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Review

REVIEW

Sleep-disordered breathing in epilepsy: epidemiology, mechanisms, and treatment

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Abstract

Epilepsy is a group of neurological conditions in which there is a pathological and enduring predisposition to generate recurrent seizures. Evidence over the last few decades suggests that epilepsy may be associated with increased sleep-disordered breathing, which may contribute towards sleep fragmentation, daytime somnolence, reduced seizure control, and cardiovascular-related morbidity and mortality. Chronic sleep–disordered breathing can result in loss of gray matter and cause deficits to memory and global cognitive function. Sleep-disordered breathing is a novel and independent predictor of sudden cardiac death and, as such, may be involved in the mechanisms leading to sudden unexpected death in epilepsy. Despite this, the long-term consequences of sleep-disordered breathing in epilepsy remain unknown, and there are no guidelines for screening or treating this population. There is currently insufficient evidence to indicate continuous positive airway pressure (CPAP) for the primary or secondary prevention of cardiovascular disease, and recent evidence has failed to show any reduction of fatal or nonfatal cardiovascular endpoints. Treatment of sleep-disordered breathing may potentially improve seizure control, daytime somnolence, and neurocognitive outcomes, but few studies have examined this relationship. In this review, we examine sleep-disordered breathing in epilepsy, and discuss the potential effect of epilepsy treatments. We consider the role of CPAP and other interventions for sleep-disordered breathing and discuss their implications for epilepsy management.

Statement of Significance

Reports from uncontrolled, observational studies have suggested that patients with epilepsy have a substantially higher prevalence of sleep-disordered breathing compared with the general population. However, well-designed studies to confirm these initial findings have not yet been undertaken. The specific clinical implications of sleep-disordered breathing in this population also remain unclear. Improvement in seizure control and daytime somnolence when sleep-disordered breathing is treated in patients with epilepsy has been reported. However, the evidence for this is limited, and there are currently no guidelines to diagnose and treat patients with epilepsy. Untreated obstructive sleep apnea may contribute towards the significant cardiovascular-related morbidity and mortality in epilepsy, and the pathology of sudden unexpected death in epilepsy.

Key words: epilepsy; sleep-disordered breathing; OSA; CSA; SUDEP; CPAP

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Key Points

- Patients with epilepsy may potentially be at increased risk of sleep-disordered breathing.
- Sleep-disordered breathing in people with epilepsy may contribute to increased sleepiness, cognitive impairments, worse seizure control, and cardiovascular morbidity and mortality.
- Antiepileptic drugs (AEDs), including valproic acid, pregabalin, perampanel, and to a lesser degree, gabapentin and vigabatrin, may cause weight gain and, as such, could increase the risk of developing or worsening OSA.
- Treatment of OSA with continuous positive airway pressure (CPAP) may improve seizure frequency in some patients with epilepsy.
- Further research into the effects of sleep-disordered breathing, and the benefits of treatment, in people with epilepsy is required.

Introduction

Epilepsy collectively refers to a spectrum of neurological disorders characterized by recurrent seizures resulting from abnormal electrical activity in the brain [1]. Since the initial observation in 1947 that epileptiform discharges could be activated by sleep, multiple studies have repeated recordings using scalp and intracranial electroencephalogram (EEG) electrodes to show that sleep has a state-dependent and temporal influence on interictal epileptiform discharges [2–4]. It has been suggested that people with epilepsy may have an increased prevalence of sleep-disordered breathing compared with the general population [5–8]. Sleep-disordered breathing refers to a group of disorders characterized by intermittent pauses in breathing, which may disrupt the normal architecture of sleep and cause increased sympathetic activation, hypoxia, hypercapnia, and shifts to cerebral blood flow [9, 10]. These include obstructive sleep apnea (OSA) disorders, central sleep apnea (CSA) syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder [11]. Data from recent studies, utilizing current scoring criteria and recommended polysomnography techniques, estimate the prevalence of moderate-to-severe sleep–disordered breathing in the general population between 24.8 and 49.7 per cent in men, and 9.6 and 23.4 per cent in women [12, 13].

Sleep-disordered breathing is also associated with significant cardiovascular-related disease and mortality including ischemic disease and sudden death [14–17]. Despite evidence over the past few decades that patients with epilepsy have increased cardiovascular-related mortality and morbidity including hypertension, heart disease, and stroke compared with people without epilepsy, few studies have examined whether the presence of sleep-disordered breathing increases this risk [18–21]. Several mechanisms associated with sleep-disordered breathing potentially facilitate seizure occurrence, which include sleep deprivation, sleep fragmentation, cerebral hypoxemia, decreased cardiac output, and cardiac arrhythmias. Although uncontrolled, observational studies have indicated that the treatment of sleep-disordered breathing may improve seizure control and daytime somnolence, this has not yet been evaluated with adequately powered randomized controlled trials [22–30]. Treatment may also improve cognitive dysfunction and mood disorders, which are common comorbidities in epilepsy patients, potentially resulting in improved quality of life [31].

In this review, we outline current epilepsy classification and treatments. We examine sleep-disordered breathing in epilepsy, including its epidemiology and pathophysiology. We discuss the possible relationship between sleep-disordered breathing and cardiovascular morbidity and mortality in epilepsy. Lastly, we review the potential consequences of epilepsy treatments on sleep-disordered breathing and examine the reported benefits of treating sleep-disordered breathing in patients with epilepsy.

Epilepsy

Epilepsy affects approximately 65 million people worldwide, making it one of the most common chronic neurological disorders in the world [32]. According to the WHO, it accounts for 0.75 per cent of the global burden of disease and over 20.6 million disability-adjusted life years [33]. The prevalence of active epilepsy in the general population is estimated at 0.5%–1%, whereas the lifetime or cumulative incidence is 2%–5% [34, 35]. Epilepsy is most common in those aged under 15 years, and those over 60 [36]. Although seizures are well-controlled in most people with epilepsy, about a third will not achieve seizure freedom, even with adequate trials of AEDs [37]. Despite the introduction of many new AEDs in the past two decades, the proportion of individuals with drug-resistant epilepsy has not changed substantially [38]. Patients with drug-resistant epilepsy have a higher risk for all-cause mortality, including sudden unexpected death in epilepsy (SUDEP) [39].

Diagnosis

Epileptic seizures are a transient occurrence of signs and/or symptoms that occur as a result of abnormal excessive or synchronous neuronal electrical activity in the brain [40]. Recently, the International League Against Epilepsy (ILAE) introduced a new "practical" definition of epilepsy [1]. A diagnosis is made when one of the following conditions is met: (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60 per cent) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome [1]. The recurrence risk may be secondary, for example, to a highly epileptogenic structural lesion, such as a stroke, a severe head injury, or a central nervous system infection. A diagnosis of epilepsy is primarily based on clinical grounds [41]. This involves a detailed clinical history and physical examination to exclude other paroxysmal events, which can mimic seizures, and provocative factors, which may lead to acute seizures [41]. Complimentary diagnostic procedures include routine EEG, magnetic resonance imaging, laboratory investigations, and genetic testing, as appropriate.

Classification

The Commission for Classification and Terminology of the ILAE recently published two position papers, which combine

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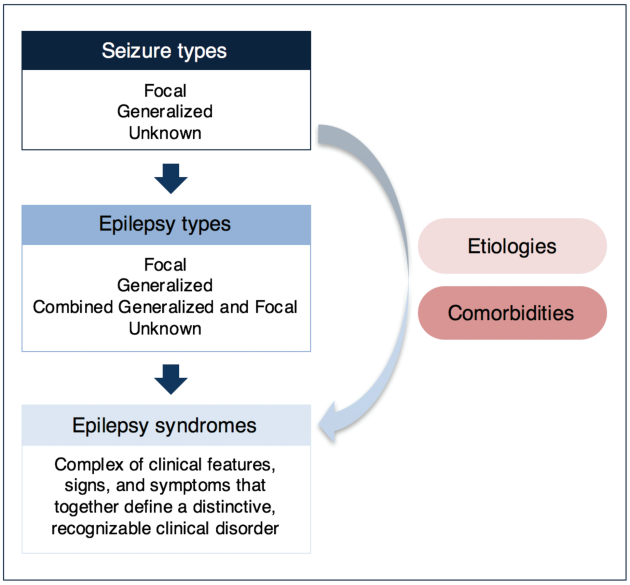

Figure 1. The current International League Against Epilepsy framework for epilepsy classification. The classification of seizures includes focal, generalized, or unknown onset. Epilepsies may be classified as focal, generalized, combined focal, and generalized or unknown. The etiologies are grouped into six main categories, which include structural, genetic, infectious, metabolic, immune, and unknown. The etiology and comorbidities should be considered at each stage of epilepsy classification.

the new seizure and epilepsy classification into a single framework [42, 43]. This is summarized in Figure 1. Classification starts with defining the seizure type(s), which is a prerequisite for determining the epilepsy type, and, if possible, the syndrome [42]. An epilepsy syndrome is a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder [44]. Common sleep-related epilepsy syndromes include sleep-related hypermotor epilepsy (formerly known as nocturnal frontal lobe epilepsy), childhood epilepsy with centrotemporal spikes (formerly known as benign epilepsy with centrotemporal spikes or rolandic epilepsy), Landau–Kleffner syndrome, epileptic encephalopathy with continuous spike and wave during stage N3 sleep, Lennox–Gastaut syndrome, and juvenile myoclonic epilepsy [44–46]. An illustrative example of sleep-related hypermotor epilepsy is provided in Table 1. These syndromes often result in presentation to sleep clinics and differential diagnosis between a sleep-related epilepsy syndrome and a primary sleep disorder can be challenging. This may be further complicated by the co-occurrence of a sleep-related epilepsy syndrome and a primary sleep disorder, such as nonrapid eye movement (NREM) parasomnias (including confusional arousals, sleep walking, and night terrors), and REM parasomnias (including REM sleep behavior disorder) in the same individual [47].

Treatment

The mainstay of epilepsy treatment is AED therapy. Some drugs are effective against both focal and most generalized seizures and include valproic acid, phenobarbital, benzodiazepines, lamotrigine, levetiracetam, topiramate, zonisamide, perampanel, rufinamide, and felbamate [48]. Carbamazepine, phenytoin, oxcarbazepine, eslicarbazepine acetate, tiagabine, lacosamide, gabapentin, pregabalin, and vigabatrin are primarily effective against focal seizures, including focal to bilateral tonic-clonic

Table 1. An illustrative case of sleep-related hypermotor epilepsy

Sleep-related hypermotor epilepsy with right frontal focal cortical dysplasia	A 44-year-old right-handed male presented to a sleep clinic with a 34-year history of "sleep attacks." According to his wife, these attacks typically arose from sleep, and consisted of prominent body rocking and violent limb trashing lasting <10 s. Initially rare, these events gradually increased in frequency and in the past 2 years, they were occurring almost every night. They also tended to cluster, with up to 50 attacks per cluster. Family history was relevant for a maternal male first cousin with unclassified epilepsy. Past medical history was unremarkable. These attacks had previously been diagnosed as "nightmares," "hysteria," and epilepsy. He had tried several antiepileptic drugs, but none controlled his events. Following review in the sleep clinic, he underwent inpatient video-EEG monitoring, which did not reveal any interictal EEG abnormalities. Several (>20) typical events were captured, most of which were associated with subtle ictal EEG changes. These consisted of low-voltage beta–gamma activity over the right fronto–central region, which preceded which preceded the clincial manifestations by 1–2 s. Subsequently, the EEG became largely obscured by EMG artefacts. Multiple brain MRI scans had been reported as normal. However, MRI reassessment in view of the EEG findings led us to identify a subtle focal cortical dysplasia in the right superior frontal gyrus. A PET scan showed a focal area of hypometabolism in the same region. The patient subsequently underwent surgical resection of the MRI lesion, and histopathological examination revealed ILAE type-IIb focal cortical dysplasia. The patient had no further "attacks" following epilepsy surgery (follow-up: 20 months). Overall, these findings are consistent with a diagnosis of sleep-related hypermotor epilepsy (formerly nocturnal frontal lobe epilepsy) associated with a right frontal focal cortical dysplasia

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seizures [48]. Ethosuximide is effective against absence seizures [48]. Drug-resistant epilepsy is defined as a failure of adequate trials of two (or more) tolerated, appropriately chosen and appropriately used AED regimens to achieve freedom from seizures [49].

Patients with drug-resistant epilepsy are often considered for resective epilepsy surgery, which involves removal of the affected neuronal tissue responsible for generating habitual seizures [50]. Temporal lobe resection (anterior temporal lobectomy or amygdalohippocampectomy) is the most common form of surgery, which is superior to prolonged pharmacological treatment [51]. Following successful surgery, most patients continue to take AEDs as withdrawal can be associated with seizure recurrence [52]. When surgical cure is not feasible, palliative epilepsy surgery, such as corpus callosotomy, hemisperectomy, or multiple subpial transections, may be considered to alleviate seizure frequency or severity [53]. Patients with drug-resistant epilepsy, who are not suitable for epilepsy surgery or who continue to have uncontrolled seizures after surgery, may be considered for other therapies. These include neuromodulation, comprising vagus nerve stimulation, deep brain stimulation of the anterior nucleus of the thalamus nerve, and responsive cortical stimulation, which delivers electrical stimulation upon detection of abnormal electrocortigraphic activity via a closed-loop implanted device [54–57]. Neuromodulatory therapies can lead to seizure reduction, but rarely seizure freedom [54–57]. The ketogenic diet, comprising the classic ketogenic diet and the modified Atkins diet, is first-line treatment for patients with GLUT-1 deficiency syndrome and pyruvate dehydrogenase deficiency, and is an effective therapy in drug-resistant epilepsy [58]. A traditional limitation of the classic ketogenic diet has been its poor long-term adherence [59]. The modified Atkins diet allows a higher carbohydrate intake, which makes it more flexible than the classic ketogenic diet, and is thereby associated with better adherence [59].

Mortality

People with epilepsy have an increased risk of developing ischemic heart disease and sudden death compared with the general population [21]. Recent studies have shown that deaths in people with epilepsy are predominantly due to cancer, cardiovascular, and cerebrovascular diseases [19, 20]. SUDEP is the leading cause of death in chronic, drug-resistant epilepsy, and a common cause of death in patients under 50 years of age [60]. It is defined as the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death of patients with epilepsy with or without evidence of a seizure, but excluding documented status epilepticus, and in whom postmortem examination does not reveal a structural or toxicological cause for death [61]. It occurs most commonly during a sleep period and patients are often found in a prone position [62, 63]. The incidence of SUDEP varies according to the cohort studied. In unselected epilepsy populations, the reported incidence is 0.9 to 2.3 deaths per 1,000 person-years, but is higher in drug-resistant cohorts (1.1 to 5.9 deaths per 1,000 person-years) and surgical candidates (6.3 to 9.3 deaths per 1,000 person-years) [64]. SUDEP is likely multifactorial, and the careful analysis of SUDEP cases occurring in video-EEG monitoring units has revealed that centrally mediated postictal cardiac and respiratory dysfunction, including postictal hypoventilation, occurs immediately after a tonic-clonic seizure [63]. Pooled data from multiple case–control studies have identified the presence and frequency of tonic-clonic seizures as the main risk factor for SUDEP [65, 66]. Patients with exclusive nocturnal seizures may also be at greater risk of SUDEP than those with diurnal seizures [62]. There is some evidence that nocturnal supervision and use of antisuffocation pillows may reduce the risk of SUDEP, whereas the utility of seizure alert alarms and sleeping on supine rather than prone position (which may on the other hand exacerbate comorbid OSA) as preventive strategies against SUDEP requires further investigation [60].

Search Strategy and Review Criteria

We searched PubMed up to April 2017, using the following terms: "epilepsy," "obstructive sleep apnea," "central sleep apnea," "SUDEP," "sudden cardiac death," "CPAP," and "cardiac arrhythmia," For studies investigating the effect of AEDs on weight, only those with a minimum treatment duration of 3 months were considered. Only articles published in English were reviewed.

Prevalence and Risk Factors of Sleep-Disordered Breathing

Obstructive sleep apnea

OSA is characterized by recurrent episodes of partial or complete pharyngeal collapse during sleep [67]. This results in a cyclic pattern of intermittent disruption of blood gas exchange causing hypoxemia and hypercapnia, and a surge in sympathetic activity resulting in increased blood pressure [67]. Fragmentation of sleep occurs because arousal from sleep is generally required to restore pharyngeal patency [67]. OSA is common, and the prevalence of clinically significant sleep-disordered breathing is estimated to be between 6.5 and 17 per cent in women, and 17 and 34 per cent in men [68–71]. The main clinical features of OSA are daytime somnolence and decreased quality of life [72]. Impaired cognition is also a feature of OSA, but multiple observational studies have demonstrated a variable relationship between cognition and OSA, and response to treatment, suggesting a complex relationship between neurocognition and OSA [73]. OSA is associated with several cardiovascular diseases including cardiac rhythm and conduction disorders, hypertension, coronary heart disease, and cerebrovascular diseases and is an independent risk factor for an increase in all-cause mortality [14–17].

Most epidemiological studies investigating the prevalence of sleep-disordered breathing in epilepsy have been hampered by methodological limitations, including a retrospective design, lack of controls, inclusion of an enriched population for sleep-disordered breathing based on questionnaires, or assessment of high-risk populations [22, 23, 28, 30, 74, 75]. Table 2 summarizes the studies that have examined the prevalence and risk factors of sleep-disordered breathing using polysomnography in epilepsy populations with no known history of a sleep disorder or significant clinical indication to suggest sleep-disordered breathing. In one study, sleep-disordered breathing (apnea–hypopnea index [AHI] ≥ 5) was reported in 69 of 125 (45 per cent) patients with epilepsy recruited from an adult neurology clinic or during prolonged video-EEG [8]. Moderate-to-severe sleep–disordered breathing (AHI ≥ 20) was observed in 27 (22 per cent) patients.

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In 43 patients with epilepsy admitted for prolonged video-EEG monitoring, we found sleep-disordered breathing (AHI ≥ 5) in 21 (49 per cent), which was moderate-to-severe (AHI ≥ 15) in nine (21 per cent) [7].

In a study of 130 outpatients with epilepsy, sleep-disordered breathing (AHI ≥10) was found in 39 (30 per cent), which was moderate-to-severe (AHI ≥15) in 21 (16 per cent) [6]. Factors associated with sleep-disordered breathing on univariate analyses were older age, increased body-mass index, male gender, dental problems, and standardized AED dose (a ratio derived from the prescribed daily dose divided by the defined daily dose) [6]. In multivariate analyses, however, only older age, dental problems, and standardized AED dose remained statistically significant.

An investigation of 39 surgical candidates with drug-resistant temporal lobe epilepsy reported that 13 (33 per cent) had a respiratory disturbance index (RDI) ≥ 5, which was moderate-to-severe (RDI ≥ 20) in five (13 per cent) [5]. A diagnosis of OSA was associated with older age, male gender, higher Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) scores, and an increased likelihood of experiencing nocturnal seizures [5].

Therefore, the prevalence of sleep-disordered breathing in individuals with epilepsy from these studies is 30%–49%, being higher in patients recruited from video-EEG monitoring units and surgical candidates (33%–49%) than those recruited from the outpatient setting (30 per cent). Most risk factors for sleep-disordered breathing identified in the general population also apply to individuals with epilepsy. However, these studies were limited by small sample sizes, lack of controls, and selection bias. The definitions used to score nocturnal respiratory events and criteria for sleep-disordered breathing have varied substantially across these studies, which may have affected the overall reported prevalence. These studies were published before the American Academy of Sleep Medicine (AASM) introduced the revised guidelines in 2012 and, as such, may underrepresent the prevalence of sleep-disordered breathing in epilepsy [76].

Screening instruments

A few authors have investigated the validity of screening instruments for OSA utilizing polysomnography in populations with epilepsy. Excessive daytime somnolence (EDS) is a frequent complaint among patients with epilepsy and is more common in participants with epilepsy compared with individuals without the disease [23, 24, 77, 78]. EDS as measured by the Epworth Sleepiness Scale (ESS) is weakly correlated with sleep-disordered breathing in the general population [79]. In epilepsy, however, EDS is thought to be related to undiagnosed comorbid sleep

Table 2. Epidemiological studies examining the prevalence of sleep-disordered breathing in adult epilepsy patients using polysomnography

Study	Participants, *n*	Age (y)	Gender, males, n. (%)	Epilepsy type(s), *n*. (%)	Seizure control, *n*. (%)	Diagnostic criteria	Principal findings, *n* (%)	Risk factors for sleep-disordered breathing
Malow et al. [5]	39	18–65	18 (46%)	Focal (temporal lobe epilepsy) 39 (100%)	NR	RDI ≥ 5[†,‡]	OSA in 13 (33%)	Older age, male gender, increased SA/SDQ score, nocturnal seizures
Weatherwax et al. [8]	125	NR	70 (56%)	NR	NR	AHI ≥5[†,‡]	OSA in 69 (45%)	NR
Chihorek et al [23]	21	≥50	11 (52%)	Focal 18 (86%), generalized 2 (10%), unknown 1 (5%)	Uncontrolled seizures 11 (52%), seizure-free 10 (48%)	AHI ≥5[†,§]	Higher prevalence of OSA in patients with uncontrolled seizures 9 (82%) than seizure-free group 2 (20%)	Increased ESS and SA/SDQ scores
Foldvary-Schaefer et al. [6]	130	≥18	44 (34%)	Focal 97 (75%), generalized 27 (21%), unknown 6 (5%)	NR; 66 (51%) >1 seizure per month	AHI ≥5[†,§]	OSA in 39 (30%)	Older age, dental problems and standardized AED dose after adjustment for covariates
Phillips et al. [7]	43	NR	22 (51%)	NR	NR	AHI ≥15[‖]	OSA in 9 (22%)	NR
Maurousset et al. [30]	27	≥50	16 (59.3%)	NR	NR	AHI >5[†,§]	OSA in 24 (88.9%)	NR

AHI = apnea–hypopnea index; NR = not reported; RDI = respiratory disturbance index.
[†]Apnea defined as a ≥90% reduction from baseline for ≥10 s.
[‡]Hypopnea scored using any reduction in airflow from baseline accompanied with either a ≥4% reduction in oxygen saturation or arousal.
[§]Hypopnea defined as a ≥50% reduction in airflow from baseline accompanied with either a ≥3% reduction in oxygen saturation or arousal.
[‖]Criteria used to score respiratory events not reported.

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disorders, such as OSA or restless legs syndrome, as opposed to epilepsy-related factors, such as AEDs [77]. In one study of 130 adults with epilepsy, no association was found between OSA and EDS [6]. This may have been related to the small sample size, or use of former AASM 2007 scoring criteria to define nocturnal respiratory events, which may have underreported the prevalence of sleep-disordered breathing. Another study investigating OSA in patients with epilepsy concluded that EDS (defined as an ESS > 10) was more frequent among individuals with OSA 6 of 29 (23.1 per cent), compared with those without the disease 1 of 11 (9 per cent; $p < 0.05$) [74]. A study examining older adults with epilepsy, those who developed epilepsy later in life or had worsening seizure control, had a higher AHI ($p = 0.002$) and ESS score ($p = 0.009$), compared with those who were seizure-free or had an improvement in seizure control [23]. These two groups were similar in age, weight, neck circumference, number of AEDs, and nocturnal seizure frequency.

In a study investigating SA-SDQ, this measure provided a sensitivity of 73 per cent and specificity of 72 per cent for mild-to-severe sleep–disordered breathing across all participants, with increased sensitivity and specificity in males than females [80]. Another study concluded that the SA-SDQ cut-off score for sleep-disordered breathing should be lower for individuals with epilepsy compared with the general population [8].

The utility of the Snoring, Tiredness during daytime, Observed apnea, high blood Pressure, Body-mass index, Age, Neck circumference, Gender (STOP-BANG) questionnaire in patients with epilepsy was explored in one study [81]. Prior to the study, only 22 of 264 (3.3 per cent) patients seen at the outpatient epilepsy clinic at the University of Cincinnati over a 4 month period had their sleeping habits assessed; eleven (1.7 per cent) had been referred to sleep medicine. After implementing the STOP-BANG questionnaire, the proportion of patients screened for OSA increased to 41.6 per cent (269/647; $p < 0.001$). Of the 269 patients screened, 84 (31.2 per cent) met criteria for high OSA risk. Forty-one patient were referred to sleep medicine, including 33 who met the STOP-BANG questionnaire criteria for OSA. Of these 33 patients, only 12 were seen by sleep medicine; 10 of the 12 patients subsequently underwent polysomnography and nine received a formal diagnosis of OSA and were offered CPAP therapy. The validity of other screening instruments of sleep-disordered breathing, such as the Berlin questionnaire, requires investigation in well-designed studies.

Central sleep apnea

CSA is characterized by a withdrawal of drive to the respiratory muscles during sleep resulting in compromised gas exchange [82]. It occurs when there is either a heightened or reduced respiratory drive, which, in turn, leads to impaired central control of respiration [82]. CSA is uncommon in the general population, with a reported prevalence of 0.4 per cent [83]. There is an increasing prevalence of CSA with age [83]. In select populations, however, CSA occurs commonly. Cheyne–Stokes breathing is a form of CSA and is characterized by a crescendo–decrescendo pattern of breathing with a central apnea or hypopnea at the nadir of ventilator effort [16]. In people with significant cardiac impairment, such as congestive heart failure, the prevalence of CSA due to Cheyne-Stokes breathing is 25%–40% [84, 85].

CSA without Cheyne–Stokes breathing can also occur secondary to a medical or neurological condition, where the majority of these patients have brain stem lesions, which have a developmental, vascular, neoplastic, degenerative, demyelinating, or traumatic basis [11]. Such conditions include neurological disorders of the central and peripheral nervous systems (e.g. amyotrophic lateral sclerosis, dementia, and multiple sclerosis) [16, 86, 87]. It is proposed that damage to areas of the brain stem responsible for the control of respiration, or progressive muscle weakness, may contribute to its pathophysiology in these conditions. Other causes of CSA include high altitude periodic breathing, chronic medication or substance use such as narcotic or opioid induced, or primary (idiopathic etiology) [88].

Despite the frequent occurrence of central apnea during seizures, the prevalence of CSA has generally not been reported in studies of patients with epilepsy. In a large retrospective study examining the prevalence of CSA among 416 participants, who were symptomatic for OSA and referred to the sleep clinic, 3.7 per cent of patients had CSA and 7.9 per cent had complex sleep apnea [89]. In this study, the reported prevalence of CSA in participants with focal epilepsy was 10.1 per cent [89]. Further studies are required to address whether certain types of epilepsy may increase the risk of CSA.

Pathophysiology of Sleep-Disordered Breathing

Antiepileptic drugs

Multiple AEDs are associated with weight gain and, as such, could potentially worsen or increase the risk of OSA. Patients with drug-resistant epilepsy on AED polytherapy may be at increased risk of obesity compared with those on monotherapy [90]. AEDs causing weight gain include valproic acid, pregabalin, perampanel, and to a lesser degree, gabapentin and vigabatrin [91–105]. The effect of carbamazepine on weight in unclear, and long-term, placebo-controlled studies are required. Lamotrigine is a weight-neural AED [106]. Felbamate, topiramate, and zonisamide can cause weight loss [107–110]. In two studies which examined patients on felbamate for at least 6 months, substantial weight loss which occurred initially was only transient, with patients returning to their baseline weight during follow-up [109, 110]. Benzodiazepines, including clobazam and clonazepam, are often used in the treatment of drug-resistant epilepsy [111]. Diazepam, clonazepam, lorazepam, and midazolam are used in the acute management of seizures and status epilepticus [111]. The use of benzodiazepines is associated with reduced upper airway muscle tone and ventilatory response to hypoxia [112]. Studies investigating the effect of benzodiazepines on OSA suggest that their use may be associated with a modest increase and prolongation of apneic events [113, 114].

In one study examining OSA, increased AED load (a ratio derived from the prescribed daily dose divided by the defined daily dose) for all medications taken was associated with increased risk of OSA, but whether this represents a marker for drug-resistant epilepsy or an effect of increased AED load remains unclear [6]. In another study, there was no marked difference in the proportion of patients on valproic acid or phenobarbital groups in the OSA group compared with those without the disease [115]. One case report documented weight gain associated with vigabatrin and the subsequent development of OSA in a patient with drug-resistant epilepsy [116].

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Seizure-related factors

Respiration can be affected by input from limbic regions to the respiratory center located in the brainstem. Stimulation of multiple cortical areas including the amygdala, hippocampal gyrus, ventral and medial temporal pole, and anterior insular and anterior limbic gyrus in human and animal models leads to an inhibition in respiration [117–121]. While seizures can often affect areas of respiratory autonomic control, focal seizures which do not spread to these regions may also cause disturbances to respiration. Multiple studies have reported and characterized the occurrence of central and obstructive ictal hypoventilation, with accompanying oxygen desaturation, occurring during both focal and generalized seizures [122, 123]. In one study, central apneas during seizures were observed in 10 of 17 (58.8 per cent) patients with epilepsy. In three patients, obstructive apneas also occurred, following the central apneas [122]. Seizures with accompanying apneas without clinical manifestation have also been reported [124]. A study assessed sleep-disordered breathing in seven patients with epilepsy and found that ictal activity did not correlate with the apneas recorded [29]. It is possible that in some patients, seizures may increase the severity of sleep-disordered breathing. In one study, the occurrence of nocturnal seizures increased the risk of OSA [5]. However, in a large retrospective study, nocturnal seizure occurrence was not associated with an increased risk of OSA [89].

Other mechanisms

Patients with epilepsy have increased disturbances in sleep and arousals, even in the absence of seizures [125]. Following an arousal, there is usually a brief period of hyperventilation, which can result in hypocapnia which in turn can lead to central apnea [82]. Additionally, hypocapnia can lead to a reduction in the activity of the upper dilator muscles, which can increase the risk of collapse [126]. The propensity to arouse may, therefore, result in the pathogenesis of further central and obstructive apneic events, upon resumption of sleep.

Potential Consequences of Untreated Sleep-Disordered Breathing

Seizure control

OSA results in altered sleep architecture [127]. Patients with OSA have increased stage N2 sleep and decreased stages N3 and REM sleep [127]. These alterations in sleep architecture may affect cortical excitability in patients with epilepsy and potentially increase the risk of seizure occurrence [128, 129]. Seizures occur commonly from NREM sleep, particularly stage N2 sleep, followed by stages N1 and N3, and are relatively uncommon out of REM sleep [130]. Individuals with OSA may be more susceptible to nocturnal seizure occurrence as OSA increases stage N2 sleep, and decreases REM sleep. In addition, they experience frequent transitions from sleep to wakefulness due to frequent arousals, which may influence seizure occurrence. In a study evaluating sleep efficacy and architecture in 22 patients with OSA randomized to either CPAP or no-treatment (control) found that stage N1 sleep was reduced and stage N3 was increased with CPAP [131]. There were, however, no marked differences in stages N2 or REM sleep from treatment with CPAP. It can be speculated that treatment of OSA with CPAP may improve seizure control by improving sleep architecture. Future studies should examine the relationship between the sleep stage at seizure onset and seizure control on CPAP.

Mortality

Untreated OSA may contribute to cardiovascular-related morbidity and mortality in epilepsy. The presence of cardiac arrhythmias may contribute to the pathophysiology of SUDEP [132, 133]. Cardiac arrhythmias are observed in up to 50 per cent of OSA patients, and rates increase with greater disease severity and marked hypoxemia [134–138]. The most commonly occurring arrhythmias observed in patients with OSA include sinus arrhythmias, sinus bradycardia, asystole, second-degree atrioventricular block, and ventricular arrhythmias including complex premature ventricular beats and ventricular tachycardia [135, 137, 139]. Most seizures are associated with sinus tachycardia, but some may be accompanied by bradycardia, atrial fibrillation, supra-ventricular tachycardia, QT interval prolongation, and asystole [140–146].

Hypoxemia associated with sleep-disordered breathing can often result in high systolic blood pressure that can induce fatal cardiovascular or cerebrovascular incidents [147]. In the general population, OSA is an independent and novel predictor of sudden cardiac death (SCD), which refers to an unexplained, sudden, and rapid cardiac death from the onset of symptoms [148]. In patients with OSA, SCD occurs more frequently at night [149]. Like SCD, SUDEP often occurs during the night and usually in association with a tonic-clonic seizure [150]. It is possible that patients with comorbid epilepsy and OSA may have an increased risk of SCD, which is one potential mechanism for SUDEP. A study among patients who had survived a near-SCD event found that a history of epilepsy was a significant predictor of life threatening ventricular arrhythmias ([HR] 3.53 [95% CI, 1.30–9.56]), cardiac death ([HR] 4.14 [95% CI, 1.30–13.14]), and all-cause mortality ([HR] 3.82 [95% CI, 1.40–10.48]) when compared with other survivors [151]. Whether these near-SCD occurrences represent SCD or SUDEP is unknown, but this study provides insights into the increased risk of sudden death and mortality in this population.

There has only been one study to date, which has examined the prevalence of OSA and SUDEP in epilepsy. A retrospective investigation of 103 patients with nocturnal frontal lobe epilepsy with at least 90 per cent of seizures occurring during sleep found an incidence of SUDEP of 0.36 per 1,000 patient-years [152]. The low incidence of SUDEP within this population may reflect the low occurrence of tonic-clonic seizures in nocturnal frontal lobe epilepsy patients. There was also a low prevalence of OSA in this population, with only 7.8 per cent having a diagnosis of mild–moderate OSA [152]. Unfortunately, the presence of mild OSA, the criteria used to score events, or the cut-off used to determine OSA was not reported in this study. It is also unclear whether polysomnography was used.

Comorbidities

Cognitive dysfunction and psychiatric disorders are common in epilepsy, particularly in patients with drug-resistant epilepsy [31]. These conditions are also common in those with

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sleep-disordered breathing [12]. Many symptoms of depressed mood, cognitive impairment, and sleep-disordered breathing overlap, including daytime sleepiness, fatigue, poor concentration, irritability, psychomotor retardation, and weight gain [153]. Treatment of sleep-disordered breathing with CPAP can result in improved cognition and mood [154]. Although this is corroborated by everyday clinical experience, it has not been investigated in ad hoc studies.

Effect of Nonpharmacological Epilepsy Treatments

Vagus nerve stimulation

There are numerous studies showing that vagus nerve stimulation (VNS) can alter the rate and amplitude of breathing when activated during sleep, causing obstructive or central apneas, and intermittent hypoxia and hypocapnia [155–158]. In a study of four patients with drug-resistant epilepsy, the number of apneas (predominantly obstructive) and hypopneas increased from baseline (before activation of the VNS) to treatment (3 months of treatment with VNS) [156]. In all participants, the AHI increased from baseline to treatment (range: 0.6–6.8 to 12.4–26.2; $p = 0.006$). These observations accord with findings from another study which found that treatment with VNS in 16 medically refractory adults was associated with mild elevations in sleep-disordered breathing in five patients from baseline (before VNS activation) to treatment (3 months following VNS activation) [157]. In these five patients, the AHI increased from baseline to treatment (range: 5.9–11.3 to 10.7–26.2). In both studies, the increase in respiratory events was not observed when the VNS was not activated. The underlying mechanisms that may cause respiratory depression in patients implanted with a VNS are unclear, but may potentially arise from altered laryngeal function from stimulation of the vagus nerve which innervates the upper airway muscles [159].

The manufacturer of VNS (Cyberonics, Inc., 2014) outlines in its safety guidelines that patients with existing OSA may have an increase of apneic events during stimulation, and that lowering stimulus frequency may prevent exacerbation of OSA [160]. The degree of sleep-disordered breathing may also be influenced by the mode of the VNS, where rapid cycling compared with standard mode increases the number of respiratory effort–related arousals per hour of sleep [161]. The output current and pulse width may also affect sleep-disordered breathing, but this remains unclear. In one case, reduction of VNS current during polysomnography eliminated sleep-related stridor [162]. Therefore, in the management of sleep-disordered breathing in patients treated with VNS, alteration of stimulation frequency, output current, or pulse-width may be beneficial.

Following VNS implantation, EDS was reported in an individual with mild-to-moderate sleep–disordered breathing, a finding which requires confirmation in future large investigations [163]. Evaluation of sleep-disordered breathing using polysomnography should be recommended in patients with epilepsy being evaluated for VNS, and following device implantation. Further studies are required to elucidate mechanisms underlying respiratory depression associated with VNS.

Epilepsy surgery

A case report of a patient with moderate sleep–disordered breathing with accompanying desaturations below 90 per cent, who underwent surgical resection of the left frontal lobe, resulted in the resolution of sleep-disordered breathing [164]. Whether this reflects improved seizure control or a common underlying mechanism is unclear. In another study examining 11 patients who became seizure-free following temporal lobe epilepsy surgery, polysomnography analysis showed improved sleep with an increase in total sleep time, including REM sleep [165]. The presence of sleep-disordered breathing, however, was not reported. Patients who have undergone successful epilepsy surgery often remain on AEDs, which may also contribute towards weight gain and elevate the risk of developing sleep-disordered breathing. Comprehensive studies examining the effect on sleep-disordered breathing following successful epilepsy surgery should be undertaken.

Treatment of Sleep-Disordered Breathing

Continuous positive airway pressure

Since the first landmark study in 1981, the application of CPAP has become gold standard for the management of OSA [166, 167]. CPAP prevents upper airway occlusion during sleep, reduces EDS, improves daytime functioning sleep, and decreases hypertension [167–171]. The effect of CPAP on cardiovascular outcomes, however, is less clear. A recent randomized controlled study involving 2717 patients aged 45–75 years with moderate–severe OSA and established cardiovascular or cerebrovascular disease treatment with CPAP did not reduce the risk of future cardiovascular endpoints, which consisted of death from cardiovascular disease, myocardial infarction, stroke, or hospitalization for heart failure, unstable angina, and transient ischemic attack [172]. The main limitation of this study was that CPAP adherence in the treated group was on average 3.3 hr per night. However, a post hoc analysis showed that there was no relationship between the duration of CPAP use and occurrence of cardiovascular events. It is possible that, in this group, treatment was commenced too late, and larger randomized controlled trials of CPAP involving individuals without established cardiovascular disease are required to determine whether CPAP reduces the risk of developing cardiovascular disease.

There have been several observational studies of CPAP in patients with epilepsy that have reported improvement in seizure control when the underlying sleep-disordered breathing was treated [29, 173, 174] (Table 3). EDS in patients with epilepsy was also significantly improved [22, 24]. In patients treated with CPAP, there have also been reported reductions in interictal epileptiform discharges on EEG [175, 176]. In an uncontrolled, single center, study of nine patients with drug-resistant epilepsy, the potential benefits of CPAP were explored following diagnostic polysomnography. Compared with pretreatment, CPAP resulted in a reduction of interictal epileptiform discharges during wakefulness and NREM sleep [176]. No changes were seen during REM sleep. CPAP improved sleep architecture by decreasing stage N1 sleep, increasing REM sleep, and decreasing the number of arousals. Although this study did not specifically assess seizure control, it may be speculated that by improving sleep architecture in epilepsy, the risk of seizure occurrence may be

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reduced. However, well-designed studies are needed to confirm this hypothesis.

Most studies have focused on whether CPAP reduces seizure frequency. A recent meta-analysis concluded that epilepsy patients with OSA treated with CPAP resulted in the reduction of seizures ([OR] 5.26 [95% CI, 2.04–13.5]) [177]. The first study to examine seizure frequency in patients with epilepsy and OSA when treated with CPAP found that three (43 per cent) of seven patients experienced a reduction in seizure frequency when treated with CPAP [29]. Two of three patients became completely seizure free. Additionally, there was one patient who had a decrease in seizure frequency and became seizure-free following epilepsy surgery. However, the individuals who became seizure-free following commencement of CPAP later died from other causes.

The largest study to demonstrate the effects of CPAP on seizure frequency was a retrospective analysis of 41 patients, in which CPAP was provided for at least 6 months with no changes to concomitant AEDs [28]. This study documented 28 patients who were CPAP compliant, and 13 who were noncompliant. Sixteen of the 28 compliant patients became seizure-free. There was no difference in seizure frequency in the noncompliant group between baseline and end of follow-up. A retrospective study compared seizure-control across three epilepsy groups: patients with OSA treated with CPAP; patients with untreated OSA; and patients without OSA [25]. Improvement in seizure control was reported in 17 of 23 (74 per cent) participants with CPAP-treated OSA, 3 of 21 (14 per cent) participants with untreated OSA, and 15 of 37 (41 per cent) participants without OSA, over a period of 12 months. There was a statistically significant difference in seizure control between participants with CPAP-treated OSA and those with untreated OSA ($p < 0.001$). There was no difference in seizure control between participants with untreated OSA and those without OSA ($p = 0.060$), or CPAP-treated OSA and those without OSA ($p = 0.057$). Following adjustment for related risk factors, such as older age, gender, body-mass index, AHI, and epilepsy duration, CPAP treatment for OSA was associated with >30-fold greater chance of ≥50 per cent reduction in seizure frequency compared with untreated OSA ([OR] 32.3 [95% CI, 5.92–266.3]).

The main limitation of these studies is that they were retrospective and uncontrolled, and that many patients were noncompliant with the therapy, resulting in their exclusion for the final analysis. Patients often had AEDs adjusted during the study, and some underwent epilepsy surgery, which may have affected seizure control and the frequency of interictal epileptiform discharges.

A randomized, double-blinded, controlled pilot study assessed the feasibility of evaluating the effect of CPAP on seizure control in drug-resistant epilepsy [27]. This study enrolled 68 participants, and randomized 35 who were demonstrated to have an AHI > 5, but no greater than 50, to either CPAP ($n = 22$) or sham-CPAP ($n = 13$) for 10 weeks. Participants in this study demonstrated reasonable adherence to therapy, using CPAP on average for 4.4 hr per night. CPAP use was associated with a significant reduction in AHI. However, there was no difference in the responder rate (≥50 per cent reduction in seizure frequency) between the two arms at the end of the study. This study provides valuable data informing about the feasibility and methodology of a future adequately powered trial. However, whether CPAP improves seizure control in patients with comorbid OSA and epilepsy remains unanswered. There is currently no evidence from well-designed studies to demonstrate that CPAP improves quality of life or life-expectancy in epilepsy. To the best of our knowledge, CPAP use has also not been associated with any serious adverse outcome in patients with epilepsy, including those with frequent seizures [27].

Whether CPAP may be beneficial in patients implanted with VNS, who have sleep-disordered breathing, remains unanswered. In one case, treatment with CPAP did not adequately control sleep-disordered breathing while the VNS was switched on 178. However, with the VNS device switched off, events were controlled on CPAP therapy [178].

Other treatments

While CPAP remains the most efficacious intervention for treating OSA, adherence to therapy can be a limiting factor. Second line therapies include oral appliances. These devices are increasingly playing a role in the management of mild-to-moderate OSA. In one participant with epilepsy treated with VNS, use of an oral appliance resulted in reduction in seizures [179]. However, it should be noted that the oral appliance did not treat the VNS-related apneic episodes. The use of one or more conservative non-CPAP alternatives, such as nasal expiratory positive airway pressure, weight loss, positional therapy, oral pressure therapy, or hypoglossal nerve stimulation, might be considered on case-by-case basis in individuals with epilepsy, but supporting evidence is lacking. Well-designed studies assessing the efficacy and safety of these alternative therapies in epilepsy populations are warranted.

The use of surgery to treat OSA may be considered as an option in carefully selected adult patients with upper airway obstruction who poorly tolerate CPAP or oral appliances. There are no studies of OSA surgery in adults with epilepsy except for a single case report of tracheostomy [173]. In children, tonsillectomy and adenoidectomy is the first-line treatment for OSA. Uncontrolled retrospective studies suggest that OSA surgery may lead to improved seizure control in pediatric epilepsies [180, 181]. In one study including 27 children with epilepsy, seizure frequency was assessed at 3 months following OSA surgery [180]. Ten patients (37 per cent) became seizure-free, three (11 per cent) experienced a ≥50 per cent reduction, and a six (22 per cent) had <50 per cent improvement. However, eight patients (29 per cent) experienced no change or even worsening of their seizure control. Well-designed studies are needed to assess the effectiveness of OSA surgery in pediatric epilepsies.

Positional therapy may be used alone or in combination with CPAP when respiratory events are predominantly associated with the supine position [182]. In two participants with epilepsy, treatment with positional therapy resulted in seizure freedom [26]. It is unclear whether positional therapy may increase the risk of SUDEP, which is often associated with the prone position. In a retrospective survey of epilepsy monitoring units, 7 of the 11 monitored SUDEP cases were nonprone prior to the terminal seizure (three awake and supine, and four asleep on their side) [63, 183]. The remaining were asleep in the prone position. However, 5 of the 7 nonprone patients became prone at the end of the terminal seizure, suggesting that sleeping in a nonprone position may not necessarily prevent SUDEP. Rather, prevention of SUDEP may be attained by avoiding prone positioning during or immediately following a tonic-clonic seizure.

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Table 3. Studies of CPAP for the treatment of OSA in patients with epilepsy

Study	Design	Subjects, *n* (%)	Age (y)	Male gender, *n* (%)	Epilepsy type(s), *n* (%)	Seizure control, *n* (%)	Treatment duration	AED's adjusted	Principal findings
Devinsky et al. [29]	Retrospective, uncontrolled	5	23–75	4 (80%)	Focal 5 (100%)	Uncontrolled seizures 5 (100%)	3 months –8 years	Yes	Improvement in seizure frequency† in three (60%) patients
Malow et al. [22]	Retrospective, uncontrolled	32 (15*)	26–75	13 (87%)	Focal 13 (87%), generalized 2 (13%)	Uncontrolled seizures 9 (60%), seizure-free 6 (40%)	2 months –7 years‡	Yes	Improvement in seizure frequency† in 5 (33%) and daytime somnolence in 12 (80%) out of 15 subjects
Vaughn et al. [26]	Prospective, uncontrolled	10	21–79	9 (90%)	Focal 9 (90%), generalized 1 (10%)	Uncontrolled seizures 10 (100%)	NR	Yes	Improvement in seizure frequency† in 5 (63%) out of 8 treated on CPAP and 2 (67%) out of 3 treated with positional therapy
Oliveira et al. [175]	Prospective, uncontrolled	8	14–73	6 (75%)	Focal 8 (100%)	Uncontrolled seizures 8 (100%)	2–3 days	No	Reduction of interictal epileptiform discharges ≥10% from baseline in six (75%) participants
Hollinger et al. [24]	Prospective, uncontrolled	29 (23*)	37–79	25 (86%)	Focal 20 (69%), generalized 9 (31%)	Uncontrolled seizures 27 (93%), seizure-free 2 (7%)	NR	NR	Improvement in seizure frequency† in 4 (33%) and daytime somnolence in 12 (100%) out of 12/23 participants who were compliant
Chihorek et al. [23]	Prospective, uncontrolled	21	≥50	11 (52%)	NR	NR	8–18 months	Yes	Improvement in seizure frequency§ in 3 (60%) out of 5 participants who were compliant and had late-onset or worsening seizures
Malow et al. [27]	RCT	35	≥18	20 (57%)	NR	Uncontrolled seizures 35 (100%)	10 weeks	No	No difference in seizure frequency
Vendrame et al. [28]	Retrospective, uncontrolled	41	21–66	29 (69%)	NR	Uncontrolled seizures 41 (100%)	6–25 months	No	16 (57%) out of 28 participants who were compliant become seizure-free
Li et al. [75]	Retrospective, uncontrolled	30 (15‡)	NR	15 (50%)	NR	Uncontrolled seizures 13 (43%), seizure-free 17 (57%)	≥6 months	Yes	Improvement in seizure frequency§ in 6 (100%) out of 15 participants who were compliant and had drug-resistant epilepsy
Pornsriniyom et al. [25]	Retrospective controlled	132 (23*)	18–76	47 (35.6%)	Focal 94 (71.2%), generalized 31 (23.5%), unknown 7 (5.3%)	Uncontrolled seizures 81 (61.4%), seizure-free 51 (38.6%)	12 months	Yes	Improvement in seizure frequency† in 17 (74%) out of 23 participants with OSA treated with CPAP, 3 (14%) out of 21 participants with untreated OSA, and 15 (41%) out of 37 participants with no OSA
Pornsriniyom et al. [176]	Prospective, uncontrolled	9	19–56	7 (78%)	Focal 7 (78%), generalized 2 (22%)	Uncontrolled seizures 9 (100%)	NR	No	Overall reduction in interictal epileptiform discharges by 25% from baseline during wakefulness and NREM sleep
Maurousset et al. [30]	Prospective, uncontrolled	5	64–81	2 (40%)	NR	Uncontrolled seizures 5 (100%)	2–23 months	NR	Improvement in seizure frequency§ in 4 (80%) patients

AED = antiepileptic drug; NR = not reported.
†Reduction in seizure frequency ≥ 50%.
‡Total number of participants who underwent CPAP therapy and were included in the final analysis.
§Reduction in seizure frequency from baseline not specified.

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Conclusions and Future Directions

Individuals with epilepsy may potentially be at increased risk of sleep-disordered breathing, but well-designed studies are lacking. Risk factors for sleep-disordered breathing in epilepsy are poorly understood, and their identification may lead to improved management. Some treatments for epilepsy may increase the risk of sleep-disordered breathing. AEDs including valproic acid, pregabalin, perampanel, and to a lesser degree, gabapentin and vigabatrin, can cause weight gain and, as such, may increase the risk developing or worsening OSA. Further studies, however, are required to determine whether this is the case, and to what degree this may have an impact on sleep-disordered breathing in this population. VNS is associated with respiratory depression, and polysomnographic evaluation of sleep-disordered breathing in patients with drug-resistant epilepsy considered for VNS should be undertaken. However, further studies on the management of these patients are required.

OSA may also increase cardiovascular-related mortality, including potentially increasing the risk of SUDEP. The prevalence of OSA in patients who have died of SUDEP need to be examined. If CPAP use is demonstrated to improve seizure control, this may reduce the risk of SUDEP. Further studies examining the occurrence of SUDEP to the prevalence and severity of OSA and associated hypoxemia, as well as other cardiovascular comorbidities, are warranted.

The effect of sleep-disordered breathing–related chronic sleep disruption on seizure control remains unclear. Treatment with CPAP may improve seizure control in some patients, but evidence for this is currently limited and the mechanisms behind this are poorly understood. Adequately powered randomized controlled trials are the ideal design to assess the effectiveness of OSA treatment on seizure control. However, these trials carry challenges that may jeopardize their feasibility, including elevated costs and ethical considerations related to the randomization of patients with OSA, at least when moderate-to-severe, to no treatment (such as sham therapy). Strategies to address these methodological issues are needed, ultimately allowing to obtain class I evidence for the role (or lack thereof) of CPAP in the treatment of epilepsy.

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Notes

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