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Sleep and Epilepsy

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Sleep and epilepsy have a complex interrelationship that is influenced by various factors, including the distinct stages of sleep. Non-rapid eye movement sleep promotes epileptic activity, while rapid eye movement sleep suppresses it. Seizures can be triggered by sleep, while sleep deprivation increases seizure susceptibility. Epilepsy disrupts sleep architecture and quality, leading to sleep disturbances and comorbidities, like sleep apnea and restless legs syndrome. Excessive daytime sleepiness and fatigue can result from epilepsy and the sedating effects of antiseizure medications. Sleep-related epilepsy exhibits seizures predominantly during sleep, with specific patterns related to sleep stages. Antiseizure medications can directly impact sleep quality and should be carefully considered when treating epilepsy patients with comorbid sleep disorders. Understanding the bidirectional relationship between sleep and epilepsy is crucial for effective management. Optimizing treatment strategies requires recognizing the effects of antiseizure medications on sleep, and addressing sleep-related issues in individuals with epilepsy.
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Keywords Sleep; Epilepsy; Effects; Antiseizure medication; Bidirectional relationship.

INTRODUCTION

The interrelationship between sleep and epilepsy is complex and involves various factors. Sleep consists of two main stages: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, each with distinct neuroanatomical, neurophysiological, and neurochemical characteristics. These stages can modulate the activation and inhibition of epileptic activity in the brain. Conversely, epileptic activity can also influence brain functions that impact the structure of sleep [1,2].

Sleep significantly influences epilepsy, with NREM sleep promoting epileptic activity and REM sleep suppressing it [3]. Sleep can trigger seizures, and sleep deprivation increases seizure susceptibility by enhancing cortical excitability and reducing seizure threshold. Epilepsy can disrupt sleep architecture and quality, leading to sleep disturbances and comorbidities, such as sleep apnea and restless legs syndrome (RLS). It also contributes to excessive daytime sleepiness and fatigue, which can be compounded by the sedating effects of antiseizure medications.

Antiseizure medications can have positive effects on sleep by controlling seizures, but they can also directly impact sleep quality and daytime drowsiness [4]. A literature review identified specific medications that improve or worsen sleep in epilepsy patients, with considerations for comorbid sleep disorders. Certain medications may worsen conditions like sleep apnea or be beneficial for sleep-related disorders like RLS, emphasizing the need for individualized treatment decisions [5].

Overall, understanding the relationship between sleep and epilepsy is crucial for the effective management of epilepsy. Considering the effects of antiseizure medications on sleep and recognizing the impact of sleep disorders, such as sleep deprivation and sleep apnea, on seizure control can help optimize treatment strategies for individuals with epilepsy. Therefore, this review aims to investigate the bidirectional relationship between sleep and epilepsy, as well as the impact of antiseizure medications on sleep.

THE INFLUENCE OF SLEEP AND CIRCADIAN RHYTHMS ON EPILEPTIC ACTIVITY

Sleep plays a notable role in epilepsy, where NREM sleep promotes epileptic activity, while REM sleep suppresses it [3,6]. Epileptic discharges in focal epilepsy are frequently activated during NREM sleep, particularly during high-amplitude widespread slow waves, indicating a correlation between epileptic activity and periods of high synchronization [7,8]. Furthermore, the occurrence of interictal epileptiform discharges aligns with the patterns of spindle frequency activity observed during the night [9,10]. In contrast, research has demonstrated that REM sleep, both with (phasic) and without (tonic) rapid eye movements, has distinct inhibitory effects on interictal epileptic activity. The greatest suppressive impact occurs during phasic REM sleep, characterized by maximum electroencephalography (EEG) desynchronization [11,12]. The distinct properties of sleep, including the focal restriction of spikes during REM sleep and the widespread revealing of additional foci during NREM sleep, can be leveraged to improve the localization accuracy in pre-surgical epilepsy evaluation [6,13,14].

Sleep can also act as a trigger for seizures in some individuals with epilepsy. Certain epilepsy syndromes, such as nocturnal frontal lobe epilepsy and some forms of generalized epilepsy, exhibit a predisposition for seizures during sleep [15-17]. Sleep has a greater tendency to trigger seizures in frontal lobe epilepsy, compared to temporal lobe epilepsy. In temporal lobe seizures, it is common for the seizures to transition into secondary generalized seizures during sleep [18,19]. The reasons behind this sleep-related seizure provocation are not fully understood but may be related to alterations in the balance between excitatory and inhibitory neuronal activity during specific sleep stages or the influence of specific sleep-related factors, such as changes in body position or sleep-related breathing abnormalities [20,21].

Sleep deprivation can have a significant impact on seizure susceptibility. Sleep deprivation can lead to increased cortical excitability and a decrease in seizure threshold, making seizures more likely to occur [22,23]. Sleep deprivation is more likely to provoke seizures in certain types of epilepsy, such as generalized epilepsies, but its effectiveness in relation to focal epilepsies is limited, with some studies showing no clear association between insufficient sleep and seizure risk [17,24]. Furthermore, disrupted sleep patterns, such as irregular sleep−wake cycles or excessive daytime sleepiness, can also contribute to seizure occurrence and worsen seizure control [25,26].

Seizures in patients exhibit cyclic and circadian patterns, with sleep/wake periodicity playing a role, and the timing of seizures varies depending on the seizure type and location [2]. Seizure frequency in epilepsy exhibits distinct day/night patterns, with variations between patients with temporal lobe epilepsy and extratemporal lobe epilepsy, influenced by sleep/wake state and circadian rhythms depending on the location of the epileptogenic region [27]. Circadian rhythms, hormonal fluctuations, neuronal excitability, and physiological changes during sleep influence seizure occurrence, and may contribute to sudden unexpected death in epilepsy (SUDEP) risk [28]. Understanding and tracking the timing of seizures can improve patient safety and treatment strategies, and enhance their sense of self-control.

THE INFLUENCE OF EPILEPSY ON SLEEP

Epilepsy can have significant effects on sleep architecture and quality, leading to sleep disturbances and alterations in sleep patterns. The presence of seizures, as well as the underlying neurological and physiological changes associated with epilepsy, can disrupt normal sleep patterns and contribute to sleep-related issues [29,30].

Sleep-related comorbidities are also commonly observed in individuals with epilepsy. One of the most prevalent comorbidities is sleep apnea, characterized by recurrent episodes of partial or complete upper airway obstruction during sleep [31,32]. Sleep apnea is more prevalent in individuals with epilepsy compared to the general population, and it can exacerbate seizure frequency and severity [31,33]. Other sleep disorders, such as RLS and periodic limb movements during sleep, are also more commonly observed in individuals with epilepsy [34,35].

In addition to the direct impact on sleep architecture, epilepsy can also lead to excessive daytime sleepiness and fatigue [36-39]. Seizure activity and interictal epileptiform discharges can disrupt normal sleep architecture, resulting in poor sleep quality and insufficient rest [40]. This can lead to excessive daytime sleepiness, reduced alertness, and impaired cognitive function during wakefulness [41,42]. Sleep-related symptoms and daytime sleepiness may be further exacerbated by the side effects of antiseizure medications, which can have sedating properties [4].

SLEEP-RELATED EPILEPSY

Sleep-related epilepsy refers to a type of epilepsy where seizures are predominantly triggered or occur during sleep [43,44]. This condition represents a distinct subset of epilepsy syndromes and is characterized by a close relationship between seizure occurrence and sleep−wake cycles [45]. Seizures occurring exclusively at night account for approximately 12%−20% of all seizures [15-17]. Certain epilepsy syndromes show a strong correlation between seizures and sleep, with sleep playing a significant role in their clinical or EEG manifestations (Table 1).

There are several specific epilepsy syndromes that fall under the category of sleep-related epilepsy. One example is nocturnal frontal lobe epilepsy, which is characterized by seizures originating from the frontal lobes of the brain during sleep. These seizures often manifest as sudden, brief, and violent movements or behavior, and they typically occur during the transition from NREM sleep to wakefulness or during NREM sleep itself [46,47]. Another example is juvenile myoclonic epilepsy (JME), where seizures typically occur shortly after awakening, often during the transition from sleep to wakefulness [17,48]. Benign epilepsy with centrotemporal spikes (BECTS) primarily affects children and is characterized by seizures that mainly occur during sleep, particularly in the first part of the night or upon awakening. The seizures in BECTS are usually focal, involving the face, tongue, and sometimes the hand [49].

Although the underlying mechanisms of sleep-related epilepsy are not fully understood, several factors likely contribute to its development. One possible factor is the influence of sleep-related neuronal and physiological changes on seizure threshold and excitability [50]. During sleep, there are fluctuations in neurotransmitter levels, alterations in neuronal synchronization, and changes in cortical excitability, which can promote the occurrence of seizures in susceptible individuals [51,52]. Additionally, specific sleep stages, such as the transition from sleep to wakefulness or the presence of NREM sleep, may provide a permissive environment for seizure activity due to the balance between inhibitory and excitatory neuronal activity [53].

EFFECTS OF ANTISEIZURE MEDICATIONS ON SLEEP

Antiseizure medications can have a positive impact on the structure of sleep by effectively controlling seizures [5,54]. However, it is important to note that these drugs can also have other effects on sleep. Some antiseizure medications can cause daytime drowsiness, or directly affect sleep quality. The ideal antiseizure medication for sleep would not alter REM sleep, while improving sleep efficiency, overall duration, and deep sleep and reducing sleep latency and arousal.

A literature review conducted on the effects of 25 antiseizure medications on sleep in patients with epilepsy, with polysomnography and subjective measures being commonly used, found eslicarbazepine acetate, lacosamide, and perampanel to improve or have no effect on sleep, while clonazepam, felbamate, lamotrigine, oxcarbazepine, and phenobarbital worsened or had no effect on sleep. Valproic acid showed mixed results. Cannabidiol, car-

Table 1. Different categories of sleep-related epilepsies and their characteristics [45]*

Category	Epilepsy syndromes	Characteristics
Sleep-associated epilepsies	Sleep-related hypermotor epilepsy	Seizures manifest as complex motor behavior or sustained dystonic posturing; genetic, structural, or unknown etiology; unfavorable long-term prognosis
	Epilepsy with centrotemporal spikes	Seizures mainly occur during NREM sleep; typically remit before or at adolescence
	Panayiotopoulos syndrome	Seizures mainly occur during NREM sleep; common in childhood; typically remits before or at adolescence
Sleep-accentuated epilepsies	Electrical status epilepticus in sleep	EEG activation upon sleep onset persisting throughout NREM sleep; neuropsychological and behavioral disturbances may be pronounced
	Landau–Kleffner syndrome	Epileptic aphasia associated with spikes and waves during NREM sleep; deficits may persist after spike waves disappear
	West syndrome	Epileptic spasms occurring in clusters after awakening; distinctive EEG pattern (hypsarrhythmia) more evident during early NREM sleep
	Lennox–Gastaut syndrome	Severe epileptic and developmental encephalopathy; tonic seizures activated by NREM sleep
Awakening epilepsies	Juvenile myoclonic epilepsy	Myoclonic seizures typically occurring shortly after awakening; seizures precipitated by sleep deprivation and forced early awakening
	Epilepsy with generalized tonic–clonic seizures alone	Generalized tonic–clonic seizures typically occurring shortly after awakening; seizures precipitated by sleep deprivation and forced early awakening

*Based on Nobili et al. *Eur J Neurol* 2021;28:15-32 [45].
NREM, non-rapid eye movement; EEG, electroencephalography.

bamazepine, and levetiracetam had no effect on sleep. Epilepsy surgery was found to benefit sleep in patients with a successful outcome. Clinicians should consider these findings when treating patients with comorbid sleep disorders [4].

In epileptic patients with coexisting obstructive sleep apnea, certain antiseizure medications, such as barbiturates and benzodiazepines, may reduce upper airway tone or alertness, potentially worsening the condition. Medications that can cause weight gain may also exacerbate sleep apnea. In the cases of obesity-related obstructive sleep apnea, medications (e.g., topiramate) that promote weight loss can be helpful. Topiramate may also be beneficial for patients with sleep-related eating disorders. Clonazepam or gabapentin may be useful for patients with RLS, and clonazepam may be effective for those with REM sleep behavior disorders [5,55].

Overall, while antiseizure medications can play a role in mitigating the detrimental effects of seizures on sleep structure, they can also have direct effects on sleep and other sleep disorders. When selecting the appropriate treatment for patients with epilepsy and sleep-related issues, careful consideration of the specific effects of each drug on sleep is important.

CONCLUSION

Sleep and epilepsy are closely linked, with sleep affecting epilepsy between seizures and treatment, and epilepsy and its treatment influencing sleep. Sleep characteristics can modulate epileptic activity, and disruptions in sleep can trigger seizures. Antiseizure medications, while primarily targeting seizures, can also impact sleep quality. Understanding the relationship between sleep and epilepsy is crucial for effective management and can lead to advancements in epilepsy treatment and improved sleep outcomes for individuals with epilepsy.

Availability of Data and Material

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the study.

Author Contributions

Conceptualization: Kwang Ik Yang. Investigation: Kyung Min Kim, Kwang Ik Yang. Writing—original draft: Kyung Min Kim, Kwang Ik Yang. Writing—review & editing: Kyung Min Kim, Kwang Ik Yang.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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