

Sleep and Epilepsy

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KEYWORDS

• Epilepsy • Sleep disturbances • Seizures • Sleep-Wake cycle • Sleep deprivation

KEY POINTS

- Epilepsy and sleep have a well-studied, intricately woven relationship. Understanding this relationship and addressing sleep problems in epilepsy patients improves quality of life in this population.
- Certain seizure types and epilepsy syndromes have patterns of temporal synchrony with the sleep-wake cycle.
- Seizures, epilepsy and treatments used for epilepsy are all capable of affecting sleep patterns and subjective sleep quality. Conversely, treatment of sleep-disordered breathing has been shown to improve seizure control.

INTRODUCTION

For more than 2000 years, scientists have recognized the bidirectional connection between sleep and epilepsy based on timing of seizures with respect to the sleep-wake cycle. In 350 BC, Aristotle noted “for sleep is like epilepsy, and, in a sense, actually is a seizure of this sort. Accordingly, the beginning of this malady takes place with many during sleep, and their subsequent habitual seizures occur in sleep, not in waking hours”.¹ In the second century AD, Soranus of Ephesus wrote, among his recommendations for the treatment of epilepsy, “sleep must be undisturbed.”² At the same time, Galen, in a commentary on Hippocrates Aphorisms, noted that “to sleep on the earth might induce the disease in adolescents.”² Not long after the time of Hippocrates, Diocles of Carystus further observed that “to go to sleep on ones back might provoke an attack....”²

In the classic treatise, *Epilepsy and Other Chronic Convulsive Diseases*, William Gowers³ documented one of the earliest formal studies of the timing of seizure occurrence in relationship to the sleep-wake cycle. He evaluated the timing of seizures in 840 institutionalized patients and found

that 21% occurred in a given patient only at night, 43% of the seizures occurred only during the day, and the remainder of the seizures occurred in patients by day and night. Seizures occurring just with waking or just with sleep onset occurred in 0.5% and 1% of patients, respectively. Two peaks were reported for the time of occurrence of nocturnal seizures. The first occurred roughly 2 hours past bedtime, and the second occurred between 4 and 5 AM. On longitudinal follow-up, he was able to conclude that the patients whose seizures only occur at night may eventually have them occur by day, but the nocturnal events will continue. But if a patient had only daytime seizures then went on to develop nocturnal seizures, the daytime seizures would disappear.³ Although this study was limited because it only consisted of clinical reports, such early observations are still of interest, because patients who present with only nocturnal seizures feel they are at little risk for daytime events.

The same peak times noted by Gowers were observed by Langdon-Down and Brain,⁴ who additionally identified a diurnal epilepsy with the first peak occurring shortly after waking between

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7 and 8 AM. These findings were again limited to clinical observations, given that Berger's first report of the human electroencephalogram only appeared the same year.⁵ The first report of the relationship of interictal epileptiform activity and sleep came from Gibbs and Gibbs in 1947,⁶ and noted an increase in interictal epileptiform activity during sleep compared with the waking state. In 1953, Janz⁷ described an epilepsy syndrome with seizures occurring within the first 2 hours after waking (awakening epilepsy). He was the first to note this type of epilepsy as having an identifiable organic cause only 10% of the time. Patients suffering from the "myoclonic epilepsy of Janz" seemed to have inherited their disease 12.5% of the time, and the onset of the seizures most often occurred between ages 10 and 25 years.⁸

The topic of epilepsy and sleep can be roughly divided into 2 parts. First, what is the effect of sleep on epilepsy? Second, what is the effect of epilepsy on sleep? Epilepsy and its treatment influence sleep. Sleep, arousal, and sleep deprivation influence epilepsy. Sleep state modulates both the occurrence of seizures and of interictal epileptiform discharges. Sleepiness and sleep disorders may coexist with epilepsy. Treatment of coexisting sleep disorders may improve seizure control in patients with epilepsy. Lennox and Lennox⁹ summarized the complexity of this relationship: "Sleep itself is a mystery, and the problem of epilepsy is not simplified by having to consider the reciprocal relationship of sleep and seizures. Possibly investigators will need to unravel the mysteries of both to fully understand either."

SLEEP AND SLEEP DEPRIVATION EFFECTS ON EPILEPSY

Patterns begin to emerge when examining the timing of seizures during sleep. Seizures predominate during non-rapid eye movement (NREM) sleep compared with REM¹⁰⁻¹² and are more likely to occur during the lighter stages of NREM sleep.^{12,13} Partial seizures are more frequent during sleep than during wake, and when they occur during sleep are more likely to secondarily generalize.^{10,12} When the anatomic origin is examined, seizures of frontal lobe origin are more likely to occur during normal sleep hours than during wake, but those of temporal, parietal, or occipital lobe origins show the opposite pattern.^{12,14,15} The link between seizure recurrence, site of seizure origin, and circadian rhythm has been supported further by studies of the timing of seizures with respect to dim light melatonin onset.¹⁶

Subsequent research supported initial clinical impressions that seizures of frontal lobe origin

have their onset out of sleep, but those of temporal lobe origin are preceded by an arousal, and the onset occurs during the waking state.^{10,17} Recordings from intracranial electrodes have found the actual onsets for all of these events tend to occur out of sleep; state transitions rather than arousals may facilitate some types of seizure recurrence.¹¹

NREM sleep has been described as a physiologic state of relative neuronal synchronization, which facilitates the recruitment of the critical mass of neurons needed to initiate and sustain a seizure.¹⁸ Generalized spike wave discharges preferentially occur during NREM sleep, particularly during the lighter stages when sleep spindles are present, supporting this idea of neuronal synchronization.^{19,20} This finding, combined with animal model evidence of the transformation of sleep spindles into spike-wave discharges, led to the hypothesis that spike-wave discharges have their origin in the pathologically altered generation of sleep spindles.²¹ More recent review of these clinical studies and animal data has raised questions about this proposition.²² Interictal discharges are more frequent during sleep than wake.^{23,24} This alone does not explain why seizures occur more frequently out of lighter stages of sleep or why certain seizures are triggered by arousals or awakenings.

Neuronal synchronization during NREM sleep results at least in part from underlying neurotransmitter changes. Pharmacologic agents, which synchronize electroencephalogram (EEG) (cholinergic and noradrenergic antagonists), tend to have proconvulsant effects, whereas agonists desynchronize EEG and have anticonvulsant effects.²⁵⁻²⁷ Histaminergic neurons in the posterior hypothalamus are one of the major excitatory sources of cortical activation during arousal. In several animal models, increased brain histamine levels elevate seizure threshold and reduce the severity and duration of seizures²⁸ and delay the development of seizure onset in genetically susceptible mice.²⁹ First-generation antihistamines (H1 receptor antagonists) act as m-current potassium channel antagonists,³⁰ and the m-current potassium channel agonist, retigabine, has anticonvulsant properties.^{31,32} Taken together, these findings explain the proconvulsant impact of commonly used antihistamines.

Patients frequently cite sleep deprivation as a trigger for seizure recurrence. This concept is supported by animal work, including the demonstration that cats are more susceptible to kindled and penicillin-induced seizures after sleep deprivation.^{33,34} Either REM or total sleep deprivation accelerates the rate of kindling in the amygdala.³⁵ Transcranial magnetic stimulation found reduced

short intracortical inhibition and increased intracortical facilitation in healthy volunteers after 24 hours of sleep deprivation; both are metrics suggesting increased cortical excitability.³⁶ An earlier study using only partial sleep deprivation failed to show the change in cortical excitability in normal controls but did show this increase in susceptible patients with juvenile myoclonic epilepsy.³⁷ Military studies reviewing the effects of sleep deprivation show that pilots are more likely to have their first generalized convulsion in the setting of sleep deprivation, and soldiers are more likely to have had prolonged sleep deprivation the night before seizure occurrence.^{38,39} Analysis of patient surveys and diaries found that sleep deprivation exacerbated seizures in patients with either temporal lobe or idiopathic generalized epilepsies.^{40,41} However, acute sleep deprivation of hospitalized patients with medically refractory partial epilepsy failed to affect daily seizure frequency.⁴² This finding may, in part, be caused by greater susceptibility to the effects of sleep deprivation in patients with idiopathic generalized epilepsies compared with those with epilepsies of focal onset.⁴³

THE EFFECTS OF EPILEPSY ON SLEEP

Comorbidities in patients with epilepsy and the secondary effects of these on sleep confound the environment for study of the effects of epilepsy on sleep in human subjects. Anxiety about the seizure disorder, coexistent depression and other psychiatric ailments, frequent arousals leading to sleep disruption, and effects of antiepileptic medications among other variables cloud the picture in understanding exclusively the effect of epilepsy on sleep in human subjects. Animal studies have helped overcome some of these confounders. A sampling of some of these studies has been provided in **Table 1**.

A seizure acutely disrupts sleep quality, and epilepsy chronically produces alterations in sleep organization and architecture. Broadly speaking, sleep architecture in patients with epilepsy is characterized by a decrease in total sleep time, frequent awakenings, frequent stage shifts, and a decrease in deep sleep, particularly in REM sleep.

Touchon and colleagues⁴⁴ reported a reduction in total sleep time and decreased REM percentage resulting from nocturnal generalized and repetitive partial seizures. This significant decrease in REM

Table 1
Some animal data on sleep architecture in models of epilepsy

Cohen and Dement, ⁹⁸ 1966, Rondouin et al, ⁹⁹ 1980	Suppression of REM sleep after electroconvulsive shock and kindling in cats
Raol and Meti, ¹⁰⁰ 1998	Seizures induced by amygdala kindling led to short-term alterations in sleep phases, with an initial increase in deep SWS and REM sleep. Consecutive seizures resulted in increases in deep NREM and decreased light NREM and REM sleep
Ayala-Guerrero et al, ¹⁰¹ 2002	NREM and REM sleep reduced in first 24 hours after kainic acid-induced SE, returning to baseline 4 days later
Yi et al, ¹⁰² 2004	Time of seizure occurrence influences the effects of seizures on sleep in adult rats
Bastlund et al, ¹⁰³ 2005	Reduction in REM sleep and prolonged wakefulness after 15 weeks of status epilepticus (complex partial seizures induced by hippocampal electrical stimulation)
van Luijtelaaar and Bikabaev, ¹⁰⁴ 2007	Drug-free naïve WAG/Rij rats had a longer lasting sleep cycle with reduced REM sleep time. Older animals showed a reduction in NREM sleep
Alfaro-Rodríguez et al, ¹⁰⁵ 2009	Carbamazepine protected against the damaging effects of kainic acid-induced seizures on sleep phases in rats
Matos G et al, ¹⁰⁶ 2010	After 60 days of status epilepticus in male adult rats after pilocarpine-induced temporal lobe epilepsy, reduction of REM sleep during the afternoon, increase in NREM Sleep and relaxed wakefulness early in the night, increase in NREM Sleep in the morning as well as decrease of sleep cycles throughout the light-dark cycle

Abbreviations: SE, Status Epilepticus; SWS, slow wave sleep.

sleep was seen in patients of temporal lobe epilepsy only when multiple seizures occurred but not with a single seizure. In patients with temporal lobe seizures, polysomnographic recordings showed a significant decrease in REM sleep percentage even when seizures occurred on the previous day.⁴⁵

When patients with primary generalized epilepsy and patients with focal epilepsy were evaluated, an increase in WASO and awakenings less than 2 minutes and greater than 2 minutes were found.⁴⁴ Total sleep time and proportion of NREM and REM sleep were unchanged. A possible mechanism proposed for sleep stage instability was an increase in norepinephrine and acetylcholine, with a corresponding decrease in gamma-aminobutyric acid (GABA). Patients with temporal lobe epilepsy were found to have significant sleep fragmentation with a decrease in efficiency index compared with frontal lobe epilepsy (FLE) and controls. However, no difference of sleep organization was seen in patients with FLE compared with controls.¹⁷ Janz⁸ reported a decrease in deep sleep in patients with generalized epilepsy. Barreto and colleagues⁴⁶ replicated these results and also described a decrease in sleep efficiency and stage 4 NREM sleep in patients with idiopathic generalized epilepsy. A more recent study of chronotype distribution reported that those with epilepsy were more morning oriented and had longer sleep duration on seizure-free days. The investigators suggest that epilepsy itself rather than seizure timing, which is often a feature of specified epilepsy syndromes, influences chronotype behavior and subjective sleep parameters.⁴⁷ In a study comparing medically refractory epilepsy patients with those with controlled epilepsy, patients in the former group were found to have significantly less total sleep time with delayed sleep latency and REM latency, poor sleep efficiency, frequent arousals, and WASO compared with the latter group. Notably, medically refractory epilepsy patients seem to think that they spent more time sleeping than their actual demonstrated sleep time by polysomnography.⁴⁸

Fewer studies have investigated polysomnographic abnormalities specifically in children. Children with medically refractory epilepsy were found to have significantly lower sleep efficiency, higher arousal index, and a higher REM sleep percentage when compared with children with controlled epilepsy.⁴⁹ A more recent study⁵⁰ found a significant reduction of total sleep time, REM sleep, stage 3 NREM sleep, and sleep efficiency as well as an increase in WASO in children with drug-resistant epilepsy. Larson and colleagues⁵¹ investigated sleep behaviors in children with epilepsy. In these

families, there were increased rates of both parent-child room sharing ($P < .001$) and cosleeping ($P = .005$) compared with controls. Also, children with epilepsy were found to have greater sleep disturbances, particularly parasomnias, night awakenings, sleep duration, daytime sleepiness, sleep onset delay, and bedtime resistance. Parents of children with epilepsy also reported increased sleep dysfunction and were more fatigued than parents of children without epilepsy.

HYPERSOMNOLENCE AND OTHER SLEEP COMPLAINTS IN EPILEPSY

Although sedation from antiepileptic drugs is usually the most commonly perceived reason for sleepiness in patients with epilepsy, other causes of hypersomnolence in the general population should be considered in the differential diagnosis. Particular attention should be paid to other possibilities like nocturnal seizure activity and psychiatric comorbidities. Treatment of sleep disorders and improved sleep hygiene often leads to improved seizure control and quality of life.

Box 1 contains a summary of some of the causes of sleepiness in epilepsy patients.

Many studies report the presence of daytime sleepiness (EDS) in the population of patients with epilepsy. The methods of assessing sleepiness vary. The Epworth Sleepiness Scale (ESS) is the most commonly administered tool. Given the subjectivity of this measure, percentages of those with EDS also are reported variably. Hence, it is controversial if hypersomnolence in these patients is in reality significantly higher than in the general population.⁵² In earlier studies, EDS measured by the ESS was found in 28% of patients with epilepsy and 18% of control subjects with other neurologic disorders.⁵³ Further, in terms of predictors of sleepiness among the epilepsy patients, the

Box 1

Causes of sleepiness in epilepsy patients

1. Anti-epileptic medications
2. Nocturnal seizure activity leading to sleep disruption
3. Psychiatric comorbidities: anxiety and depression
4. Primary sleep disorders: sleep-disordered breathing, periodic limb movements in sleep (PLMS), restless legs syndrome, narcolepsy, and other hypersomnia syndromes, insufficient sleep syndrome, circadian rhythm disorders, poor sleep hygiene
5. Underlying cause of epilepsy itself

number or type of antiepileptic medication, seizure frequency, epilepsy syndrome (partial vs generalized), or the presence of sleep-related seizures were not found to be significant. Chen and colleagues⁵⁴ estimate the prevalence of EDS among patients with epilepsy at 20%, significantly increased compared with controls (7%). A Brazilian study with 99 unselected patients from an outpatient epilepsy clinic found EDS complaints in 47.5% of their population. EDS was most closely associated with anxiety and neck circumference.⁵⁵ In 50 patients with juvenile myoclonic epilepsy, EDS (ESS scores of more than 11) was documented in 17% and disturbed sleep was reported despite adequate seizure control. However, because these patients were on valproate monotherapy, the investigators concede that the role of this medication could be contributory.⁵⁶

A study of sleep disorder symptoms in patients with simple partial, complex partial, and generalized seizures compared with normal control subjects reported significantly more sleep disorder symptoms in patients with simple partial and complex partial seizures, especially frequent night awakenings. Independent of seizure type, patients with more frequent seizures also had the most sleep disturbances.⁵⁷ In a study of 33 patients with nocturnal frontal lobe epilepsy (NFLE) and 27 controls, “tiredness after awakening” and “spontaneous mid-sleep awakenings” were found to be more frequent in

NFLE patients than in controls (36.4% vs 11.1%, $P = .04$, and 50.0% vs 22.2%, $P = .03$).⁵⁸ An investigation of sleep hygiene based on a questionnaire compared 244 patients who had focal or generalized epilepsy with 205 healthy subjects and reported higher scores on ESS in those with snoring, apneas, or recurrent seizures in the last year, in the epilepsy patients.⁵² Another questionnaire-based study from the Netherlands reported a 2-fold higher prevalence of sleep disturbance in patients with partial epilepsy when compared with controls. de Weerd and colleagues⁵⁹ reported an association between the presence of a sleep disturbance and impairment in quality of life. In a small case-control retrospective study with neuropsychological testing, 31 elderly patients with epilepsy were compared with 31 age-matched healthy controls. Although none of the controls had depression, 18% of the patients were depressed.⁶⁰

EFFECTS OF ANTIEPILEPTIC MEDICATIONS ON SLEEP

It is difficult to draw conclusions about the effects of antiepileptic medications (AEDs) given the complications from the effects of epilepsy itself on the patient's sleep. Hence, some of these data are also gathered from investigations on normal volunteers. A summary of the effects of some of the commonly used AEDs on sleep is provided in **Table 2**.

Table 2
Antiepileptic drugs and effects on sleep

Medication	Effects on Sleep
Carbamazepine	Variable reports: No significant effect (Legros and Bazil, ¹⁰⁷ 2003) Increased TST and SWS, decreased REM density with unchanged REM latency and percentage (Sammaritano and Sherwin, ¹⁰⁸ 2000) Acute decrease in REM, not seen chronically (Gigli et al, ¹⁰⁹ 1997)
Phenytoin	Decrease in sleep efficiency, decrease in sleep latency, decrease in stages 1 and 2, decrease in REM, variable reports on effects on slow wave sleep
Valproate	Many studies report little or no effect. Some report increase in stage 1 sleep
Gabapentin	Increases SWS and REM sleep, reduces stage 1 sleep, reduces number of awakenings, improves sleep stability (Placidi et al, ¹¹⁰ 2000; Foldvary-Schaefer, ¹¹¹ 2002)
Lamotrigine	Increases REM sleep, reduces SWS, reduces stage shifts, improves sleep stability (Placidi et al, ¹¹² 2000)
Oxcarbazepine	Increases SWS and REM in rats (Ayala-Guerrero et al, ¹¹³ 2009)
Topiramate	No significant increase in daytime sleepiness measured by MSLT (Bonanni et al, ¹¹⁴ 2004)
Levetiracetam	Increase in TST, sleep efficiency and stages 2 and 4 (Bell et al, ¹¹⁵ 2002; Cicolin et al, ¹¹⁶ 2006; Cho et al, ¹¹⁷ 2011). Decrease in REM sleep time and percentage in patients (Zhou et al, ¹¹⁸ 2011)
Felbamate	Higher incidence of insomnia, alerting effect

Abbreviations: SWS, slow wave sleep; TST, total sleep time.

Although AEDs are often thought to be paramount in causing sleepiness in the epilepsy population, a definite cause-and-effect relationship between these 2 factors is not proven.⁶¹ When daytime sleep tendency was measured with mean sleep latency tests (MSLTs) in Swedish children with epilepsy, patients continued to have significantly higher sleep tendency even after discontinuation of their AEDs. This sleep tendency could be not be attributed to medications, recent seizures, or their disease.⁶² Hence, it is important to examine other causes of hypersomnolence in this population. Primary sleep disorders should be suspected, especially in those on low doses of AEDs, on AED monotherapy, and with well-controlled seizures.

When medications are thought to be the primary cause of hypersomnolence, certain simple strategies may be used to alleviate symptoms:

1. Simplify drug regimen, if possible to monotherapy.
2. Switch to less sedating medications. In general, most of the more recently released antiepileptic medications are less sedating than the older drugs. If sedating medications cannot be avoided, they may be moved to the night, or their largest dose can be administered at night.
3. Switch to extended-release formulations.

When selecting AEDs for patients with epilepsy and sleep disorders, as in other patients with epilepsy, one should also bear in mind the effects of AEDs on the underlying sleep problem. For instance, barbiturates and benzodiazepines may worsen comorbid obstructive sleep apnea (OSA) by influencing upper airway muscle tone. AEDs that are known to be associated with weight gain (eg, valproate) may also worsen OSA. Patients with insomnia may benefit from the more sedative drugs, preferably taken at bedtime.

PRIMARY SLEEP DISORDERS IN EPILEPSY

Identifying sleep disorders complicating epilepsy requires careful history taking. The time required is certainly worth the effort in comprehensively treating these patients with the goal of improving their quality of life. Initial studies focused on the co-occurrence of OSA with epilepsy^{63–65} as well the potential of improved seizure control with treatment of OSA. Malow and colleagues⁶⁶ have worked extensively on this interface. In a large study, 63 epilepsy patients referred for either a combination of or isolated EDS, suspected OSA, or nocturnal spells were evaluated by polysomnography (PSG). MSLTs were also performed in 33 patients. OSA was diagnosed in 44 patients

(71%). Narcolepsy and insufficient sleep syndrome were diagnosed in one patient each. Although 11 patients had greater than 20 PLMs per hour, these were not associated with arousal. Thereafter, many studies have examined the relationship between OSA and epilepsy. A total of 10.2% of 283 adult patients with epilepsy studied by PSG were found to have coexistent OSA.⁶⁷ Kaleyias and colleagues⁴⁹ report a 20% prevalence of coexistent OSA and epilepsy in children.

In children with epilepsy and sleep disruption evaluated by polysomnography, uncontrolled epilepsy was found to be a risk factor for OSA.⁶⁸ A Brazilian study prospectively screening 98 adult patients with epilepsy for risk of OSA using the Berlin questionnaire placed the prevalence of this risk at 55.1%.⁵⁵ The risk was related primarily to large neck circumference, high body mass index and anxiety. More recently, in medically refractory epilepsy patients, diabetes and snoring were found to be predictive of a diagnosis of OSA.⁶⁹ Conversely, OSA was found to be a contributing risk factor for worsening seizure frequency in older adults with epilepsy.⁷⁰

Less is known about the incidence of other sleep disorders in this population. Restless legs syndrome was described in 2 subjects taking methosuximide and phenytoin.⁷¹ Two patients were found to have PLMs in a case series of 6 patients not on anticonvulsant therapy.⁷² A case report of zonisamide-induced restless legs syndrome is also described.⁷³ Only isolated case reports of narcolepsy concurrent with epilepsy are found in the literature. In one case, a previously healthy 40-year-old man had hypersomnolence and narcolepsy before the subsequent appearance of complex partial seizures 18 months later; magnetic resonance imaging found a progressively enlarging lesion in the left frontotemporal region. His seizures were medically refractory and culminated in an episode of complex partial status epilepticus. He underwent a partial resection, and the pathology was found to be consistent with Rasmussen's syndrome. The authors raise the possibility of a common autoimmune etiology for the 2 disorders.⁷⁴ A second report described a 5-year-old boy who had a valproate-responsive myoclonic epilepsy at age 4 years and narcolepsy with cataplexy 6 months later.⁷⁵ Although the former case does suggest the possibility of a common underlying etiology, the latter could simply be the coincidental occurrence of both conditions in a single patient (a statistical inevitability). Coexisting REM behavior disorder with epilepsy has been reported in 2 case series by the same group.^{76,77} There are diagnostic dilemmas given the nature of involuntary nocturnal movements.

Parasomnias in epilepsy patients also present this diagnostic difficulty, because, in most cases, the diagnosis is based only on a history of involuntary nocturnal movements. An increased frequency of parasomnias has been reported not only in patients with NFLE, but also in their relatives when compared with controls.⁷⁸ The association was strongest with the NREM arousal disorders (such as sleep walking, sleep terrors, and confusional arousals). A questionnaire-based study described a higher occurrence of parasomnias ($P < .01$) among children with idiopathic generalized epilepsy when compared with siblings and healthy controls. They also found a higher density of paroxysmal EEG activity was related to parasomnias, suggesting that sleep fragmentation from epilepsy contributes to altered arousal mechanisms in these children.⁷⁹ In adults, an association between parasomnias and epilepsy was not found.⁸⁰

Oliveira and colleagues⁸¹ describe a decrease in EEG interictal epileptiform activity after continuous positive airway pressure (CPAP) therapy. In a pilot study, 3 adult patients and one child, all with coexistent epilepsy and OSA, had at least a 45% reduction in seizure frequency during CPAP treatment.⁸² Several other studies have reported significant improvement in seizure frequency after the use of CPAP in CPAP-compliant patients with epilepsy and OSA.^{83,84}

Melatonin has been studied to treat sleep disorders in children, and note should be made to its anticonvulsant effect seen in animal models.^{85–89} Some studies in children with epilepsy have been reviewed in **Table 3**.

VAGAL NERVE STIMULATION AND SLEEP

In treating patients with epilepsy who are treated with vagal nerve stimulation (VNS), it is worthwhile

to keep in mind the association with sleep-disordered breathing described in literature. In 4 epilepsy patients who were evaluated with PSG before and after 3 months of treatment with VNS, consistent sleep-related decreases in airflow and effort synchronized to VNS activation were identified.⁹⁰ Although these events did not meet clinical criteria for apneas and hypopneas, it was noticed that they occurred more frequently during VNS activation. In one of the patients who had a pre-treatment apnea-hypopnea index of 4, the post-treatment apnea-hypopnea index increased to 11.3. Stimulus frequency, when reduced, helped ameliorate VNS-related apneas and hypopneas. No such significant effect was seen with altering stimulus intensity, pulse width, or signal on time. VNS-induced airway changes or alterations in sleep architecture were suggested as possible causes of these respiratory events. In a subsequent communication, Murray and colleagues⁹¹ suggested that tachypnea accompanying VNS stimulation was somehow related to sleep-disordered breathing. Increases in esophageal pressure were also seen with respiratory events, which, in one patient, responded to CPAP therapy.⁹² Malow and colleagues⁹³ also describe increase in daytime alertness with VNS treatment at low stimulus intensities, likely caused by enhanced cholinergic activation. A case report of a medication-resistant epilepsy patient with VNS, for whom adequate CPAP titration could be achieved only with the VNS device turned off, raises the question of whether these patients should undergo polysomnographic studies (both diagnostic and therapeutic) with the device turned off.⁹⁴ Papacostas and colleagues⁹⁵ report a case of a woman with medication-resistant epilepsy in whom VNS induced central sleep apnea, which resolved on adjustment of VNS parameters. In children on VNS therapy, changes in respiratory patterns are

Table 3
Melatonin in epilepsy

Authors	Results of Study
Coppola et al, ¹¹⁹ 2004	In 25 patients (children, adolescents, and young adults) with mental disabilities, melatonin in nightly doses of 3 mg escalated up to 9 mg if necessary improved sleep latency and other subjective parameters of sleep
Gupta et al, ¹²⁰ 2005	In 31 children with epilepsy, oral melatonin reduced parasomnias and improved sleep latency and quality
Elkhayat et al, ¹²¹ 2010	Oral melatonin in children with intractable epilepsy resulted in significant improvement in bedtime resistance, sleep latency and duration, frequent awakenings, sleep-walking, EDS, nocturnal enuresis, bruxism, sleep apnea, and ESS scores as well as reduction in seizure severity
Uberos et al, ¹²² 2011	Nightly oral 3-mg dose of melatonin improved sleep efficiency and seizure frequency

also described, although no significant hypoxia or hypercapnia have been reported.⁹⁶

When evaluating patients on VNS therapy, the possibility of either inducing or worsening pre-existing sleep-disordered breathing should be kept in mind. Reducing the stimulus frequencies or the signal off time when feasible are strategies to minimize this effect. If necessary, PSG studies before and after VNS device implantation and after VNS parameter adjustment in symptomatic patients should be considered.

SUMMARY

The bidirectional nature of the interaction between epilepsy and sleep is revealed in multiple observations. Interictal epileptiform discharges and the timing of seizures in some epilepsy syndromes show patterns of temporal synchrony with the sleep-wake cycle. Sleep deprivation is associated with an increase in cortical excitability. Both seizures and epilepsy are capable of altering sleep microarchitecture and macroarchitecture, sleep-related behaviors, and subjective sleep quality. Patients with epilepsy have a variety of sleep-related symptoms, which may be caused by AEDs or primary sleep disorders. Recognition of sleep deprivation as a cause of lowering of seizure threshold is a frequently addressed topic in the seizure clinic now and in the past. However, discussion of the patient's sleep patterns, with particular attention to possible sleep disorders that are coexistent with epilepsy, is often overlooked. Because sleep disturbances have been found to be one of the main predictors in quality of life in epilepsy,⁹⁷ and because there are effective treatments available, addressing these efficiently is integral to the overall management strategy for these patients.

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