Sleep and Epilepsy
Opportunities for Diagnosis and Treatment

Bradley V. Vaughn, MDa, *, Imran Ali, MDb

KEYWORDS
• Sleep • Epilepsy • Sleep disorders • Nocturnal seizures

KEY POINTS
• Sleep complaints are common in patients with epilepsy and may be related to their underlying epilepsy, the treatment of epilepsy, or other sleep-related issues.
• Epilepsy can cause sleep disruption, and treatment of epilepsy may also improve sleep.
• Sleep disorders are common in patients with epilepsy.
• Treatment of sleep disorders may help reduce recurrent seizures.
• Nocturnal seizures are associated with stereotypic behavior.

INTRODUCTION
Epilepsy and sleep have a complex bidirectional relationship. The condition of epilepsy and some of its treatments can cause sleep disruption and may exacerbate some sleep disorders. Epileptic seizures and interictal discharges can cause sleep fragmentation and changes in sleep architecture. Sleep, alternatively, provides an opportunity for clinicians to better diagnose and treat epilepsy. For many patients with epilepsy, the interictal and sometimes ictal manifestations are best observed during specific sleep states. The act of sleep deprivation as well as oversleeping for some may increase the likelihood of seizure recurrence. There are considerable data that improvement in sleep hygiene and the treatment of sleep disorders can significantly improve outcomes in epilepsy. Individuals with epilepsy frequently complain of symptoms of disturbed sleep. These complaints may come in the form of easily recognizable symptoms, such as daytime sleepiness or insomnia, or in more subtle complaints, such as loss of quality of life or an increase in seizure frequency.

Patients may have their seizures only associated with sleep. Some epileptic syndromes are defined by their sleep-related association. Clinicians must be able to...
differentiate between a sleep disorder and/or a problem related to epilepsy and its treatment. Patients with epilepsy may also display unusual nighttime events due to seizures or other nonepileptic events, such as parasomnias. These patients can provide a challenge to even the most astute clinicians. Some specific nocturnal epilepsies, however, have characteristics that help identify these patients. This article explores the interactions of sleep and epilepsy and discusses how these may be useful for clinicians.

SLEEP DISRUPTION IN EPILEPSY

Epidemiology

Patients with epilepsy, as with patients with other neurologic disorders, have a greater prevalence of sleep disturbance than normal subjects. Miller\(^1\) found that more than two-thirds of patients with epilepsy seen at a university epilepsy center have complaints regarding sleep. He found 68% complained of feeling sleepy during the day, and 39% complained of difficulty falling asleep or staying asleep. Approximately 42% believed that their sleep issues interfered with their daytime performance. De Weerd\(^2\) reported in 2004 that 39% of a cohort of 486 adults with partial epilepsy had sleep complaints compared with 19% in the control group. Khatami\(^3\) surveyed 100 patients with epilepsy and found that 30% of epilepsy patients had sleep complaints compared with 10% of their control population and patients with epilepsy also had higher prevalence of sleep maintenance and insomnia symptoms (52% vs 38%). Similarly, Chen\(^4\) found in a survey of 117 patients with epilepsy that 20% had excessive sleepiness (compared with 7% of healthy controls) and elevated scores on the Pittsburgh Sleep Quality Index. Chen was also able to show that poor seizure control was associated with an increased the odds ratio of 2.42 for poor sleep compared with healthy controls. Using the Epworth Sleepiness Scale (ESS), Malow and colleagues\(^5\) similarly reported that 28% of 158 adult epilepsy patients surveyed had an elevated score (>10 points), with 44% of subjects reporting a moderate or high tendency to fall asleep while watching television.\(^5\) Similarly Giorelli\(^6\) found that 47% of their cohort had ESS scores over 10, which were reportedly not related to sleep deprivation. Increase in complaints of excessive daytime sleepiness (EDS) is also seen in children with epilepsy. Using the Pediatric Daytime Sleepiness Scale, Maganti\(^7\) reported that children with epilepsy have a higher prevalence of EDS.

Objective sleep studies of patients with epilepsy suggest that there is an increased prevalence of sleep disorders. Patients with primary and focal onset epilepsy have greater sleep fragmentation and sleep stage shifts compared with nonepileptic controls.\(^8\) Zanzmera,\(^9\) using a case-control cohort format, showed that those with refractory epilepsy have longer sleep latency, delayed rapid eye movement (REM) sleep latency, greater number of arousals, overall less sleep (340.4 min [147–673] vs 450.3 min [330–570]) and lower sleep efficiency (80.45% [40.5–98.0] vs 95.45% [88.4–99.7]). This study also showed that those with refractory epilepsy were more likely to have sleep apnea than those with controlled epilepsy (20% vs 0%) on polysomnography (PSG). Sleep-related respiratory disturbances have been well documented in patients with epilepsy. PSG investigation of individuals with epilepsy by Malow\(^10\) showed that approximately one-third of patients with medically refractory epilepsy had an apnea hypopnea index (AHI) of greater than 5 and approximately 10% of the patients had periodic limb movement index greater than 20 events per hour. Manni\(^11\) screened 283 adults with epilepsy for symptoms of sleep apnea and found 40 at risk and 29 to have an AHI great than 5 events per hour. In a case-control study of 53 older adults, Chihorek\(^12\) found that 52% of patients who had
late-onset epilepsy or worsening seizures had an AHI greater than 5, and 33% had an AHI greater than 10. These studies seem to indicate that the prevalence of sleep apnea increases with the presence of refractory epilepsy.

Obstructive sleep apnea (OSA) may also influence the prevalence of epilepsy. Seizures as a direct result of apnea are rare. In one patient, an apnea in sleep reportedly caused a seizure after severe oxygen desaturation and cardiac arrest. Yet, Sonka found in their cohort that 4% of patients with OSA had epilepsy. This prevalence exceeds that of the general population. More than three-fourths of these patients had seizures only during sleep and most of the events were generalized seizures. Although this study may be skewed by variances in referral patterns, the elevated prevalence raises the question of sleep apnea provoking seizures or unmasking an underlying potential for seizures.

Pathophysiology

The dynamic relationship of sleep on epilepsy is evident by the impact of each state on the other. As discussed previously, epilepsy disrupts sleep and sleep influences epilepsy. The epileptic process may directly contribute to the sleep disturbance. In animal studies, discharges from the amygdala or mesiotemporal structures produce arousals. Touchon showed that patients with epilepsy have greater sleep fragmentation and instability on seizure-free nights compared with nonepileptic controls. Touchon reported a decrease in sleep efficiency, increase in sleep stage shifts, and periods of wakefulness in patients with primary generalized epilepsy or complex partial seizures compared with normal controls. Touchon also noted that the disruption was greater in individuals with focal onset seizures. These individuals had more stage shifts, less deep sleep, and sleep fragmentation. Sleep fragmentation by awakenings was greater in untreated, newly diagnosed patients. Touchon reported that after treatment with carbamazepine for 1 month, the newly diagnosed epilepsy patients showed improvement in these parameters. Parrino also found that patients with frontal lobe foci have a distinct appearance to their sleep showing more A1 component of cyclic alternating pattern.

Although this work was in focal onset epilepsy, Peled showed that bursts of generalized spike-wave complexes can appear in stages 2 and 3 of non-REM (NREM) sleep and occur with K complexes and arousals. Some of these bursts produced nonconvulsive body movements, resulting in significant sleep fragmentation and decreased amounts of REM sleep. Three patients treated with antiepileptic medications showed reduced paroxysmal events during sleep, increased REM sleep, increased sleep efficiency, and improvement in daytime sleepiness. Not all interictal discharges, however, result in arousals. In temporal lobe epilepsy, Malow and colleagues found that interictal discharges were rarely associated with arousals from sleep and were most prevalent with the onset of SWS. This study used surface electrodes and did not look at other features, such as autonomic arousals or other physiologic parameter shifts. In humans, interictal activity can be associated with limited physiologic changes. Interictal discharges have been reported to change the cardiac cycle times and, in animals, may produce significant changes in hypothalamic function. The relationship of these brief discharges to sleep has yet to be fully defined. The chaotic nature of these discharges, however, may disrupt various neuronal drivers and the microarchitecture involved in the regulation of sleep or its many physiologic features.

Seizures also acutely alter the mechanism involved in sleep-wake state determination. Frequent nocturnal seizures can also produce significant sleep disturbance as evident in patients with frontal lobe seizures who may experience multiple seizures in a single night. The disruption caused by seizures frequently results in
patients having additional postictal somnolence and sleep disruption. Patients with nocturnal seizures are subjectively and objectively sleepy on the day after a seizure. The changes produced by seizures also produce sleep fragmentation and suppression of REM sleep. Touchon showed, in a study of 77 subjects with primary or secondarily generalized tonic-clonic seizures, that subjects had reduced total sleep time, a decreased percentage of REM sleep, increased wake time after sleep onset, and an increased stage 2 sleep on nights after generalized seizures compared with seizure-free nights. They also reported that, in 80 subjects, recurrent partial seizures during sleep decreased the percentage of REM sleep. Similarly, other investigators reported this REM-suppressing effect of seizures as well as other effects on sleep organization. Investigation by Crespel and Baldy-Moulinier reported that individuals with partial or generalized seizures had decreased amounts of REM sleep on nights with seizures. Besset found that patients with seizures had a reduction in total sleep time and REM sleep when compared with patients without seizures. Comparing nights when seizures occurred versus seizure-free nights, Bazil reported that nighttime seizures reduced sleep efficiency and REM and stages 2 and 4 sleep and prolonged REM latency and increased drowsiness as measured by the maintenance of wakefulness test on the following day. Bazil also found by studying patients in an epilepsy monitoring unit that when seizures occurred during the day, REM sleep was significantly decreased the ensuing night, with decreased amount of stage 4 sleep. This finding demonstrates that the effect of seizures to alter the regulation of sleep and wake last into the following day.

Sleep also influences the expression of interictal and ictal discharges. Sleep may activate interictal activity in approximately one-third of epileptic patients and up to 90% of subjects with sleep-related, or state-dependent, epilepsies. Findings on electroencephalogram (EEG) recording sleep, however, after the administration of chloral hydrate only changed the clinical management in less than 3% of patients. Degen showed an increase in interictal activity on EEG recordings that included sleep and an even greater number of and locations on recordings after sleep deprivation. Sleep deprivation EEG recordings have interictal spike frequency similar to those found on overnight recording EEG recordings.

Curiously the effect of sleep deprivation activating interictal activity recorded on EEG does not extend to magnetoencephalography as reported by Heers. This may be related to differentiating characteristics of magnetic field potentials. Sleep deprivation has long been an established method used to trigger epileptic-related activity and is frequently used in long-term epilepsy monitoring settings to promote seizures. Sleep deprivation exacerbates seizures in some patients with epilepsy whereas other patients have little exacerbation with sleep deprivation. Janz noted that sleep deprivation frequently provokes seizures in the awakening epilepsies. This also seems true for some focal onset epilepsies. Rajna and

<table>
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<td>Interictal discharge</td>
<td>May cause arousals, sleep stage shifts, or autonomic effects or have no effect</td>
</tr>
<tr>
<td>Complex partial seizure</td>
<td>Increase sleep fragmentation, decrease REM sleep</td>
</tr>
<tr>
<td>Generalized seizure</td>
<td>Increase sleep fragmentation and decrease REM sleep, decrease wakefulness on the following day</td>
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<th>Table 1</th>
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Vaughn & Ali
Veres found that in 9 of 14 patients with temporal lobe epilepsy, seizures are more likely to occur on the days after sleep deprivation. The mechanism by which this activation occurs is unresolved but may be related to the change in state or related to a loss of natural suppression of the aberrant activity. Sleep deprivation for these patients may occur from a variety of causes, such as schedule limitations, medication effect, epilepsy, or other dysomnias. No matter the cause, these studies demonstrate the importance of correcting potential causes of sleep deprivation to improve seizure control.

Sleep disorders may also increase the likelihood of recurrent seizures. OSA seems to increase the frequency of seizures. This may be related to the recurrent oxygen desaturation, the sleep fragmentation, or sleep deprivation. Sleep apnea is known to cause sleep deprivation as well as sleep fragmentation. This direct sleep disruption deprives patients from attaining restorative sleep as well as increasing the time spent in stages of sleep vulnerable to seizure induction. Sleep apnea also produces oxygen desaturation and hypoxia. Although there was little correlation between the lowest oxygen desaturation and the improvement of seizure frequency in the reported case series, oxygen desaturation is noted to decrease potential seizure inhibitory mechanisms. Although any of these mechanisms may be relevant, further research has yet to determine this mechanism.

Sleep stage influences the appearance of interictal activity. Recording through the night shows interictal activity increases with entrance into the deeper stages of NREM sleep. These interictal discharges are more frequent with the onset of the deeper stages of sleep and show greater spatial variability. Shouse postulated that the availability of neurons to be recruited into the epileptic discharge may be an important factor into the effect of sleep on discharge occurrence. In REM sleep, interictal discharges are less frequent and more focal. In patients with depth electrodes placed in the mesial temporal lobes, Staba showed that single neurons had significantly higher burst rates and synchronous discharges during episodes of slow wave sleep and REM sleep and not wakefulness when compared with nonepileptic hippocampal neurons. Although these findings suggest that the epileptogenic site may be more autonomous than other areas of the brain and thus less influenced by sleep regulation, REM sleep activation may explain the decrease of epileptic activity in REM sleep. Several investigators have postulated the corollary hypothesis that the increased activity in REM sleep leaves fewer neurons available for recruitment into an epileptic discharge. Yet, REM sleep has antiepileptogenic effect beyond temporal activation of the neurons. Animal models have also shown that REM-NREM sleep

<table>
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<th>Table 2</th>
<th>Effect of sleep on epilepsy</th>
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<td><strong>State</strong></td>
<td><strong>Effect on Epilepsy</strong></td>
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| NREM sleep | Increase in interictal discharges, frequency, and spatial distribution  
|          | More common seizures (especially frontal and temporal that occipital or parietal) |
| REM sleep  | More well-localized and less-frequent interictal discharges  
|          | Fewer seizures |
| Arousal    | May cause more seizures frontal or primary generalized seizures |
| Sleep deprivation | Increases interictal discharges on EEG even during awake  
|          | Increases likelihood of recurrent seizures |
| Oversleeping (>10 h) | Seems to increase likelihood for recurrent seizures |
stages to have complex influences on seizure activity. As in humans, NREM sleep and slow wave sleep have been associated in animals to promote the propensity of interictal discharges and REM sleep to suppress seizure discharges. In the kindling model, animals kindled in NREM sleep require fewer overall current and sessions than those kindled in REM sleep. Selective deprivation of REM sleep in animals reduces the required current to elicit seizure activity in other stages of sleep and awake. The converse of this is also true. Kumar increased REM sleep through microinjection of cholinergic agonist and demonstrated significant increase in threshold to produce after discharges in the amygdala during the subsequent period of wakefulness. These findings suggest that REM sleep has broader reaching antiseizure effect than immediate activation of the cortex.

Sleep also has a significant impact on seizures. Most seizures occur out of NREM sleep, with the highest rate per hour occurring from stage 2 sleep. Seizures are also noted to frequently occur in relationship to an awakening. This finding has raised significant debate if the seizure caused the arousal or the arousal promoted the seizure. REM sleep has the lowest rate of seizures. This antiseizure property seems to hold true for both the overall sleep time and the seizure rate per hour of REM sleep when compared with other states.

Key Clinical Features and Diagnosis

Patients with sleep complaints typically present as 1 of 3 major categories: EDS, insomnia, or unusual nocturnal events. Clinicians faced with caring for patients with epilepsy should be aware that patients may complain of sleep or may assume that their symptoms are normal for an individual with epilepsy. In addition, patients may not have the ability to perceive nor report sleep-related symptoms. Thus, clinicians must look for other clues of sleep disorders, such as change in daily activities, behavioral issues, or increase in seizure frequency. For patients with epilepsy who present with a sleep issue, clinicians can use a standard clinical approach with several key points. General categories of causes, include circadian rhythm issues, intrinsic and extrinsic sleep disturbances, substances or disorders altering the brain’s sleep-wake networks, other medical and psychiatric disorders. The clinician should also search for behaviors that interfere with sleep while also being aware that epilepsy and its treatment may also be partly responsible (Fig. 1). Clinicians need to obtain a typical detailed history, including information regarding the clinical course, the degree of impact on the patient, the sleep-wake pattern, report from bed partner or caretaker on sleep activities, dietary and activity schedule, medications (including timing and dosage schedule, over-the-counter agents, and herbs), seizure frequency intensity, and timing. Circadian rhythm disorders should be considered in patients with epilepsy. Many of these patients have sedentary lifestyles, take a variety of supplements, and may have limited exposure to circadian time clues. In addition, these patients may experience brief shifts or attenuations in the circadian rhythms from seizures or medications. Some of the circadian rhythm issues may be related to lower melatonin levels. In one study in children, Paprocka found that those with refractory epilepsy had lower melatonin compared with those with controlled epilepsy. Similarly patients with epilepsy may also have other sleep disorders, such as sleep apnea, periodic limb movements, or restless legs syndrome (RLS), which disturb their sleep and produce daytime sequelae. Patients should be questioned regarding presence of snoring, witnessed apnea, excessive movements at night, and presence of unrefreshing sleep. The presence of these symptoms should trigger consideration of overnight PSG. Intrinsic dysfunction in the regulation of sleep, such as narcolepsy or idiopathic hypersomnia, can also produce significant daytime sleepiness and patients may require...
overnight PSG and a multiple sleep latency study. Affective disorders are also common in patients with epilepsy and may account for some of the symptoms of insomnia, fatigue, and sleepiness. Lastly, patients with epilepsy are also treated with centrally acting medications to control their seizures. These medications can influence the sleep-wake control mechanisms. Many of these medications produce side effects, which include somnolence or insomnia (Table 3). Most of the traditional anticonvulsants have sleepiness as a side effect. Although this is most notable for the barbiturates and benzodiazepines, others, such as carbamazepine, phenytoin, valproate, gabapentin, topiramate, vigabatrin, levetiracetam, oxcarbazepine, and clozabam, can produce complaints of somnolence or fatigue. Medications, such as felbamate, ethosuximide, lamotrigine, and zonisamide, may induce insomnia. Some medications, such as gabapentin, pregabalin, and tiagabine, increase slow wave sleep. Drugs may also produce metabolic and endocrine changes that promote appropriate sleep and wakefulness. Enzyme-inducing medications may increase the metabolism of medications used to treat hypersomnolence or insomnia.

Approach to the Epilepsy Patient with Daytime Sleepiness

EDS should be approached by clinicians considering a variety of causes (Fig. 2). Daytime sleepiness is common in epilepsy patients, but this symptom is frequently dismissed as an acceptable side effect of therapy. For many of these patients, the authors’ clinical experience has shown that multiple factors contribute to this symptom (Box 1). Patients should be questioned regarding their daily habits, total time dedicated to sleep, wake and sleep schedule, timing of medication, factors that disrupt sleep, and symptoms of other sleep disorders. Many times a sleep diary combined with a seizure diary may provide clues to the impact of schedule on symptoms. Although the ESS has

![Fig. 1. This figure shows the major groups of causes of sleep disturbance, frequently seen in patients with and without epilepsy. CHF, congested heart failure; GERD, gastroesophageal reflux; PLMD, periodic limb movement disorder; PSTD, post traumatic stress disorder.](image-url)
Table 3
Antiepileptic medication effects on sleep

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sleep Complaint</th>
<th>Sleep Efficiency</th>
<th>Total Sleep Time</th>
<th>Sleep Latency</th>
<th>Arousals</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stages 3 and 4</th>
<th>REM Sleep</th>
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<tr>
<td>Phenobarbital</td>
<td>Sleepiness</td>
<td>No change</td>
<td>No change</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>No change</td>
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<tr>
<td>Phenytoin</td>
<td>Sleepiness</td>
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<td>No change</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>No change</td>
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<tr>
<td>Carbamazepine</td>
<td>Sleepiness</td>
<td>↑</td>
<td>No change</td>
<td>↓</td>
<td>↓</td>
<td>No change</td>
<td>No change</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Valproate</td>
<td>Sleepiness</td>
<td>No change</td>
<td>No change</td>
<td>↑</td>
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<td>No change</td>
<td>↑</td>
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<tr>
<td>Ethosuximide</td>
<td>Insomnia</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
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<td>No change</td>
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<tr>
<td>Felbamate</td>
<td>Insomnia</td>
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<tr>
<td>Gabapentin</td>
<td>Sleepiness</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
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<td>↑</td>
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<tr>
<td>Lamotrigine</td>
<td>Insomnia</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
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<td>No change</td>
<td>No change</td>
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<tr>
<td>Vigabatrin</td>
<td>Sleepiness</td>
<td>?</td>
<td>No change</td>
<td>No change</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
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</tr>
<tr>
<td>Tiagabine</td>
<td>Varies</td>
<td>No change</td>
<td>No change</td>
<td>–</td>
<td>↓</td>
<td>No change</td>
<td>↑</td>
<td>No change</td>
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<tr>
<td>Levitiracetam</td>
<td>Sleepiness</td>
<td>↑</td>
<td>↑</td>
<td>No change</td>
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<tr>
<td>Pregabalin</td>
<td>Sleepiness</td>
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never been validated in patients with epilepsy, useful information can aid clinicians. Individuals with a score of 10 or greater are considered to have excessive sleepiness. Malow showed that elevated scores on the ESS in epilepsy patients were more commonly associated with symptoms of OSA and RLS than the number or type of anti-epileptic medication or seizure frequency. Patients with symptoms, such as snoring, witnessed apnea, or unrefreshing sleep, which suggest nocturnal disturbance, should have an overnight in-laboratory PSG. For some patients, frequent nocturnal interictal discharges and nocturnal seizures may also cause significant sleep disruption and result in daytime sleepiness of patients with epilepsy. Extended EEG montage or video-EEG with PSG may be extremely valuable to elucidate the extent of the sleep disruption. For other complex patients, multiple sleep latency testing may also quantify the degree of daytime sleepiness and the occurrence of inappropriate REM sleep. This testing paradigm is specifically helpful for evaluating the presence of narcolepsy but may also provide helpful information for idiopathic insomnia.

**Approach to the Patient with Epilepsy and Insomnia**

Insomnia seems to disrupt sleep in approximately 40% of individuals with epilepsy. Patients with insomnia and epilepsy can be approached using a standard sleep medicine paradigm aimed at identifying potential contributing factors (Box 2, Fig. 3). At first glance, the issues of sleep schedule, sleep hygiene, and stimulus control need to be addressed. Additionally, patients need to be questioned regarding issues of sleep disruption, snoring, apnea, depression or anxiety, and psychological stressors. Patients with epilepsy may also have a reclusive or sedentary lifestyle, which is a contributor to nocturnal sleep disruption. Some patients use caffeine or other

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**Fig. 2.** This algorithm shows the clinical approach to EDS in a patient with epilepsy starts with a detailed history focusing on the possible causes outline in Fig. 1 and Box 1. AED, anti-epileptic drugs; CPAP, continuous positive airway pressure; MSLT, multiple sleep latency test; MVTS, movements; SZZ, seizures.
over-the-counter stimulants to counteract the sedating symptoms of the antiepileptic medications. Patients should be warned not to consume caffeine or other stimulants in the late afternoon and evening hours. Patients may have schedule limitations due to medications or work or driving restrictions; thus, timing of exercise and meals needs to be reviewed. Sleep environment may also play a role. Patients with seizures may have anxiety regarding issues of their epilepsy or fear of recurrence of seizures during their sleep. These fears may be expressed by maladaptive behaviors, such as sleeping with the television or light on or sleep in settings where other individuals can observe them. These individuals may benefit from education, reassurance, and counseling. For some patients, relaxation techniques, biofeedback, and stimulus control may also be helpful. The authors have not used sleep restriction, one of the most effective cognitive behavioral therapies for insomnia, for fear of increasing seizures. Insomnia may occur on the basis of frequent arousals caused by epileptic activity. For these patients, higher doses of antiepileptic medication at night and optimization of seizure control may improve symptoms. Patients should be queried about symptoms suggesting RLS or excessive movement in sleep or sleep apnea and referred for PSG when these diagnoses are suspected. Patients with vagus nerve stimulators may also be a greater risk for sleep apnea. Depression or anxiety occurs in more than 40% of patients with epilepsy and may contribute to the complaint of insomnia. In such cases, patients can be treated with antidepressant and antianxiety medications to benefit both the affective and sleep disorder.
Box 2
Differential diagnosis for insomnia

Intrinsic sleep disruption
- Sleep apnea
- Periodic limb movement disorder
- Narcolepsy

Extrinsic sleep disruption
- Inadequate sleep environment
- Inadequate sleep hygiene

RLS
- Primary insomnia
  - Idiopathic insomnia
  - Psychophysiologic insomnia
  - Paradoxic insomnia
- Circadian rhythm disorder
- Psychiatric disorders
- Medication/herbs and supplements
- Epileptic-related sleep disruption
- Neurologic degenerative disorder
- Metabolic/endocrine dysfunction

Fig. 3. This algorithm shows the clinical approach to insomnia in a patient with epilepsy starts with a detailed history focusing on the possible causes (outlined in Fig. 1 and Box 2). AED, antiepileptic drugs; CPAP, continuous positive airway pressure; MSLT, multiple sleep latency test; MVTS, movements; Szs, seizures.
Some antiepileptic medications, such as felbamate, ethosuximide, zonisamide, and lamotrigine, can provoke insomnia. These medications may be necessary for control of the seizures but may be given earlier in the evening or doses spread out through the day. Alternatively, a more sedating medication may be substituted or if the insomnia-producing antiepileptic medication is required for seizure control. Patients undergoing medication tapers may also experience insomnia due to removal of sedating medication.

**Treatment**

Treatment of sleep symptoms in patients with epilepsy should be directed toward 3 primary components. Patients should have the epilepsy optimally treated, the sleep schedule and hygiene should be optimized, and any underlying sleep disorder should be directly treated. With this 3-pronged approach, patients gain the mutual benefit of improving sleep and epilepsy. Optimizing the treatment of epilepsy can improve sleep. Touchon showed in some patients that epileptic discharges can cause sleep disruption; the use of carbamazepine decreased arousals and fragmentation. For these patients, sleep disruption may be treated with higher doses of antiepileptic medication before the sleep period. Yegnanan showed that dividing doses so that two-thirds or greater of the total carbamazepine or phenytoin dose was in the evening was associated with fewer side effects, better compliance, and improved seizure control. Anticonvulsants can produce both symptoms of daytime sleepiness and insomnia. These medications are frequently considered by patients and their physicians the cause of their sleep complaints, yet appropriate timing of doses may improve these symptoms. Traditional anticonvulsants are more commonly associated with somnolence, although some of the newer agents also produce similar effects (see Table 3). The course of antiepileptic medication use in patients with epilepsy should be for clinicians to start one medication at a low dose and titrate the dosage until either the patient is seizure-free or develops intolerable side effects. When antiepileptic medications are suspected of causing the daytime sleepiness, the medication dosage may be shifted to more at night or substituted with a less sedating medication. Considering the potential for enhancement of sleep, sedating medications may be dosed so that the peak effect is during the usual sleep period. This technique is also helpful in the treatment of nocturnal seizures when patients can tolerate higher drug levels during sleep. Patients also may choose the time they take their medications based on their own circadian preference. Therefore, patients who are night owls may elect to stay up later and take the medications to promote late night alertness and cause more nighttime sleep disturbance.

Patients may have a variety of opportunities to improve sleep. Patients with chronic conditions frequently have maladaptive behaviors that have a negative impact on their sleep. These factors should be addressed with education regarding sleep hygiene. Patients should be counseled to have a regular sleep routine that persists 7 days per week, avoid caffeine and other stimulants, exercise regularly, and eat meals on a regular basis. Late night activities and interaction with electronics that produce light, social interaction, or are stimulating may disturb sleep and should be avoided. Some patients may not be willing to make these types of long-term lifestyle changes. The authors have found that making deals for trial periods, tracking symptoms and seizures, documenting the instructions on written materials, and explaining the treatment plan to both patient and a family member is a valuable method to circumvent lapses in memory. Additionally, melatonin may provide some benefit for help reinforce a sleep-wake schedule by having patients take exogenous melatonin 1 hour to 2 hours before the set bed time. This therapy seems to help with schedule and may reduce seizure frequency.
Sleep disorders may influence the frequency of seizures and treatment of disorders, such as sleep apnea, may improve a patient’s sleep symptoms and seizure frequency. This is best demonstrated in the relationship between OSA and epilepsy. Several investigators have shown in a significant proportion of patients that treatment of the OSA improved their seizure control. The first report of treatment of sleep apnea in a patient with epilepsy was in 1981, by Wyler and Weymuller. Their patient underwent tracheostomy and attained control of the generalized seizures and improvement in partial seizures. Investigators have found a range of benefits for patients with epilepsy once the sleep apnea is treated. The authors’ original report showed that 40% of the cohort attained seizure freedom and another 10% had greater than 95% reduction in seizures with treatment of the OSA alone. In a pilot randomized controlled study, Malow showed trends toward seizure reduction in a group of patients with intractable epilepsy. The observations have been extended into the pediatric population. Patients with epilepsy can be effectively treated with continuous positive airway pressure positional therapy and surgery. Continuous positive airway pressure masks need to be fitted appropriately but also designed to easily disconnect to avoid patients becoming entangled during a seizure. In the authors’ center, the use of full-face masks is avoided if a patient has a history of postictal vomiting. Similarly, dental devices may be used if a patient does not have a history of ictal or postictal vomiting and the device is tightly fitted to avoid aspiration.

Antiepileptic medications may be chosen to aid with both the epilepsy and sleep disorder. Topiramate has been suggested to aid in the treatment of apnea based on its carbonic anhydrase inhibitor property and the potential for causing weight loss. Additionally, topiramate is used in the treatment of nocturnal eating syndrome and in one case of exploding head syndrome. Gabapentin, pregabalin, and carbamazepine have been reported as beneficial in RLS and neuropathic pain disorders. Gabapentin and pregabalin also increase slow wave sleep and some investigators have hypothesized the use of these medications may influence daytime attention by improving sleep quality. In addition, clonazepam has been the mainstay of therapy for patients with REM sleep behavior disorder (RBD). As discussed previously, the side effects of certain antiepileptic medications may be used to counter the complaints of insomnia or EDS. Patients with significant sleepiness but without an identifiable cause may be potential candidates for stimulant therapy. Amphetamines may increase frequency of seizures and should be used with extreme caution. With any stimulant use, clinicians should carefully monitor patients to assess the impact both on the epileptic seizures and potential for drug interactions. Whatever the cause, improving the sleep and daytime alertness of individuals with epilepsy may have benefits reaching beyond traditional symptoms of sleep disorders.

Prognosis

Patients with epilepsy and sleep complaints have an overall good prognosis of being helped if the underlying sleep dysfunction can be identified. This requires diligent investigation on the part of clinicians and significant participation on the part of patients and caretakers. Optimization of the treatment of epilepsy and sleep are the keys to improvement.

NOCTURNAL SEIZURES

Introduction

Approximately 20% of patients seen in the epilepsy clinics have seizures or ictal events that occur predominantly or exclusively at night. Most of these patients have
focal-onset seizures emanating from frontal or temporal lobes, but some patients, including those with frontal or temporal lobe epilepsy, have identifiable nocturnal epilepsy syndromes. Some of these syndromes are associated with exclusive nocturnal seizure activity, such as benign childhood epilepsy with centrotemporal spikes that does not seem to produce daytime sequelae, whereas others, such as Landau-Kleffner syndrome (LKS) or continuous spike and wave during sleep, can produce devastating daytime cognitive dysfunction without clear nighttime seizures.

Similarly, in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), a nicotinic receptor abnormality is intimately associated with sleep-related seizures. In benign nocturnal childhood epilepsy (Panayiotopoulos syndrome), sleep-related seizures are accompanied with a variety of autonomic symptoms, such as nocturnal vomiting. Generalized epilepsies, such as juvenile myoclonic epilepsy, are typically associated with seizures on awakening. Myoclonus, absence seizures, and generalized tonic-clonic seizures are all more likely to occur within 1 hour to 2 hours of awakening and are exacerbated by sleep deprivation. Other generalized epilepsies, such as infantile spasms, may also cluster in the morning hours after arousal. These variety of behaviors associated with seizures can make identification of epilepsy a challenge for clinicians.

**Epidemiology**

In the 1800s, Gower found 21% of the institutionalized epilepsy patients to have seizures strictly when asleep and 42% to have seizures strictly when awake. These results are similar to Janz’s and Billiard’s studies of epileptic patients one century later. Patients with frequent nocturnal seizures more often are found to have frontal lobe epilepsy, although this pattern has also been noted in temporal lobe epilepsy. Some sleep-related epilepsy disorders are common, such as benign childhood epilepsy with central temporal spikes, which comprises approximately 15% to 25% of all childhood epilepsy, whereas other sleep-related epilepsy syndromes, such as ADNFLE, are rare. Seizures on awakening are common and can be a useful diagnostic clue in some patients. Primary generalized epilepsy accounts for approximately 15% of all epilepsy, and juvenile myoclonic epilepsy, the classic awakening epilepsy, accounts for approximately 20% of idiopathic primary generalized epilepsy.

More than 3% of adults and 10% to 30% of children have nocturnal events (epileptic and nonepileptic) and some classical symptoms can be easily confused. The prevalence of nonepileptic parasomnias in patients with epilepsy is not well known. Khatami found in their survey the prevalence of parasomnias in epilepsy patients was no greater than that of their control group. Approximately 30% of children have disorders of arousal, such as sleepwalking or sleep terror events, and the reported prevalence in adults ranges from 2% to 5%. Violence can occur in many of these types of nocturnal events.

**Pathophysiology**

Sleep seems to be a vulnerable state for seizures and, as discussed previously, this may be related to greater neuronal synchronization during sleep state. REM sleep seems protective against epileptic seizures. For some distinct forms of nocturnal epilepsy, sleep and arousals may demonstrate the state dependent receptor abnormality. The Italian form of ADNFLE, originally described by Lugaresi, is an example of this vulnerability. Passed in an autosomal dominant pattern, patients have recurrent nocturnal events characterized by brief tonic movements, nocturnal dystonia, paroxysmal arousals, and nocturnal wandering. Patients may demonstrate any combination of these behaviors with few EEG changes and normal daytime EEGs. The genetics of this disorder was originally described in Australia and,
Table 4
Distinguishing features of nocturnal events

<table>
<thead>
<tr>
<th>Feature</th>
<th>Disorders of Arousal (Sleepwalking, Sleep Terrors, Confusional Arousals)</th>
<th>REM Behavior Disorder</th>
<th>Nocturnal Seizures</th>
<th>Behavioral Events</th>
<th>Rhythmic Movement Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of occurrence</td>
<td>First third of night</td>
<td>During REM</td>
<td>Anytime</td>
<td>Anytime</td>
<td>Start of sleep</td>
</tr>
<tr>
<td>Memory of event</td>
<td>Usually none</td>
<td>Dream recall</td>
<td>Usually none</td>
<td>None</td>
<td>Variable</td>
</tr>
<tr>
<td>Stereotypical movements</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Eyes open</td>
<td>Yes</td>
<td>No</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>PSG findings</td>
<td>Arousals from stage N3 sleep</td>
<td>Excessive EMG tone</td>
<td>Potentially</td>
<td>Occur from awake state</td>
<td>Rhythmic movement artifact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>during REM</td>
<td>epileptiform activity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
subsequently, in Italy. These patients frequently respond to anticonvulsant therapy. The Australian form of ADNFLE has been linked to chromosome 20q 13.2 to the CHRNA4 gene. An abnormality of the neuronal nicotinic acetylcholine receptor subunits have been found in association with this disorder. Although augmentation of acetylcholine does not seem to alter the frequency or intensity of the seizures, nicotine may influence some function of select receptor abnormalities. The mechanism for other nocturnal epilepsy syndromes has yet to be determined. The benign childhood epilepsies seem to have a combination of multiple genes influence the presence of the EEG findings and the seizures.

**CLINICAL SYMPTOMS**

**Seizure-Related Behavior**

Nocturnal seizures can produce a wide range of behaviors depending on the location of the seizure discharge. Nearly any behavior that can be produced by the brain can be exhibited as a seizure, but the hallmark of seizures is their stereotypic nature of the behavior. Frontal and temporal lobes are the most common sites for seizure foci, and these are areas more commonly involved in sleep-related epilepsies. Seizures involving the frontal lobes may evoke tonic posturing, complex bizarre motor activity, thrashing, and even violent behavior other characteristics that may suggest nonepileptic events or parasomnias. These events can be abrupt and involve unilateral and bilateral movements. Temporal lobe seizures usually produce episodes of staring, psychic phenomena, and occasionally complex behaviors. Temporal and frontal lobe seizures can also evoke a wide range of autonomic symptoms, such as bradycardia, asystole, tachycardia, and emesis, and respiratory disturbances, such as central apnea and irregular breathing. Parietal-onset seizures are more likely to evoke disturbances or distortion of sensory perception. Occipital lobe-onset seizures are usually associated with visual phenomena, visual distortion, or eye movement.

After a seizure, patients are frequently confused and disoriented. The authors have recorded wandering behavior, pronounced violence, rhythmic movement, snoring, and even psychosis as postictal events. The confusion may resolve over minutes or may only improve after a patient sleeps. Postictal somnolence is common and can make differentiating seizures from parasomnias difficult. Memory loss is a frequent feature of complex partial or generalized seizures. Patients without bilateral temporal lobe involvement during the seizures can retain memory for the events and, therefore, may have complex behaviors with retained memory. These patients are frequently misdiagnosed as having psychogenic disorders. Seizures may be influenced by the time of day or underlying circadian rhythm. Quigg demonstrated that temporal lobe seizures are more common in the afternoon for both humans and rats, but extratemporal seizures did not have a circadian pattern. Quigg also found that seizures produce phase shifts in the circadian rhythm of animals. Loddenkemper reports slightly different findings in the relationship of time to seizure type in children, showing an increase in generalized seizures after awakening and more frontal lobe seizures at night. Although it is difficult to separate, seizures may be influenced by both circadian and sleep-wake states, and some epilepsies are recognized to produce seizures predominantly at a particular time of day (Table 5). Some of these seizure types are distinct epileptic syndromes.

**Autosomal Dominant Nocturnal Frontal Lobe Epilepsy**

ADNFLE is a well-recognized genetic syndrome related to a defect of the neuronal nicotinic acetylcholine receptor subunit. ADNFLE is characterized by a triad of
paroxysmal arousals, episodic nocturnal wandering, and paroxysmal dystonic posturing.\textsuperscript{76–82} Previously known as hypnogenic paroxysmal dystonia or nocturnal paroxysmal dystonia, this is characterized by repeated dystonic or dyskinetic episodes occurring at night. The dystonic movements can involve a single extremity or up to all 4 extremities and neck and occasionally involve vocalization. Patients may frequently recall portions of the event. They typically occur out of NREM sleep and demonstrate in 2 major forms: short duration (15–60 seconds) and long duration (up to 60 minutes). Patients may have multiple spells per night or may have clusters of spells with quiescent periods. Nocturnal paroxysmal dystonia is considered a form of frontal lobe epilepsy. These events may have no or subtle EEG-associated changes. Some patients may note less frequent events with the use of nicotine.\textsuperscript{87} The family history can be difficult to obtain, because the spells may not be recognized by or acknowledged to other family members. Approximately 1 in 2 of these individuals has daytime seizures. Most patients respond to anticonvulsant medication, with carbamazepine, oxcarbazepine, and lamotrigine as likely agents given their propensity for interaction and stabilize the nicotinic receptor.\textsuperscript{88,89}

Benign focal epilepsy with centrotemporal spikes (BECTS) or benign rolandic epilepsy is another form of inherited epilepsy with nocturnal seizures.\textsuperscript{71} Patients typically present with episodes of hemifacial and body tonic activity, drooling, and speech impairment. These events occur approximately 20 minutes to 2 hours after going to bed. EEG usually demonstrates a high-amplitude centrotemporal spike and wave discharge associated with bifrontal positivity. Patients are often treated with anticonvulsant medications (valproate and carbamazepine), which are highly efficacious; typically the seizures diminish with age. Although clinicians debate who needs treatment, most agree children with generalized tonic-clonic seizures should be treated. The prognosis of this form of epilepsy is good, with or without medications. Some research suggests that children with this syndrome have partial speech and language impairment, yet the effect of treatment on the ultimate outcome is still unknown.\textsuperscript{90} There are some data that suggest cognitive impairment is associated with frequency of interictal nocturnal spikes and suppression of those may improve outcome, although this approach is debatable.\textsuperscript{90}

**Landau-Kleffner Syndrome and Continuous Spike and Wave During Sleep or Electrical Status During Sleep**

LKS is an acquired disorder characterized by decline in verbal fluency and centrotemporal spike in sleep.\textsuperscript{90–92} These patients may not have frank seizures but are noted to

<table>
<thead>
<tr>
<th>Epilepsy</th>
<th>Time of Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNFLE</td>
<td>Nocturnal</td>
</tr>
<tr>
<td>BECTS</td>
<td>Nocturnal (more likely first half of night)</td>
</tr>
<tr>
<td>Benign nocturnal childhood occipital epilepsy</td>
<td>Nocturnal</td>
</tr>
<tr>
<td>Panayiotopoulos syndrome</td>
<td>Nocturnal</td>
</tr>
<tr>
<td>Continuous spike and wave during sleep</td>
<td>Discharge during sleep</td>
</tr>
<tr>
<td>or electrical status during sleep</td>
<td></td>
</tr>
<tr>
<td>LKS</td>
<td>Intercital discharge in sleep</td>
</tr>
<tr>
<td>Primary generalized seizures with awakening/ juvenile myoclonic epilepsy (awakening)</td>
<td>On awakening (more common in morning)</td>
</tr>
</tbody>
</table>
have expressive and receptive language difficulties. This syndrome is potentially a more focal form of continuous spike and wave during sleep. This syndrome is associated with seizure-like electrical activity that replaces the normal features of sleep on EEG. Patry described 6 children in whom the background electrical activity was replaced with slow 1-Hz to 2.5-Hz generalized spike and wave discharges in sleep. These children also may not have significant nocturnal behavioral manifestations, but they have cognitive and psychological deficits. Many of these children have nocturnal and diurnal absence, focal motor, and generalized tonic-clonic seizures.

Both LKS and ESES are associated with childhood onset; progressive cognitive decline is associated with focal (LKS) or generalized (ESES) discharges during NREM sleep. Response to standard antiepileptic medications is usually poor and, in cases of LKS, steroids or intravenous immunoglobulin as well as novel surgical therapy, such as multiple subpial transections, may improve outcome. Patients have been reported to respond to levetiracetam, intravenous immunoglobulin, or corticosteroids.

**Benign Nocturnal Childhood Occipital Epilepsy (Panayiotopoulos Syndrome)**

This syndrome, first described in 1989, was originally characterized by the constellation of nocturnal seizures, tonic eye deviation, and nocturnal vomiting, typically starting in childhood and ending in early adolescence. The EEG demonstrated epileptiform discharges in the occipital region. Further descriptions have expanded the spectrum of clinical manifestations demonstrating cases in which there is overlap with other focal idiopathic epilepsies, such as benign rolandic epilepsy and other generalized epilepsy syndromes. This syndrome is noted to respond well to medications and seems a self-limited form of epilepsy. Benign occipital epilepsy of childhood is frequently confused with nocturnal migraine. With the complexity of these behaviors, an overlap in presentation among patients with seizures and parasomnias can easily be seen.

**Primary Generalized Seizures on Awakening/Juvenile Myoclonic Epilepsy**

Patients with Primary Generalized Seizures upon Awakening or Juvenile Myoclonic Epilepsy have seizures frequently within 1 hour to 2 hours after awakening. The seizures may be simple myoclonic jerks or include generalized tonic-clonic seizures. Epileptic-based myoclonus usually occurs in clusters soon after awakening. The rapid jerk of myoclonus can involve any portion of the body. Myoclonus associated with the awakening epilepsies frequently occurs soon after arousal. The jerks can occur in a rapid succession or as single events and may lead into a generalized tonic-clonic seizure. Sleep deprivation exacerbates seizures significantly in this form of epilepsy. They should be differentiated from hypnic jerks, which occur at sleep onset, and periodic limb movements, which occur mostly during NREM sleep. These types of seizures are more likely to respond to first line agents such as valproate, topiramate, levetiracetam, and lamotrigine, whereas zonisamide, clonazepam, and phenobarbital, which are helpful second-line agents.

**Approach to Nocturnal Events and Epilepsy**

The cornerstone of any evaluation of nocturnal events is the history and physical examination. Although there are no absolutes, the foundation of the evaluation is based on the accurate description of the behaviors. Key is the account of the events from witnesses who may give cardinal clues to the cause. Features of stereotypic behavior and a repetitive nature of the events point to a possible underlying epileptic disorder. Patients usually do not have memory for the seizures, and the seizures can occur at any time in the sleep period (day or night). Features in the history, such as
frequency of events, time of events in the sleep period, family history of nocturnal events, seizures or parasomnias, and a history of recent stressors or spells during wakefulness are also important. Most nocturnal seizures occur in NREM sleep, whether they are of temporal or frontal onset. Rare REM-related seizures have been described involving recurrent dreams and dreams, similarly to RBD. Other investigators have described seizures involving recurrent dreams. Patients can have a variety of nocturnal behaviors, such as ambulation, confused wandering, or screaming, which seem similar to events of sleepwalking or sleep terrors. Some seizures have a repetitive nature that can be easily confused with rhythmic movement disorder. The overlap of these symptoms can make classification of these extraordinary events difficult.

The physical examination may provide clues to focal neurologic lesions that may increase the likelihood of certain disorders. Focal lesions in the cerebrum increase the risk epileptic seizures, whereas findings indicative of Parkinson disease suggest the possibility of RBD. For epilepsy, historic features, such as stereotyped events, the occurrence of a seizure while awake, or family history of seizures, add to the evidence supporting a diagnosis of nocturnal seizures.

Many times, distinguishing NREM parasomnias from frontal lobe seizures can be difficult, especially because there is significant overlap in PSG features. Derry and colleagues found seizures more likely to come out of stages 1 and 2 sleep whereas parasomnias were from stages 3 and 4 sleep. They also found the captured seizures events were concordant with the historical features of the events, but the parasomnias varied. The prevalence of REM sleep–related parasomnias, such as RBD, is unknown but seems to increase with age. Zacconi proposed that multiple events per night and a continuum of minor to major behaviors was more frequently seen in nocturnal frontal lobe epilepsy than NREM parasomnias. The physical examination is frequently normal, but findings may indicate cerebral insults or other evidence of potential increased risk for seizures. Many clinicians consider a response to anticonvulsant therapy supporting evidence of the diagnosis of epilepsy. In the authors’ opinion, the response to anticonvulsant therapy should not be considered supportive evidence, because anticonvulsants have diverse neuropharmacologic effects.

Traditional analog PSG has several technical disadvantages. The limited encephalographic electrode placement decreases the likelihood of capturing an epileptiform discharge. The common paper speed of 10 mm per second is also inadequate for observing many ictal epileptic events and does not allow identifying interictal abnormalities. For PSG evaluation of these patients, the display windows should show 10 seconds of data and the array of cephalic electrodes increased. The display of the EEG data can be easily performed with current digital equipment the display window; however, greater coverage with cephalic electrodes requires more channels of EEG displayed and comfort of the reader in detecting epileptiform activity. Incorporation of a full 10-electrode to 20-electrode array and paper speed of 30 mm per second are helpful in evaluating for seizures. Foldvary found that a 7-channel EEG montage and increasing paper speed to 30 mm per second improved the detection epileptic events to greater than 80%. These settings and expanded electrode array allow for better differentiation of the epileptiform discharges from potential normal variants or artifacts.

Patients suspected of having epilepsy are typically studied with routine EEG. EEG is frequently normal in individuals with sleep-related epilepsies and the absence of an epileptiform discharge does not rule out the possibility of epilepsy. Sleep also plays a significant role in the prevalence, morphology, and location of interictal discharges. Interictal discharges are more common in NREM sleep, whereas REM sleep demonstrates some antiepileptic qualities.
Patients who continue to have events despite multiple medication trials may be considered for further evaluation. Capturing multiple events on video-EEG recording and comparing behaviors, EEG, and other measures, such as postictal prolactin levels, can lead to a greater chance of obtaining an accurate diagnosis.

TREATMENT

Treatment of nocturnal seizures may be challenging. Even in the best of circumstances, seizures are frequently missed, but seizures during the night are typically not witnessed unless they involve significant motor components. If patients are having seizures only at night, clinicians should strive to use medications that can achieve drug levels in the brain quickly and avoid daytime side effects. Alterations in medication dosing may be used to control daytime seizures. These typically come in the form of standard release forms, because extended-release medications may outlast the sleep period. Clinicians may need to use multiple medications if patients fail monotherapy trials. Patients with ADNFLE are more likely to respond to lamotrigine or carbamazepine, whereas patients with benign childhood epilepsy with centrotemporal spikes seem to respond well to carbamazepine or levetiracetam. Individuals with nocturnal occipital lobe seizures are also likely to respond to carbamazepine, and those with awakening primary generalized seizures respond well to valproate or topiramate.

Patients and families should be cautioned regarding the safety of the patients who have nocturnal seizures. Patients may have wandering as part of the postictal confusion; thus, safety guards and removal of potential hazards may be helpful. Additionally, patients’ families should be advised on first aid for seizures, a protocol for when to use emergent intranasal or rectal medication, and when to contact emergency services. More recently, circadian rhythm influence on pharmacokinetics has been suggested in a small study examining phenytoin. The circadian rhythm influences drug absorption, protein binding, distribution, clinical effect, and metabolism and excretion. Two studies suggest that epilepsy patients may have more favorable seizure control and less side effects with chronopharmacology two-thirds or greater of their traditional meditation (phenytoin or carbamazepine) given in the evening. Although these studies are preliminary, they do open an area of interaction of the circadian rhythm, pharmacokinetics, and brain response that may prove fruitful in the treatment of epilepsy.

PROGNOSIS

Most patients with nocturnal seizures or awakening epilepsy seem to respond to medication. This condition may be more refractive to therapy especially for those individuals with complex epilepsies, underlying neurologic deficits, and frontal lobe seizures. Attention to type and timing of medication may influence the outcome.

FUTURE DIRECTION

The complexity of the interaction of sleep and epilepsy demands further research dedicated to delineating the mechanisms of both sleep regulation and the development of epilepsy. Each type of epilepsy may have its own vulnerabilities and interaction with the sleep-wake regulatory processes. Further work is also needed to fully determine which patients are most likely to benefit to improvement in sleep and if improvement in sleep should be included in a package of therapies to prevent the development of intractable epilepsy.
Case report

A 24 year old male with a history of generalized tonic-clonic seizures, presumed from a primary generalized epilepsy, presents with an increase in seizures over the past two years. The patient noted that although his seizures were previously controlled with valproate, and now were averaging one to three seizures per week. The patient noted most of his seizures occurred in morning, but rarely during the night. In recounting the evolution of his seizures, the patient noted after he finished college, he gained approximately 40 lbs. He also noted that he was more tired during the day and he suffered from morning headaches. Upon questioning his family complained about his snoring, but no one witnessed apneas. His Epworth Sleepiness Scale total score was 9 and his STOPBANG score was 5. Physical exam showed a mild elevated heart rate of 84 bpm, blood pressure of 123/82 mm Hg, BMI 32, clear oral pharynx and trace pretibial edema. The patient underwent overnight polysomnography which showed an apnea hypopnea index of 15.6 events per hour with desaturation to 85%. The patient had frequent generalized spike and wave discharges, especially with arousals.

The patient subsequently completed a positive airway pressure titration showing resolution of the obstruction at 10 cm H2O. The patient started CPAP and within the first week noted resolution of the morning seizures. At his 1 month follow-up clinic visit, the patient had an Epworth Sleepiness Scale total score of 8, and only one recurrent seizure after he fell asleep without the CPAP. The patient was counseled about weight control, diet and exercise. One year later, the patient was converted from valproate to lamotrigine, and subsequently had 25 lb weight loss. A repeat sleep study showed an apnea hypopnea index of 6.8 and the patient elected to continue the CPAP therapy.

This case demonstrates that sleep may impact epilepsy. For this patient recurrent seizures were the chief complaint but further investigation revealed the underlying provocative factor was the sleep apnea. The associated symptoms of sleepiness, morning headache and weight gain are important clues. The patient’s Epworth Sleepiness Scale total score was below the typical threshold of 10 for sleepiness but the STOPBANG score of 5 is very suggestive of sleep apnea. Although most patients will have some symptoms of sleep apnea, the clinician should be cognizant that these patients may not have typical features of sleep apnea. For this patient the weight gain was most likely a combination of medication effect, valproate, and lifestyle. The clinician needs to be aware that medications to treat seizures can improve sleep by decreasing nighttime seizure activity, but also may interfere directly or as in this case indirectly. The case also demonstrates that the treatment of the sleep disorder can improve the epilepsy and sleep symptoms. These patients can tolerate CPAP but close follow up to ensure compliance is key.

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