck: 3 | Normal: 18<br>Short neck: 10 | 0.026$^{\chi 2}$ |
| BMI | 28.87±7.28 (17.30-46.10) | 24.03±4.19 (17.30-33.60) | 33.70±6.47 (23.10-46.10) | <0.001¶ |
| Epilepsy seizure type (n) | FIAFBTC: 30<br>GMTC: 14<br>GMMC: 6<br>FAMAC: 3<br>FAMCC: 3 | FIAFBTC: 14<br>GMTC: 6<br>GMMC: 4<br>FAMAC: 2<br>FAMCC: 2 | FIAFBTC: 16<br>GMTC:8<br>GMMC: 2<br>FAMAC:1<br>FAMCC: 1 | 0.566$^{\chi 2}$ |
| Seizure frequency (number per year) | 5.02±4.63 (1-12) | 3.25±3.83 (1-12) | 6.79±4.73 (1-12) | 0.530¶ |

PrS-E: Patients with primary snoring and epilepsy, Severe OSAS-E: Patients with severe obstructive sleep apnea syndrome and epilepsy, SD: Standard deviation, F: Female, M: Male, N: Normal delivery, CS: Caesarean section, BMI: Body mass index, FIAFBTC: Focal onset impaired awareness focal to bilateral tonic-clonic seizures, GMTC: Generalized onset motor tonic-clonic seizures, GMMC: Generalized onset motor myoclonic seizures, FAMAC: Focal onset awere motor automatsims seizures, FAMCC: Focal onset awere motor clonic seizures, ¶: Mann-Whitney U testi, $^{\chi 2}$: Chi-square test

had seizures once a year, and 10 patients (36%) experienced seizures less than once a year. The results of the study demonstrated a significant decrease in seizure frequency and excessive daytime sleepiness following SBD treatment (p=0.004 and p<0.001, respectively). The rate of pathological EEG findings also decreased after treatment for PrS.

In the PrS-E group, before SBD treatment, 16 patients (57%) were on monotherapy, and 12 patients (43%) were on polytherapy. After treatment, 23 patients (89%) were on monotherapy, while 3 patients (11%) remained on polytherapy, showing a statistically significant change in treatment approach (p=0.002) (Table 3).

In severe OSAS-E group, following treatment for severe OSAS, it was observed that seizure frequency decreased in 13 patients (46%), increased in 1 patient (4%), and remained unchanged in 14 patients (50%). Overall, there was a significant reduction in both seizure frequency and daily excessive sleepiness complaints following treatment (p<0.001). Additionally, a comparison of pre- and post-treatment EEG examinations showed a significant decrease in pathological findings (p<0.001).

In severe OSAS-E group regarding medication use, the number and/or doses of medications remained unchanged in 17 patients (61%), while 11 patients (39%) experienced a reduction in the number and/or doses of medications. In terms of monotherapy *versus* polytherapy, 12 patients (43%) were on monotherapy and 16 patients (57%) were on polytherapy before treatment. After treatment, 14 patients (50%) were on monotherapy, and 14 patients (50%) were on polytherapy. However, this change in therapy was not statistically significant (p=0.895) (Table 4).

An evaluation of the impact of modifications to antiseizure treatments on snoring, revealed that the weight reduction associated with these changes led to a decrease in snoring among 4 patients (14%) diagnosed with PrS and treated for sleep-disordered breathing. Conversely, weight gain in

| Table 2. Polysomnographic data of all patients and both groups | | | | |
|---|---|---|---|---|
| | **All patients (n=56) mean ± SD (minimum-maximum)** | **PrS-E (n=28) mean ± SD (minimum-maximum)** | **Severe OSAS-E (n=28) mean ± SD (minimum-maximum)** | **p-value PH+E vs. severe OSAS-E** |
| Apnea-hypopnea index | 23.67±24.96 (0.10-89) | 1.44±1.48 (0.10-4.90) | 45.89±15.57 (30.10-89.00) | <**0.001**¶ |
| N1_latency (min.) | 16.56±12.04 (0.30-49.50) | 13.56±13.05 (0.30-49.50) | 19.57±10.31 (10.10-47.30) | **0.003**¶ |
| N2_latency (min.) | 27.97±28.52 (2.80-180.30) | 25.81±36.68 (2.80-180.30) | 30.13±17.39 (13.40-96.50) | **0.002**¶ |
| N3_latency (min.) | 52.79±49.37 (9.30-281.30) | 59.86±66.27 (9.30-281.30) | 45.71±21.68 (17.30-107.50) | 0.476¶ |
| REM latency (min.) | 156.95±93.38 (41.50-473) | 140.15±75.69 (41.50-379.00) | 173.75±106.99 (46.30-473.00) | 0.210¶ |
| N1 duration (%) | 7.38±5.92 (0.30-23) | 5.78±4.81 (0.3-19.10) | 8.98±6.55 (0.50-23.00) | 0.053¶ |
| N2 duration (%) | 46.74±11.22 (22-71.20) | 44.19±9.75 (22.00-61.30) | 49.29±12.17 (25.80-71.20) | 0.096¶ |
| N3 duration (%) | 28.65±12.67 (0.80-60.90) | 30.72±9.37 (10.30-54.30) | 26.57±15.17 (0.80-60.90) | 0.125¶ |
| REM duration (%) | 16.02±7.02 (0.60-40) | 18.10±8.23 (0.6-40.00) | 13.94±4.85 (4.80-26.80) | **0.022**¶ |
| Respiratory arousal index | 24.29±70.66 (0-417) | 1.25±2.81 (0.00-12.00) | 47.32±95.19 (0.00-417.00) | <**0.001**¶ |
| Leg movement arousal index | 16.11±19.08 (0-77) | 24.96±21.25 (0.00-77.00) | 7.25±11.30 (0.00-42.00) | <**0.001**¶ |
| Sleep efficiency (%) (total sleep time/total recording time) | 83.63±8.60 (70-99.40) | 89.63±7.64 (75.30-99.40) | 77.63±4.19 (70.00-84.60) | <**0.001**¶ |
| Min. $SatO_2$ | 84.23±10.14 (54-97.70) | 91.35±5.61 (73.00-97.70) | 77.11±8.54 (54.00-87.00) | <**0.001**¶ |
| Pre-treatment ESS | 9.73±6.77 (1-24) | 3.75±2.25 (1.00-10.00) | 15.71±3.76 (10.00-24.00) | <**0.001**¶ |
| Post-treatment ESS | 4.66±2.89 (1.00-12.00) | 2.50±1.26 (1.00-6.00) | 6.82±2.39 (3.00-12.00) | **0.036**¶ |
| PrS-E: Patients with primary snoring and Epilepsy, Severe OSAS-E: Patients with severe obstructive sleep apnea syndrome and epilepsy, SD: Standard deviation, ESS: Epworth Sleepiness Scale, min.: Minute, ¶: Mann Whitney U, REM: Rapid eye movement | | | | |

| Table 3. Pre- and post-treatment evaluation of PrS-E patients | | | |
|---|---|---|---|
| | **Pre-treatment Mean ± SD (min.-max.)** | **Post-treatment Mean ± SD (min.-max.)** | **p** |
| Seizure frequency (per year) | 3.25±3.84 (1.00-12.00) | 2.11±2.13 (1-8) | **0.004**¶ |
| EEG findings (normal/pathological) | 14/14 | 19/9 | 0.344$^{\chi^2}$ |
| ASD treatment (monotherapy/polytherapy) | 16/12 | 23/3 | **0.002**$^{\chi^2}$ |
| ESS | 3.75±2.25 (1.00-10.00) | 2.50±1.26 (1.00-6.00) | <**0.001**¶ |
| PrS-E: Patients with primary snoring and epilepsy, EEG: Electroencephalography, ASD: Antiseizure Drug, ESS: Epworth Sleepiness Scale, SD: Standard deviation, min.: Minimum, max.: Maximum, $\chi^2$: Chi-square test, ¶: Wilcoxon test | | | |

| Table 4. Pre- and post-treatment evaluation of severe OSAS-E patients | | | |
|---|---|---|---|
| | **Pre-treatment Mean ± SD (min.-max.)** | **Post-treatment Mean ± SD (min.-max.)** | **p** |
| Seizure frequency (per year) | 6.79±4.73 (1-12) | 4.32±3.21 (1-8) | <**0.001**¶ |
| EEG findings (normal/pathological) | 3/25 | 16/12 | <**0.001**$^{\chi^2}$ |
| ASD treatment (monotherapy/polytherapy) | 12/16 | 14/14 | 0.895$^{\chi^2}$ |
| ESS | 15.71±3.76 (10.00-24.00) | 6.82±2.39 (3.00-12.00) | <**0.001**¶ |
| EEG: Electroencephalography, ASD: Antiseizure drug, ESS: Epworth Sleepiness Scale, SD: Standard deviation, Min.: Minimum, Max: Maximum, $\chi^2$: Chi-square test, ¶: Mann-Whitney U test | | | |

4 patients (14%) resulted in increased snoring, which was attributed to weight gain associated with valproate treatment for other conditions. Snoring patterns unchanged in 20 patients (72%) (Supplementary Table 1). Additionally, 15 patients (53%) reported a positive effect on sleep, such as falling asleep faster and maintaining sleep continuity, while 3 patients (11%) experienced negative effects, including difficulty falling asleep and staying asleep. Sleep patterns remained unaffected in 10 patients (36%).

An analysis was conducted to evaluate the effects of changes in antiseizure treatments on snoring among patients diagnosed and treated for severe OSAS. The results showed that weight

reduction due to ASDs led to a decrease in snoring in 8 patients (29%), while weight gain caused an increase in snoring in 4 patients (14%). Snoring patterns remained unchanged in 16 patients (57%) (Supplementary Table 2).

The impact of reducing ASDs on sleep was also analysed. Positive effects were observed in 17 patients (61%), characterized by reduced sleep latency and improved sleep continuity. Conversely, 4 patients (14%) experienced negative effects, including difficulty falling asleep and maintaining sleep, while 7 patients (25%) showed no change in sleep.

The impact of the reducing antiseizure medications on the occurrence of snoring was analyzed in both groups. The results showed that the intervention was effective in 12 patients (43%), and ineffective in 16 patients (57%) in the severe OSAS-E group. Conversely, it was effective in 8 patients (29%) and ineffective in 20 patients (71%) in the PrS-E group. Although the intervention appeared to be more effective in the severe OSAS group, the difference between the groups was not statistically significant (p=0.403).

## Discussion

Epilepsy and SBD are among the most common neurological conditions encountered. Both sleep and epilepsy are dynamic processes within the central nervous system that influence one another. These conditions can occur independently or coexist. This study focused on patients with PrS-E and severe OSAS-E.

To date, studies on the association between PrS-E have only been conducted in children, making this the first study to evaluate this relationship in adults. Furthermore, no prior studies have compared the PrS-E and severe OSAS-E groups. This study also evaluated the clinical impact of treatments for both epilepsy and SBD.

In this study, demographic data, disease duration, clinical findings, polysomnographic data, seizure types, seizure frequency, and EEG results were assessed for both groups.

In both the PrS-E and severe OSAS-E groups, SBD treatment was observed to have a positive effect on epilepsy, while antiseizure treatment improved sleep structure and reduced complaints such as had a positive effect on epilepsy, and antiseizure treatment was effective in improving sleep structure and reducing complaints such as snoring through different mechanisms. While improvements in sleep structure and SBD-related symptoms, in addition to EEG findings in the epilepsy clinic, were observed in both groups following treatment, the severity of these improvements was found to be more pronounced in the severe OSAS-E group.

Numerous studies have been conducted to explore the association and frequency of epilepsy with SBD yielding varied results. In a study patients with epilepsy, the risk of OSAS in epilepsy patients was shown to be higher than in the general population, with an overall prevalence of 9%.[16] In studies conducted within our country, the prevelance of OSAS among patients diagnosed with epilepsy has been reported to range from 10% to 55%.[17,18] A meta-analysis of 26 studies estimated the prevalence of OSAS in epilepsy patients at approximately 33.4%.[19] OSAS has been shown to be more common in drug-resistant epilepsy. OSAS is reported in 10% of adult epilepsy patients, 20% of children with epilepsy, and 30% of patients with drug-resistant epilepsy.[20] In this retrospective study, 28 patients with PrS-E and 28 patients with severe OSAS-E were identified. The relatively small sample size, particularly in the severe OSAS group, was attributed to the retrospective design of the study, which may have been influenced by data loss.

Sleep interruption and deprivation in OSAS have been showed to increase the incidence of epilepsy.[20] Conversely, the hyperpolarisation-synchronisation of thalamocortical neurons caused by hypoxia during non-REM sleep in OSAS patients plays an significant role in the activation of epileptic neurons. Frequent nighttime awakenings in OSAS also promote synchronization, thereby lowering the seizure threshold.[21] However, it is important to note that epilepsy, including refractory epilepsy, can occur not only in OSAS patients but also in those with PrS-E. Pathophysiologically, both PrS and severe OSAS disrupt sleep microstructure by reducing cerebral oxygen levels, leading to spike discharges and paroxysmal activity on EEG. Sleep spindles, particularly during superficial sleep stages, are thought to contribute to seizure development and propagation. This leads to occurence of seizures both during and outside the ictal phase, while also disrupting sleep structure.[22] Generalized tonic-clonic seizures are more frequent during non-REM sleep and less common during REM sleep.[21] Generalized epileptiform discharges and interictal epileptiform activity are more commonly observed in non-REM sleep than in REM sleep.[23] Additionally, focal onset seizures, particularly those originating from the temporal lobes, are more frequently observed in patients with severe OSAS. Nocturnal seizures are commonly reported in individuals with OSAS, with focal seizures often associated with specific cortical regions, most notably the temporal lobes. The association between sleep fragmentation, hypoxia, and autonomic dysregulation in severe OSAS may increase the risk of focal seizures due to the heightened stress on the brain.[24]

In this study, the most prevalent seizure type observed in patients with SDB and epilepsy was focal onset impaired awareness seizures progressing to bilateral tonic-clonic seizures, followed by generalised onset motor tonic-clonic seizures. This pattern was observed to be analogous in both PrS-E and severe OSAS-E groups.

PrS is a commonly observed in children and affects approximately 30-50% of the adult population, with a higher prevalance among middle-aged men.[6] Severe OSAS is most common in individuals aged 40-65, with its prevalence declining after age of 65.[24,25] While severe OSAS is more common in older adults, PrS can occur across all age groups. In our study, the mean age was 27 (range: 18-56) in the PrS-E group and 49 (range: 18-72) in the severe OSAS-E group. The prevalence of PrS was found to be three times more common in males, while OSAS was found to be 1.8 times more prevalent in males.

A substantial body of research has been conducted employing PSG in patients with sleep-disordered breathing.[26-28] PSG examinations of patients with OSAS have reported that REM sleep duration is shortened, while N1 and N2 stages are

prolonged.[29] In our study, we observed that in the severe OSAS group, sleep efficiency and minimum oxygen saturation were lower, N1 and N2 latencies were prolonged, LM increased, N1 and N2 durations were prolonged, N3 and REM durations were shortened, and arousals were more frequent. Consequently, the ESS values were significantly higher in the severe OSAS group compared to the PrS group. Interestingly, sleep efficiency was also decreased in the PrS group, which was thought to be related to the co-occurrence of epilepsy, as epilepsy itself can disrupt sleep architecture. Additionally in the severe OSAS group, EEG examinations frequently revealed pathological findings with epileptiform discharges. A subsequent analysis of epileptic seizure characteristics revealed that the seizures were predominantly focal onset impaired awareness seizures progressing to bilateral tonic-clonic seizures. The treatment of epilepsy associated with SBD was another key area of discussion. Notably, antiseizure treatment in both study groups-particularly in the severe OSAS group-was predominantly administereted as polytheraphy, often involving three or more drugs.

The data collectively suggested that seizures in these patients demonstrated resistance to treatment. The presence of SBD was identified as a potential contributing factor to this resistance.

In the second phase of our study, after SBD treatments were administered to both groups, we re-evaluated and compared seizure frequency, EEG findings, antiseizure treatments. Shortened REM sleep, which normally suppresses epileptic activity, can increase seizure susceptibility. This highlights the importance of PAP therapy, which not only corrects hypoxia but also prolongs REM sleep, thereby reducing the likelihood of seizures.[29] PAP treatment has been shown to help control seizures more effectively and reduce epileptiform activity on EEG.[14] Retrospective studies further indicate that it decreases seizure frequency and alleviates prolonged daytime sleepiness.[13] Additionally, treating sleep disorders has been associated with a reduction in spike activity rates during the first sleep cycle, particularly in slow-wave sleep and across the entire cycle.[22,30-32] Improvements in EEG findings, combined with reduced seizure frequency and severity following SBD treatment, have also been linked to decreases in both the number and dosage of ASDs.[33,34] In our study, following the implementation of PAP therapy, which was utilised by all severe OSAS-E group patients, showed a significant reduction in seizure frequency. However, there was no significant change in ASD regimens (polytherapy vs. monotherapy). It is hypothesized that the more frequent and severe epileptic seizures observed in the severe OSAS group may be attributed to the smaller reduction in the number of drugs and the use of three or more drugs in polytherapy treatment. Literature has also emphasized the reduction in seizure frequency and severity after surgical treatment for adenoid hypertrophy, a primary cause of snoring in children.[35,36] In contrast, this study examined the effects of appropriate treatments on adults with PrS, focusing on seizure frequency before and after treatment. The findings revealed a significant reduction in seizure frequency, shighlighting a potential therapeutic benefit for individuals with this condition. However, no significant changes were observed in EEG findings, likely because the EEG results were normal or nearly normal before treatment. It was also noteworthy that the transition from polytherapy to monotherapy was more prevalent in the PrS-E group.

Excessive daytime sleepiness and frequent nighttime awakenings are among the most common complaints in epilepsy patients.[32] Acute neurochemical changes in the brain caused by seizures can disrupt sleep and wakefulness. Seizures and epileptic discharges during sleep interfere with both the initiation and maintenance of sleep. Generalized and partial seizures occuring during sleep may reduce TST and REM sleep, contributing to sleep disturbances.[32,37]

Studies have also shown that, even during seizure-free periods, epilepsy patients experience sleep issues such as reduced sleep efficiency, altered sleep stages, and increased wakefulness, leading to morning fatigue and daytime sleepiness.[38,39] In this study, the mean ESS score in the PrS-E group was 3.75 before SBD treatment, and decreased to 2.50 after treatment. In the severe OSAS-E group, the mean ESS score was 15.71 before treatment and decreased to 6.82 after treatment.

In addition to the effects of SBD on epilepsy, ASDs can also alter the natural architecture and organization of sleep, affecting sleep stages and wakefulness.[40] The use of antiseizure medications has been showed to exacerbate SBD, primarily due to the relaxation of upper airway muscles and the elevation of he arousal threshold through various mechanisms. Spontaneous arousals and frequent awakenings caused by ASDs significantly disrupt the sleep patterns of epilepsy patients.[39,41] Medications such as phenobarbital, valproate, gabapentin, and pregabalin have been shown to negatively impact OSAS.[42] Patients with drug-resistant epilepsy on polytherapy may have a higher risk of obesity compared to those on monotherapy.[43] ASDs associated with weight gain include valproic acid, pregabalin, gabapentin, and vigabatrin.[44,45] While the effect of carbamazepine on weight remains unclear, lamotrigine generally does not affect weight. In contrast drugs such as felbamate, topiramate, and zonisamide are linked to weight loss.[46,47] Weight gain associated with ASDs may also exacerbate OSAS.[48]

ASDs affect not only weight and metabolism but also sleep patterns. Medications such as phenobarbital, phenytoin, carbamazepine, valproate, gabapentin, topiramate, vigabatrin, levetiracetam, pregabalin, oxcarbazepine, rufinamide, and clobazam are reported to increase sleepiness. Conversely ethosuximide, felbamate, lamotrigine, and zonisamide may cause insomnia. Additionally phenobarbital, phenytoin, carbamazepine, and pregabalin have been shown to reduce sleep latency.[49]

The findings of the this study demonstrated that the majority of patients diagnosed with PrS-E who received SBD treatment did not require changes to their epilepsy treatment. An increase in the use of monotherapy was observed, while snoring decreased in some cases, and excessive daytime sleepiness diminished in others, corresponding with a reduction in ASD use. Additionally more than half of these patients experienced faster sleep onset and improved sleep continuity, leading to an overall enhancement in sleep structure.

Approximately one-third of patients receiving PAP therapy for severe OSAS-E demonstrated a significant reduction in snoring, which was attributed to a reduction in ASDs (though polytherapy was often continued) and weight loss. Additionally, notable improvements were observed in sleep initiation and continuity for most patients with severe OSAS-E, along with a more pronounced reduction in excessive daytime sleepiness.

### Study Limitations

In summary, the treatment of both epileptic seizures and SBD resulted in a reduction in the number and dosage of ASDs, improved sleep structure, and decreased daytime sleepiness and snoring, particularly in the severe OSAS group. However, the study's limitations include its small sample size and retrospective design. This study is the first to report on these features in the PrS-E group. However the study design, which included PSG testing before and after treatment, limited ability to compare PSG data comprehensively. This methodological limitation is an important aspect that should be addressed in future research.

## Conclusion

In conclusion, understanding the relationship between epilepsy and sleep disorders, as well as identifying and treating coexisting sleep-related issues, can reduce the frequency and severity of epileptic seizures, decrease the number and dosage of ASDs, and improve EEG findings. Effective seizure management and optimization of medication regimens can enhance sleep quality, including the ability to fall asleep and maintain asleep, while significantly reducing snoring and daytime sleepiness.

### Ethics

**Ethics Committee Approval:** This study was conducted as a retrospective study following the approval of Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee (approval number: 307, date: 25.07.2022).
**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: Ü.Ö., A.K.A., Concept: A.K.A., H.Y., Design: A.K.A., Data Collection or Processing: Ü.Ö., Analysis or Interpretation: A.K.A., M.B., H.Y., Literature Search: Ü.Ö., M.B., Writing: Ü.Ö., A.K.A., M.B., H.Y.
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| **Supplementary Table 1. Treatments used by PrS-E patients before and after treating SBD** | |
|---|---|
| **ASDs used before SBD treatment in PrS-E group** | **ASDs used after SBD treatment in PrS-E group** |
| VPA 2x1000 mg, TPM 2x100 mg | TPM 2x100 mg |
| CBZ 2x400 mg | CBZ 2x200 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| CBZ 2x400 mg, LEV 2x1000 mg | LEV 2x500 mg |
| CBZ 2x400 mg | CBZ 2x200 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| VPA 2x1000 mg, LTG 2x100 mg | VPA 2x500 mg, LTG 2x100 mg |
| LEV 2x1000 mg | LEV 2x1000 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| LEV 2x1000 mg, OXC 2x600 mg, PHN 3x100 mg, CBZ 2x400 mg | LEV 2x1000 mg, OXC 2x600 mg |
| CBZ 2x400 mg, VPA 2X1000 mg | CBZ 2x400 mg |
| CBZ 2x400 mg | CBZ 2x200 mg |
| CBZ 2x400 mg, LEV 2x1000 mg, PRG 2x300 mg | LEV 2x500 mg |
| LTG 2x100 mg | LTG 2x100 mg |
| PHN 3x100 mg, OXC 2x600 mg | PHN 3x100 mg, OXZ 2x600 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| LEV 2x100 mg, CBZ 2x400 mg | LEV 2x500 mg |
| LTG 2x100 mg, CBZ 2x400 mg | LTG 2x100 mg |
| CBZ 2x400 mg | CBZ 2x400 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| LEV 2x1000 mg | LEV 2x1000 mg |
| LEV 2x1000 mg, PHN: 3x100 mg, VPA 2x500 mg | LEV 2x1000 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| LTG 2x100 mg | LTG 2x100 mg |
| CBZ 2x400 mg, LEV 2x1000 mg | LEV 2x500 mg |
| VPA 2x1000 mg, LEV 2x1000 mg | LEV 2x500 mg |
| LEV 2x1000 mg | LEV 2x1000 mg |
| PrS-E: Patients with primary snoring and epilepsy, SBD: Sleep-related breathing disorders, ASD: Antiseizure drug, VPA: Valproate, TPM: Topiramate, CBZ: Carbamazepine, LEV: Levatiracetam, LTG: Lamotrigine, OXC: Oxcarbazepine, PHN: Phenytoin, PRG: Pregabalin | |

| **Supplementary Table 2. Treatments used by severe OSAS-E patients before and after treating SBD** | |
|---|---|
| **ASDs used before SBD treatment in OSAS-E group** | **ASDs used after SBD treatment in OSAS-E group** |
| VPA 2x1000 mg | VPA 2x500 mg |
| LEV 2x1000, VPA 2x500 mg, LCZ 2x100 mg, PHN 3x100 mg | LEV 2x500 mg, VPA 2x500 mg, LCZ 2x100 mg |
| LEV 2x1000 mg, VPA 2x500 mg, PHN 3x100 mg | LEV 2x1000 mg, VPA 2x500 mg |
| LEV 2x1000 mg, CBZ 2x400 mg | LEV 2x1000 mg, CBZ 2x400 mg |
| TPM 2x100 mg | TPM 2x100 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| LEV 2x1000 mg | LEV 2x1000 mg |
| LEV 2x1500 mg, LTG 2x100 mg, CBZ 2x400 mg, VPA 2x500 mg | LEV 2x1000 mg, LTG 2x100 mg |
| LEV 2x1000 mg, CBZ 2x400 mg | LEV 2x1000 mg |
| CBZ 2x400 mg, LEV 2x1000 mg, PHN 3x100 mg | CBZ 2x400 mg, LEV 2x1000 mg, PHN 3x100 mg |
| TPM 2x100 mg, LEV 2x1000 mg, VPA 2x1000 mg | TPM 2x100 mg, LEV 2x1000 mg |
| LEV 2x1500 mg, VPA 2x1000 mg | LEV 2x1500 mg, VPA 2x1000 mg |
| VPA 2x1000 mg, LEV 2x1500 mg | VPA 2x1000 mg, LEV 2x1500 mg |
| LEV 2x1500 mg, CBZ 2x400 mg, VPA 2x500 mg | LEV 2x1500 mg, CBZ 2x400 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| TPM 2x100 mg, VPA 2x1000 mg, LEV 2x1000 mg | TPM 2x100 mg, VPA 2x500 mg, LEV 2x1000 mg |
| PHN 3x100 mg, CBZ 2x400 mg | PHN 3x100 mg, CBZ 2x400 mg |
| VPA 2x1000 mg | VPA 2x1000 mg |
| PHN 3x100 mg | PHN 3x100 mg |
| TPM 2x100 mg | TPM 2x100 mg |
| PHN 3x100 mg, LEV 2x1000 mg | PHN 3x100 mg, LEV 2x1000 mg |
| LEV 2x1000 mg, CBZ 2x400 mg | LEV 2x1000 mg, CBZ 2x400 mg |
| LEV 2x1000 mg | LEV 2x1000 mg |
| CBZ 2x400 mg | CBZ 2x400 mg |
| LEV 2x1000 mg, LTG 2x100 mg | LEV 2x1000 mg, LTG 2X100 mg |
| LEV 2x1000 mg, LTG 2x100 mg, VPA 2x500 mg | LEV 2x500 mg |
| VPA 2x1000 mg | VPA 2x500 mg |
| VPA 2x1000 mg | VPA 2x500 mg |
| OSAS-E: Obstructive sleep apnea syndrome-epilepsy, SBD: Sleep-related breathing disorders, ASD: Antiseizure drug, VPA: Valproate, LEV: Levatiracetam, LCZ: Lacosamide, PHN: Phenytoin, CBZ: Carbamazepine, TPM: Topiramate, LTG: Lamotrigine | |