Neurotherapeutics (2021) 18:170–180
https://doi.org/10.1007/s13311-021-01021-w

REVIEW

Sleep and Epilepsy: a Focused Review of Pathophysiology, Clinical Syndromes, Co-morbidities, and Therapy

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Accepted: 28 JMarchanuary 2021 / Published online: 30 March 2021

Abstract

A healthy brain requires balancing of waking and sleeping states. The normal changes in waking and sleeping states result in neurophysiological conditions that either increase or decrease the tendency of seizures and interictal discharges to occur. This article reviews the manifold and complex relationships between sleep and epilepsy and discusses treatment of the sleep-related epilepsies. Several forms of epilepsy predominantly or exclusively manifest during sleep and seizures tend to arise especially from light NREM sleep. Diagnostic interictal epileptiform discharges on the electroencephalogram are also most likely to be activated during deep NREM sleep stage N3. Epileptiform discharges and antiepileptic medications may in turn detrimentally impact sleep. Co-morbid sleep disorders also have the potential to worsen seizure control. Sleep has an important key association with sudden unexpected death in epilepsy (SUDEP). Further research is necessary to understand the complex relationships between sleep and epileptic disorders and their treatments.

The systematic study of sleep and epilepsy is a relatively young discipline. A number of interactions between the two have become apparent, and these are bidirectional. Appropriately, the first description of sleep apnea came from the eminent French epileptologist Henri Gastaut in 1965 [1]. Sleep disruption of any kind, including sleep disorders, can worsen epileptic seizures and contribute to the burden of epilepsy.

Sleep stages have an impact on the activation and manifestations of seizures, including both the type of seizures and the likelihood of seizures occurring. It has also become clear that there is a strong association between the sleep state and risk of SUDEP.

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Seizure-related effects on sleep include interruption of sleep by ictal events and interictal epileptiform discharges. Some anti-seizure medications also influence sleep structure independently of their effects on seizures. In this article, we will explore the relationship between seizures and sleep, including the effect of therapies for seizures upon sleep.

Epidemiology

Simply recording sleep during an EEG will increase the likelihood of detecting epileptiform activity, and recording of overnight sleep improves the yield of interictal epileptiform discharges compared with routine daytime EEGs [2].

The specific effects of temporal lobe seizures on sleep structure were examined in patients undergoing video-EEG monitoring [3]. When patients with temporal lobe epilepsy were compared under baseline conditions (seizure free) vs. after daytime complex partial or secondarily generalized seizures, there was a significant decrease in REM sleep the following night, without significant changes in sleep efficiency or in other sleep stages. When seizures occurred at night, the subsequent decrease in REM sleep was more pronounced than sleep subsequent to preceding daytime seizures, and there were also increases in stage 1 sleep and decreases in sleep efficiency following nighttime seizures [3]. A case report of a patient with generalized convulsive

epilepsy but no other neurological conditions revealed decreased REM and N3 sleep for 4 nights following status epilepticus [4].

Pure sleep epilepsies may represent 3–45% of epilepsies, depending on how such epilepsies are defined. Seizures arising either exclusively from sleep, or at least 90% from sleep occur in between 7.5 and 45% of patients with epilepsy [5]. Such seizures are nearly 80% focal onset. The risk of seizures while awake is present even in "pure sleep epilepsies" and is 13% within 6 years and 30.9% within 10 years [6]. Predictors of break-through seizures during the day include withdrawal of therapy, polytherapy, and high seizure burden [7].

When a first seizure arises from sleep, there is a higher risk for recurrence within the first 2 years of follow-up, conferring a similar increased risk as if the patient had previous symptomatic brain pathology on imaging or an epileptiform abnormality on EEG [8]. Such patients may merit consideration of anti-seizure medication even following a first seizure given their higher risk for recurrence [9, 10].

Pathophysiology

Human sleep in adults occurs in cycles that last an average of 90–100 min each, although sleep cycles in infants and children are usually shorter at approximately 60 min. In the first third of the night, slow-wave sleep (N3) preferentially occurs, rather than REM sleep, but as the night progresses, the contribution of REM sleep increases [11]. Sleep cycles are characterized by an evolution from Non-Rapid Eye Movement (NREM) sleep N1, N2, and N3, with progressive sleep depth manifested by increasing amounts of slow-wave activity, followed by REM sleep, which is characterized by faster and desynchronized activity similar to wakefulness.

Healthy young adults spend nearly 7.5 h sleeping and 80% of this time is spent in NREM sleep, while 20% represents REM sleep. N3 (slow-wave) sleep accounts for about 20% of the total sleep time in this age group. With aging, sleep becomes more unstable, with reduced sleep efficiency (the amount of sleep time for the total time in bed), and by increased microarousals. The amount of N3 and REM gradually decrease, with commensurate increases in NREM stages N1 and N2 [12].

The main promoters of wakefulness are the cholinergic pedunculopontine and laterodorosal tegmental nuclei; the noradrenergic locus coeruleus, the serotoninergic raphe nuclei, the histaminergic tuberomammillary nucleus, and the glutamatergic parabrachial nucleus. These regions project primarily to the lateral hypothalamus, thalamus (mainly intralaminar and reticular thalamic nuclei), basal forebrain, and cortex. The basal forebrain also supports arousal along with the posterior half of the lateral hypothalamus, where the orexin neurons are located. The main NREM sleep-promoting region is the ventrolateral preoptic nucleus (VLPO) in the anterior hypothalamus, which contains the inhibitory neurotransmitters GABA and galanin, and the VLPO maintains mutually inhibitory connections with most of the mesopontine nuclei related to arousal [13]. This process allows rapid transitions between these behavioral states. Analogous to wakefulness and sleep transition, mutual inhibitory activity also promotes transition between NREM and REM sleep stages. The pontine brainstem network structures necessary for activating REM sleep (i.e., so called "REM-on" region) includes the excitatory glutamatergic subcoeruleus neurons and the cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei, which reciprocally inhibit the GABAergic neurons located in the ventrolateral periaqueductal gray matter and the adjacent lateral pontine tegmentum (i.e., reciprocal inhibition with the REM-off neurons) that instead promote NREM sleep [13].

Sleep appears to play an important role in synaptic plasticity. Awake learning leads to increased synaptic strength, which is associated with higher energy consumption, greater demand for synaptic substrates, and loss of selectivity of neuronal responses (strengthened synapses have broader responses to external stimuli). Over the course of the day, this leads to cellular stress and reduced signal-to-noise ratio, which impairs our ability to learn. During sleep, there appears to be a process of renormalization of synaptic strength, with global down-scaling (or down-selection) of synaptic connections that are less critical or important for reduction and elimination, while critical synapses are maintained and further stengthened. Synapses related to new stimuli or processes that are learned during the day will remain more active during slow-wave sleep, while others remain less active. It is controversial whether there is synaptic potentiation or relative potentiation of memory-specific synapses in the setting of global down-scaling, but the overall process contributes to sleep-dependent memory consolidation and synaptic homeostasis [14]. Because synaptic strength correlates with cortical excitability, cortical excitability increases with wakefulness and reduces after sleep [15]. Importantly, both seizures and interictal spikes during wakefulness promote synaptic potentiation, which may undergo the same processes of sleep-dependent memory consolidation. It appears that patients with focal epilepsy have altered sleep homeostasis associated with cognitive impairments [16], and that pathologic neural processes may utilize physiologic mechanisms of synaptic plasticity to further strengthen epileptogenic networks [17].

Sleep impacts seizures and interictal epileptiform activity in a number of ways. For many years it has been recognized that interictal epileptiform discharges may be activated only during sleep, increasing the diagnostic

yield of electroencephalography [18], and sleep deprivation has been shown to activate interictal epileptiform discharges independent of sleep duration or depth (Fig. 1) [19]. Interictal epileptiform discharges are activated maximally during slow-wave sleep, but decreased during rapid eye movement sleep [20].

NREM sleep is characterized by hypersynchronization of thalamocortical pathways. N3 (slow wave) sleep leads to activation of interictal epileptiform discharges, high frequency oscillations including ripples (80–250 Hz) and fast ripples (250–1000 Hz). NREM state-dependence for cortical "up" and "down" states is related to the integrating influence of cortically generated infraslow cortical oscillations, which are closely associated with paroxysmal events during NREM sleep such as interictal spiking, as well as the physiogical elements of NREM sleep architecture such as spindles and K complexes [21]. Interictal epileptiform discharges and high frequency oscillations are particularly frequent during the transitions between "up" and "down" cortical states in relation to infraslow oscillations [22]. REM sleep appears to be inhibitory to interictal discharges and seizures [2, 23, 24]. Though rare during REM sleep, epileptiform discharges when present during REM sleep tend to have better localizing characteristics as compared with those occurring during NREM sleep [20]. REM sleep is protective against seizures compared with the wake state [24].

Epileptic seizures appear to appropriate the processes of synaptic homeostasis and memory consolidation during N3 sleep, strengthening epileptogenic networks in refractory focal epilepsies [25]. In contrast, nocturnal seizures have been associated with deterioration of visual memory performance, suggesting sleep-related seizures may adversely impact sleep-dependent memory consolidation [26].

Interictal spikes are most frequent in N3 sleep but sleep-related seizures most frequently arise instead from N1 or N2 NREM sleep stages [6, 27]. Extratemporal seizures, especially frontal lobe seizures, are more likely to begin during sleep than are temporal lobe seizures [6, 28]. On average about one-third of focal seizures begin in sleep, and focal seizures (particularly temporal onset) are more likely to become bilateral tonic-clonic seizures than during wakefulness [6, 27].

Sleep deprivation has been thought to increase seizure frequency, but formal studies of the influence of sleep deprivation on seizure occurrence have revealed conflicting results, with some studies showing a lack of effect in epilepsy monitoring [29], whereas co-morbid sleep disorders which worsen sleep duration or quality such as chronic insomnia and sleep apnea have generally been associated with worsened seizure frequency [30].

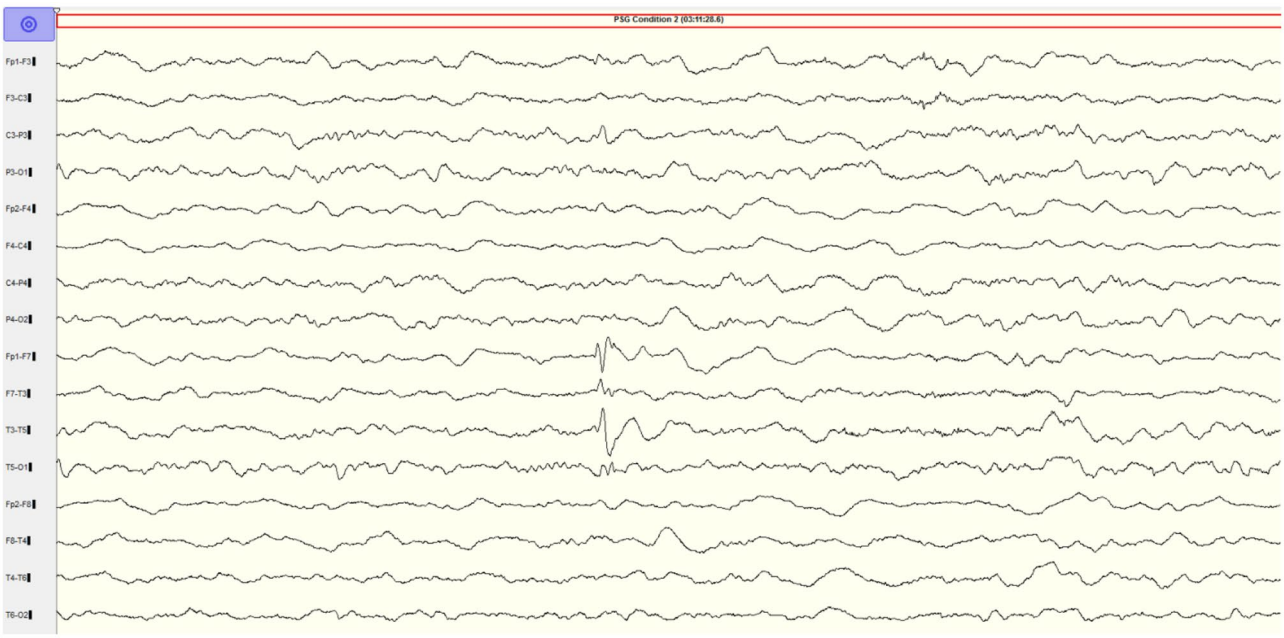

Fig. 1 Focal spike during N3 sleep in a patient with focal left temporal lobe epilepsy. The figure demonstrates an interictal epileptiform (spike and slow wave) discharge activated during the sleep electroencephalogram during N3 (slow wave) sleep, the stage which is most facilitatory for epileptiform activity. A spike-wave discharge with phase reversal is seen, indicating maximal electronegativity at the F7 electrode, which corresponds to the left anterior temporal region. Example shown is a 10-s screen, with sensitivity 7 uv/mm, HFF = 70 Hz, LFF = 0.3 Hz; longitudinal bipolar montage

Clinical Syndromes

In this section, we will discuss several common sleep-related epilepsies, including sleep-related focal extratemporal epilepsy (including the specific entity of sleep-related hypermotor epilepsy, also known as SHE); benign epilepsy of childhood with centrotemporal spikes (BECTS, also known as benign rolandic epilepsy); the epileptic encephalopathies (i.e., Lennox-Gastaut or Landau Kleffner syndromes, or Epileptic Encephalopathy with Continuous Spike-and-Wave during Sleep); and the arousal epilepsies in which generalized seizures are most frequent following awakening in the morning or following periods of sleep, of which the most common prototype is juvenile myoclonic epilepsy.

Of the sleep-related focal epilepsies, the extratemporal epilepsies (and especially frontal lobe epilepsies) are commonly primarily or exclusively nocturnal and may exhibit complex behaviors that are unwitnessed. Along with other nocturnal seizures, these are more frequent in NREM sleep than in REM sleep [31, 32] Some of these seizure-related behaviors may even substantially disturb sleep architecture and result in consequences of daytime somnolence, which may be improved by effective seizure treatment [31]. Another characteristic of frontal lobe seizures is that clear epileptiform activity is often not seen on routine EEG, potentially adding to the diagnostic challenge [33].

Sleep-related hypermotor (SHE) epilepsy is a distinctive type of sleep-related focal extratemporal epilepsy and was previously classified as nocturnal frontal lobe epilepsy [34–36]. Seizures are characterized by abrupt motor behaviors of variable complexity during sleep. Diagnosing such patients is problematic because the EEG findings may be difficult to identify because of movement and muscle artifact. Some patients have a genetic basis for SHE. Mutations can be inherited or spontaneous but inherited forms are still a minority of cases [37]. The most commonly identified pathology is focal cortical dysplasia [38].

Most sleep-related epilepsy syndromes develop in adolescence or childhood. Landau-Kleffner syndrome usually develops between ages 2 and 8 years and is associated with acquired aphasia and a characteristic EEG pattern of seizures primarily during sleep. Landau-Kleffner has an EEG pattern of bilateral posterior temporal spike and wave discharges that are activated in N3 sleep [39]. The characteristic language deficit might develop as a result

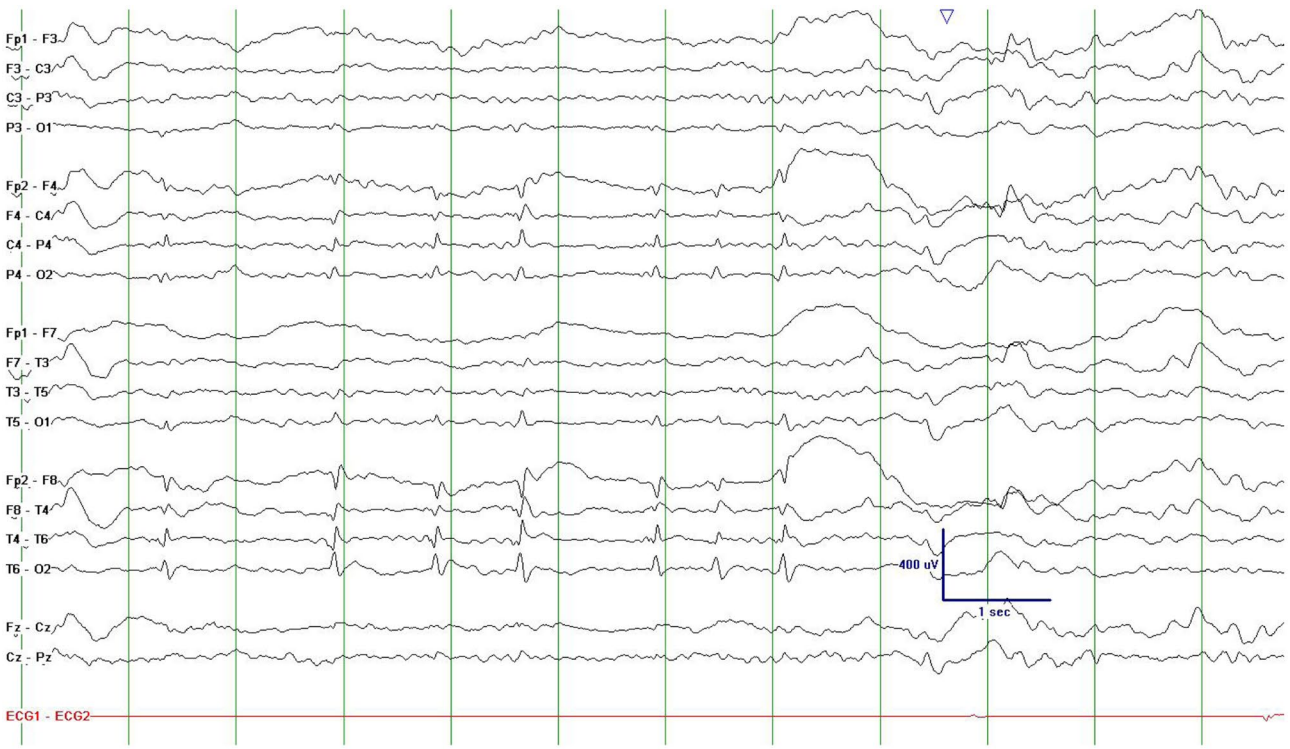

Fig. 2 Sleep activation of focal interictal epileptiform activity in a child with benign centrotemporal epilepsy. A train of repetitive focal interictal epileptiform activity in the form of centro-temporal spike discharges is seen in the example below during N2 sleep. Example shown is a 10-s screen, with sensitivity 15 uv/mm, HFF = 70 Hz, LFF = 0.3 Hz; longitudinal bipolar montage.

of abnormal metabolism from the enduring epileptiform discharges [40].

The EEG pattern of Benign Childhood of Epilepsy with Centrotemporal Spikes (aka Benign Rolandic Epilepsy) features characteristic centrotemporal spikes, as shown in the example in Fig. 2 below [42]. Clinically, patients present with seizures during sleep with hemiconvulsive seizures. Seizures usually occur immediately following an awakening from sleep. Electrical status epilepticus of sleep shows nearly continuous epileptiform activity in the ictal-interictal continuum throughout non-REM sleep, which subside during REM sleep and wakefulness. Seizures commonly resolve in adolescence. This may be seen in children with Landau-Kleffner syndrome and benign childhood epilepsy with centrotemporal spikes [43].

Seizures that occur shortly after awakening, typically either myoclonic or bilateral tonic clonic seizures are characteristic of juvenile myoclonic epilepsy (JME). The EEG pattern includes generalized atypical spike-wave discharges (bilateral multiple spike and wave or poly spike and wave discharges); a typical example of sleep activation of generalized interictal epileptiform activity as seen in JME is shown in Fig. 3 [41]. It is not uncommon that subtle myoclonus, especially in the morning, is mistaken for simple clumsiness for many years before the true diagnosis is recognized.

Approach to the Diagnosis of Sleep-Related Epilepsies

The approach to diagnosing the sleep-related epilepsies is similar to that of diurnal epilepsies and begins with a comprehensive history and examination. Next, interictal electroencephalography (EEG) and brain magnetic resonance image (MRI) are necessary to aid determination of the electroclinical syndrome [44, 45]. Interictal EEG has a variable yield in sleep-related epilepsies, having a relatively high diagnostic yield of 70–90% in benign epilepsy of childhood with centrotemporal spikes, to a relatively lower yield (i.e., estimated 25–56% overall) in other sleep-related focal epilepsy syndromes [46, 47]. Video-EEG monitoring and/or video-EEG polysomnography may also be necessary for confirming the diagnosis if it remains uncertain what type of nocturnal events the patient is having.

The Differential Diagnosis of Nocturnal Events

Other nocturnal events may mimic the sleep-related epilepsies and are discussed elsewhere in this issue of Neurotherapeutics (see reviews on NREM parasomnias and REM sleep behavior disorder; Table 1). Distinguishing sleep-related epilepsies and post-ictal state from parasomnias can be difficult

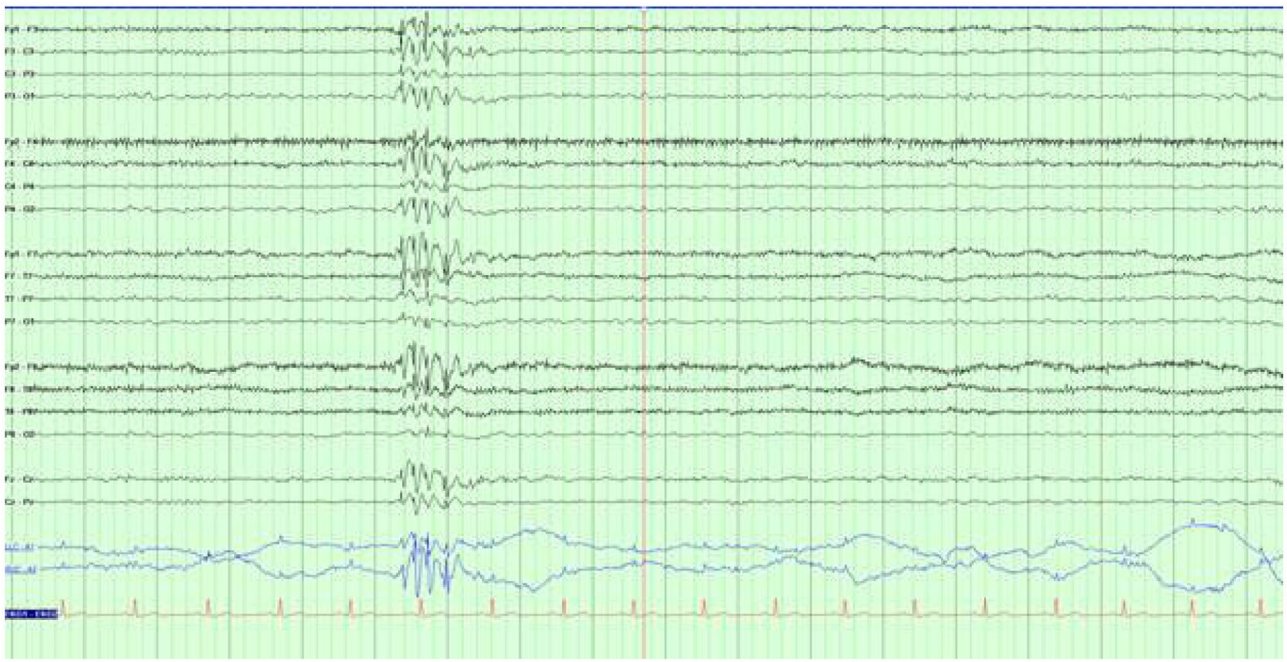

Fig. 3 Sleep electroencephalogram showing activation of generalized epileptiform activity. Generalized spike and wave discharges typical of juvenile myoclonic epilepsy (JME) are shown in the sixth second. Example shown is a 20-s screen, with sensitivity 15 uv/mm, HFF = 70 Hz, LFF = 0.3 Hz; longitudinal bipolar montage

Table 1 Differential diagnosis and common clinical features between sleep-related epilepsies and other nocturnal events

Nocturnal event	Aura/ Preceding symptoms	Major clinical features	Temporal duration	Frequency of events	Electrographic manifestations
Sleep-related epileptic seizure	Variable	Stereotyped between episodes, variable hypermotor movements, tonic posturing, or rhythmic clonic movements depending on seizure type/lobe of origin	Seconds to 1–2 min	Variable, from multiple seizures per night to sporadic (i.e., few per month or year)	Variable, rhythmic ictal pattern with or without muscle/movement artifact obscuration; (Extratemporal seizures often show no clear reliable or discernable ictal EEG change relative to artifact)
Disorder of arousal (NREM parasomnia)	Absent	Typically somnambulism (sleep walking), sleep terrors, confusional arousals from N3/N2	Minutes	1 or fewer per night, rarely multiple nightly	Arousal from N3 or N2 sleep during polysomnography/sleep EEG
REM sleep behavior disorder	Absent	Complex vocal and motor behaviors, often violent dream enactment	Minutes	Several attacks per night or week	REM sleep without atonia during polysomnography
Rhythmic movement disorder	Absent	Repetitive rhythmic movements such as head banging or body rocking	Several minutes	Every night	Rhythmic artifact corresponding directly to movements
Psychogenic non-epileptic spells	Variable	Variable and atypical movements lacking stereotypy	Several minutes	Highly variable, often multiple times per night or week	Spells solely during recorded wakefulness or following an arousal from sleep

NREM non-rapid eye movement sleep, *N2* Stage 2 NREM sleep, *N3* Stage 3 NREM sleep, *REM* rapid eye movement sleep, *EEG* electroencephalogram

in certain cases, since clinical features may be highly similar, such as arousal from sleep, confusion and amnestic behavior, excessive motor behaviors, and ambulation. The patient may have no memory of the events, so diagnosis is based on the limited observations of others. A diagnosis of sleep-related epilepsy is favored when clinical features of stereotypy, a high frequency within a single night, ensuing confusion or other postictal features of tongue biting, incontinence, or Todd's paralysis or language disturbance follow episodes, or accompanying ictal EEG abnormalities are present. NREM parasomnias are usually less frequent and often have even more prolonged confusion than in focal seizures, and REM parasomnias typically involve behaviors involving complex motor acts of dream enactment or recall of preceding dreams. The timing of frequent episodes can also be a clue, with non-REM parasomnias tending to occur early in the night, REM parasomnias more toward early morning, and epilepsy seizures more random in distribution.

Sleep-related focal epilepsies, especially those involving hypermotor seizures, arise predominantly from light NREM sleep [48] and often are frequent with recurrence several times within a single night and involve highly stereotyped complex motor behaviors that may begin either during childhood or as an adult [48]. NREM parasomnias are considered to be disorders of arousal and typically may occur during the first half of the night (and especially during the first one third of a night) since they arise most often from N3 (slow wave) sleep, and these events can be associated with triggering factors such as sleep deprivation, environmental noise, or sleep disorders that trigger arousals like apneas or hypopneas during sleep. Like seizures, NREM parasomnias most often have prominent amnesia. NREM parasomnias begin especially in childhood or adolescence and tend to decrease in frequency or resolve entirely during early adulthood. REM parasomnias less often are confused with seizures and include nightmare disorder, isolated sleep paralysis, and REM sleep behavior disorder. Of these, REM sleep behavior disorder has the most potential to emulate sleep-related seizures given features of complex vocal or motor behaviors, but these events tend to instead occur in the second half of the night when REM sleep episodes are most frequent and may involve features of dream enactment or recall in contrast to sleep-related seizures [44, 49].

One clinical tool that may be considered to help in distinguishing sleep-related hypermotor epilepsy from NREM parasomnias is the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale [49]. The FLEP scale aids especially in distinguishing between possible NREM parasomnias and sleep-related hypermotor focal seizures, but its ability to distinguish seizures from REM sleep behavior disorder appears to be limited. The FLEP scale may be best considered as a screening tool for triage to additional confirmatory evaluation with video-EEG polysomnography, rather than making a definitive diagnosis per se [50].

Sleep Co-morbidities in Epilepsy

The most common sleep disturbances in people with epilepsy are excessive daytime sleepiness, insomnia, and sleep disordered breathing [30, 51–54]. Sleepiness in people with epilepsy can be variously associated with one or more factors such as nocturnal seizures, antiepileptic drugs causing sedation, inadequate sleep hygiene and insufficient sleep, or co-morbid sleep disorders [51].

Either daytime seizures, night time seizures, or both can negatively impact sleep architecture and quality, causing reduced sleep efficiency, increase in REM latency, and reduced NREM and REM sleep continuity and percentages [3]. Seizures can cause sleepiness, as shown with evidence for objective sleepiness following seizures by modified maintenance of wakefulness tests [3]. Several antiepileptic drugs such as phenobarbital, benzodiazepines, and phenytoin can increase light NREM sleep and reduce REM and N3 (slow wave) sleep, and these shifts from deeper to lighter sleep stages mediated by antiepileptic medications may reduce the quality and restorative nature of sleep. In addition to the deleterious influences of seizures and antiepileptic therapies, co-morbid sleep disorders are actually likely the primary driver causing symptoms of sleepiness and sleep disturbance in people with epilepsy [51], and clinicians should screen for possible primary sleep disorders in patients with sleep-related epilepsy, and in patients with refractory seizure disorders. The most frequent sleep co-morbidity in refractory epilepsy patients is obstructive sleep apnea (OSA). One study examined 50 epilepsy patients who were referred for polysomnography, and 54% had OSA while 32% had periodic leg movements of sleep [51]. In another study of 63 epilepsy patients who underwent polysomnography, 71% had OSA, while narcolepsy, insufficient sleep syndrome, and nocturnal seizures were also identified [55].

When there is a high pretest probability for moderate severity OSA by screening measures, referral for polysomnography or home sleep apnea testing should be considered [51, 52, 55]. OSA appears to worsen seizure frequency and possibly seizure type and severity, probably due to sleep fragmentation and hypoxemia, and nasal continuous positive airway pressure (CPAP) therapy has been shown to be associated with improved seizure frequency, as well as typical improvements in daytime alertness and quality of life [52, 54]. Further details on treatment of OSA in general populations are found in the separate article in this issue of Neurotherapeutics by Raphelson and colleagues entitled, "Positive Airway Pressure in Sleep Disordered Breathing."

Restless legs syndrome (RLS) is characterized by an urge to move the legs, or sometimes an urge to move that is felt concomitantly or even solely in the arms or in other body regions that is predominant in the evening hours, and is relieved by

getting up to walk or leg movement. RLS may also have deleterious impact on sleep quality in people with epilepsy. There is overlap in the treatment options for RLS and epilepsy, as gabapentin, pregabalin, and benzodiazepnes may provide efficacy both for focal seizures and relief of RLS symptoms. Other RLS treatments include iron replacement when indicated in patients with reduced or even low normal body iron stores, or dopamine agonists including pramipexole, ropinirole, or rotigotine. For further details on RLS and its treatment, please see the comprehensive review by Gossard and colleagues entitled, "Restless legs syndrome: contemporary diagnosis and management" in this Neurotherapeutics issue.

Chronic insomnia is also frequent in epilepsy patients, involving around 50% of patients in some studies. The first-line treatment option for patients with chronic insomnia in current practice is cognitive behavioral therapy, which involves an integrative approach of counseling and education targeting improvement of behaviors that serve to reinforce insomnia (i.e., adhering to a regular sleep schedule including bedtime and time of awakening, restriction of the overall time in bed, and stimulus control measures such as avoidance of clock watching and getting up to leave the bedroom when sleepless), which is also enhanced by instruction in relaxation measures (i.e., progressive muscle relaxation, deep breathing) and mindfulness approaches including reduction in negative thoughts about sleep. For further details on the management of insomnia in general, see the reviews in this issue of Neurotherapeutics by Wing entitled, "Non-pharmacological approaches for management of insomnia" and also "Pharmacological management of insomnia" by Kolla and colleagues. Medication intervention trials of hypnotic agents specifically in epilepsy populations have been limited. There has been some small-scale clinical trials of melatonin suggesting it may benefit sleep quality in children and adolescents with epilepsy, but further definitive large-scale trials are needed to confirm the efficacy and safety of melatonin treatment in people with epilepsy [56–58]. A potential concern with melatonin is the need to monitor for severe daytime sedation in patients having a rare SNP of CYP1A2 leading to slow melatonin metabolism, which may occur in some children or adolescents with autism spectrum disorder, which may often overlap with epilepsy in those with neurodevelopmental disorders [59, 60].

Sleep and Risk of Sudden Unexpected Death in Epilepsy

Sudden unexpected death in epilepsy (SUDEP) is defined as a non-traumatic, non-drowning, unexpected (witnessed or unwitnessed) death, occurring in an otherwise healthy person with epilepsy. When witnessed, SUDEP deaths have been most often preceded by a bilateral (i.e., generalized) tonic-clonic seizure. SUDEP has an incidence of approximately 1 per 1000 person years, but is more frequent in refractory epilepsy populations in which SUDEP is approximately 1% per year.

SUDEP occurs most frequently between the ages of 15 to 40 years. The causes and mechanisms that underlie SUDEP remain poorly understood. Risk factors for SUDEP include long duration of seizures, male sex, refractory epilepsy with frequent seizures (especially bilateral (aka generalized) tonic-clonic seizures), antiepileptic medication polytherapy, developmental delay, brain lesions, and non-adherence to medications. Near-SUDEP events that have been witnessed and recorded in inpatient epilepsy monitoring units demonstrated that post-convulsive post-ictal central apneas, especially when associated with generalized EEG suppression following seizures, may be a biomarker for SUDEP risk [61, 62].

Between 40 and 60% of SUDEP deaths are sleep-related, which is disproportionately elevated when one considers that sleep is only about one-third of the day. Which mechanisms underlie the association between sleep and SUDEP are unknown [63]. Prone position is another factor associated with SUDEP. One possibility remaining to be explored is a recently identified association between SUDEP risk (as indexed by the SUDEP-7 profiling tool) and OSA, but further prospective research is necessary to determine whether OSA may be a SUDEP risk factor [64].

Therapeutics for Sleep-Related Epilepsies

The overall therapeutic approach for sleep-related epilepsy is similar to that for the diurnal epilepsies. The initial management for sleep-related epilepsies is selection of antiepileptic drug therapy appropriate for the electroclinical epilepsy syndrome (i.e., most drugs may be efficacious for a focal syndrome, and a "broad spectrum" therapy such as levetiracetam, lamotrigine, topiramate, or valproic acid for a generalized epilepsy syndrome). Determinants of antiepileptic drug selection include individual patient characteristics (i.e., age, sex, race) co-morbidities such as pain/migraine/mood disorders, and co-medications (i.e., oral contraceptives, anticoagulants). Oftentimes, when sleep quality is poor or there are co-morbid insomnias, individualizing the selection of an antiepileptic drug toward a medication that may promote or enhance sleep is desirable, although this practice has not been studied extensively previously.

Several antiepileptic drugs have been shown to improve measures of sleep efficiency and/or shorten sleep latency in healthy volunteers and epilepsy patients, including gabapentin, tiagabine, pregabalin, clobazam, and carbamazepine [65]. Certain antiseizure medications may aggravate daytime sleepiness, especially

high-dose levetiracetam, phenobarbital, and valproate, although nearly all antiepileptic drugs may cause somnolence at high doses. Non-pharmacological treatments may improve alertness, including vagus nerve stimulation, although conversely VNS may also cause sleep apnea and sleep-related stridor, and thereby potentially worsen sleepiness at higher output currents, whereas stimulation parameter adjustment may obviate or improve these adverse effects of VNS [66–68]. The ketogenic diet has been found to improve N3 sleep [69]. Successful epilepsy surgery has also been shown to improve daytime sleepiness and objective nocturnal sleep measures in post-operative follow-up polysomnography [70]. Clinical trials of specific antiepileptic drug therapies aimed at improving sleep quality have been rare. One randomized, double-blind, placebo-controlled crossover trial analyzed sleep and cognitive outcomes of patients with focal epilepsy with co-morbid insomnia treated with adjunctive pregabalin 150 mg BID (an alpha-2-delta ligand receptor agonist medication which promotes N3 sleep and decreases arousal) or placebo for two weeks, followed by washout and crossover to the opposite treatment for 2 weeks, and found evidence for improved sleep depth (increased N3 and decreased N1, i.e., enriched slow wave sleep and diminished transitional/shallow sleep), as well as improved attention on test 1 of the Rey-Auditory Verbal Learning Test following pregablin treatment [71]. Another study analyzed the impact of levetiracetam 1000 mg/day vs. carbamazepine controlled release 400 mg/day on polysomnographic measures of sleep efficiency and architecture and found that levetiracetam therapy improved sleep efficiency while carbamazepine controlled release improved slow wave sleep percentage [72]. Future research analyzing the impact of antiepileptic drug interventions on subjective and objective sleep measures is a significant need in the field.

When diagnosis of sleep-related seizure vs. parasomnia still remains uncertain, clonazepam is sometimes a reasonable initial empiric choice, since it possesses efficacy for both types of nocturnal events. In the case of sleep-related hypermotor epilepsies, sodium channel blocking antiepileptic drugs such as carbamazepine, oxcarbazepine, lacosamide, topiramate, or lamotrigine are likely to be the best therapeutic choices [73].

In patients who have refractory sleep-related focal epilepsies, non-pharmacological therapies should be considered, including epilepsy surgery, neurostimulation, or sometimes dietary therapies. Resection surgery outcomes for sleep-related epilepsies are similar to those of other focal epilepsies involving waking seizures.

Conclusions

Epilepsy and sleep have a reciprocal relationship, in that some epilepsy syndromes have an intimate relationship with the state of sleep, while seizures and antiepileptic therapies can also worsen sleep. Interictal epileptiform activity is particularly activated during the state of N3 sleep, and light NREM sleep activates, while REM sleep tends to diminish seizure and interictal epileptiform discharge occurrence. Mimickers of sleep-related epilepsy include other nocturnal events such as sleep-related movement disorders and parasomnias during either NREM or REM sleep. Sleep disorders are frequent co-morbidities in people with epilepsy, especially obstructive sleep apnea, but restless legs syndrome, chronic insomnia, and certain parasomnias are also more frequent in epilepsy patients. Clinicians should evaluate all epilepsy patients for sleep co-morbidities, referring patients for polysomnography in patients who are sleepy. Early recognition of co-morbid sleep disorders can help in improving seizure burden, quality of life and functioning of epilepsy patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-021-01021-w.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Funding This publication was supported by NIH/NCRR/NCATS CCaTS Grant Number UL1 TR002377 and NIH/NIA R34AG056639.

Declarations

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