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Epilepsy and sleep disturbance

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Abstract

Sleep disturbance is common in epilepsy, the nature of sleep disturbances in epilepsy is diverse, and the etiologies are complex. Evidence suggests that having epilepsy and the occurrence of seizures, as well as some AEDs, are associated with significant sleep disruption. The occurrence of seizures can have profound effects on sleep architecture lasting much longer than the postictal period. Persistent daytime drowsiness in patients with epilepsy is not always due to the side effects of some AEDs and may be independently linked with sleep fragmentation. Significant sleep disruption in epilepsy has been associated with impaired quality of life and impaired seizure control. All aspects of sleep medicine are important in the management of epilepsy and are confounded by the occurrence of seizures, the location of seizures, and the beneficial and detrimental effects of AEDs. Sleep should be proactively evaluated, and sleep disturbances should be treated as part of the total care of patients with epilepsy.

Keywords: Epilepsy; Sleep; REM sleep; Polysomnography; Anticonvulsant drugs

1. Introduction

Ineffective or inadequate sleep is common in epilepsy patients. Although our society tends to accept poor sleep as the norm, it can result in considerable impairment of daytime functioning and quality of life even in people without chronic illnesses. In patients with epilepsy, the consequences are potentially more severe than among those without epilepsy. Inadequate sleep can exacerbate daytime drowsiness and memory dysfunction, which are common to this group, and can contribute to intractable seizures. Of even more concern is the potential for a continual cycle of sleep disruption, worsening seizures, and further impairment of sleep that can be responsible for intractability of epilepsy in some patients. Despite this, many treating physicians overlook the potential for treatable causes of sleep disruption in patients with epilepsy with the result that optimal outcome may not be achieved.

The causes of sleep disturbance in epilepsy are many and include factors that are also relevant to the general population, such as insufficient sleep, inadequate sleep hygiene, coexisting sleep disorders, and circadian rhythm disturbances. Furthermore, in epilepsy, evidence suggests that the very presence of epilepsy itself can disrupt sleep, and even more evidence shows that seizures themselves can disrupt sleep, even when they occur during wakefulness. A further complication in the management of sleep disruption in epilepsy is that anticonvulsant drugs can alter sleep, both beneficially and detrimentally, and these effects appear independent of their anticonvulsant actions.

In this article, the potential causes of sleep disturbance are reviewed with an emphasis on those that are most common in patients with epilepsy. The impact of these disorders is discussed, followed by a review of the potential impact of anticonvulsant drugs. Attention to sleep should be an essential part of the total care of patients with epilepsy.

2. Potential causes of sleep disruption in epilepsy

Several studies have confirmed that sleepiness and sleep disorders are common in epilepsy. De Haas et al. showed that patients with partial epilepsy have twice the prevalence of subjective sleep disturbance over the last 6

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months as controls (39% vs 18%) and that the presence of sleep disturbance is associated with further significant worsening of quality of life beyond that attributable to just having epilepsy (which was significantly worse than that of matched controls) [1]. In addition, this large study showed that the presence of sleep disturbance in patients with partial epilepsy was not significantly linked to the number of antiepileptic drugs (AEDs) being taken, suggesting that sleep disturbance in partial epilepsy is, at least in part, independent of drug treatment and may be inherent to the disorder itself. Malow et al. [2] used the Epworth Sleepiness Scale (ESS) to demonstrate that patients with epilepsy had increased daytime drowsiness compared with controls (neurology patients without epilepsy). Epilepsy was not a predictor of high score (more daytime sleepiness) when a sleep apnea scale was included, suggesting that this treatable condition may be responsible for much of the problem in patients with epilepsy. A similar investigation was performed prospectively in children by Stores et al. [3] using a nonstandardized sleep questionnaire and the Conners Revised Parent Rating Scale. Children with epilepsy showed higher scores for poor-quality sleep, anxiety about sleep, and disordered breathing. Similar findings were seen in a survey given to parents of 89 children with idiopathic epilepsy [4]. Children with epilepsy had more sleep problems than did controls, and these were associated with seizure frequency, age, paroxysmal activity on EEG, duration of illness, and behavioral problems.

Possible reasons for disrupted sleep fall into several categories, including insufficient sleep, inadequate sleep hygiene, coincident sleep disorders, and the effects of seizures themselves. The effects of AEDs, a further confounding consideration, are reviewed in Section 5.

2.1. Insufficient sleep syndrome

One of the more common reasons for inadequate sleep is perhaps the most obvious: failing to spend enough time in bed. This is common in the general population, and it is largely a cultural phenomenon. The demands of modern society, including work, family, and leisure time, often cause persons to limit their sleep. Although most believe this to be benign, chronic sleep deprivation can clearly result in neurocognitive deficits [5]. This is corroborated by the "Sleep in America" poll of more than 1000 adults conducted by the National Sleep Foundation in 2002 [6]. Epilepsy patients are certainly not immune from this, although the magnitude of this "behavioral" problem in the epilepsy population is unknown.

2.2. Sleep hygiene

Sleep hygiene is a fairly straightforward concept, but it is one with which a large number of patients are unfamiliar and which a large number of physicians have forgotten. Review of sleep hygiene can also be time consuming, and in a busy office practice, it is easy to overlook.

The basic principle of sleep hygiene is optimization of the conditions for sleep. Contrary to many persons' beliefs and to the accepted norms of American society, humans do not have full voluntary control over sleep, as they do with (at least to a greater extent) eating and voiding. Many would like to believe that sleeping and waking are like a switch—on and off—but this is simply not true. Although sleep cannot be fully controlled, it can be encouraged and optimized, and this is the principle of sleep hygiene.

First, sleep should have regular timing. Humans have many processes that are based on circadian rhythms, and sleep is among them. Core body temperature and release of hormones, including melatonin, cortisol, and growth hormone, are others. All these processes can adapt to outside influences (as in changing time zones or during shift work); however, these changes occur gradually, and rapid alterations in daily schedules are not well tolerated. As such, optimum sleep cannot be attained when awaking at 6:00 AM on weekdays and noon on weekends. Napping excessively can disrupt sleep. If a 4-hour nap is taken until 6:00 PM, then the patient will clearly not be tired at midnight. He or she will then stay up late and will either need to sleep late in the morning (further disrupting sleep) or will awaken early, possibly taking another nap during the day because of excessive tiredness.

Second, the sleep environment should be optimized, physically and psychologically, for sleep. Physically, the bedroom should be suitably dark and quiet. It should be shielded from distracting noise (e.g., traffic, other people who arise earlier). The bed itself should be comfortable, and the temperature should be optimized. Psychologically, the bedroom, and particularly the bed, should be associated with sleep and not with other (particularly active) activities. People should refrain from activities other than sleep and sex in the bed, particularly stressful activities, e.g., working, studying, balancing one's checkbook. It is also sometimes necessary for some persons to avoid reading or watching television in bed. Sleeplessness in bed should be treated not by ruminating and staring at the clock; this tends to again associate the bed with anxiety. Patients should, in such cases, arise from bed and do quiet activities, returning to bed only when sleepy.

Finally, outside activities that can influence sleep must be monitored. Activities that tend to stimulate—particularly exercise—should be avoided late in the day (although exercise itself generally improves nighttime sleep). Alcohol before bedtime should be avoided. Although it can help induce drowsiness, it can result in early-morning awakening. Caffeine, chocolate, nicotine,

and other stimulants should be avoided late in the day. In addition, it is important that persons do not spend too long in bed and oversleep for prolonged periods after the normal sleep cycle has completed.

While these principles are relatively simple, it is amazing how many patients and physicians do not think of or know about them. Brief counseling in sleep hygiene, or giving patients information about it, can make a big difference in the quality of many patients' sleep.

2.3. Sleep disorders

Daytime sleepiness is common in the general population, and it is nearly universal among certain populations with epilepsy, but sleep disorders are frequently overlooked and not actively investigated in the evaluation of a patient. Many practitioners attribute consistent tiredness in epilepsy to an unavoidable effect of antiseizure medication. While some medications can produce drowsiness (see Section 5), persistent tiredness due to medications should not be tolerated in any case, and in many patients, another cause may be present. A careful history and, when indicated, overnight polysomnography can reveal specific, treatable disorders, can greatly improve patient quality of life, and, in some cases, can improve seizure control.

Studies of epilepsy patients with sleep disorders show a variety of mostly treatable conditions, some of which might be overlooked or misdiagnosed. In a retrospective study of 63 epilepsy patients who underwent polysomnography [7], the vast majority (78%) were referred for obstructive sleep apnea, while many others (46%) were referred for excessive sleepiness and 19% for characterization of nocturnal spells. Studies diagnosed obstructive sleep apnea in 71% of referrals, 96% of whom were referred for that reason. Other diagnoses made included one patient each with narcolepsy and insufficient sleep syndrome and four with nocturnal seizures. Six patients had frequent periodic limb movements, but these were not clinically significant. In a similar investigation, Beran et al. [8] reported on 50 epilepsy patients referred to a sleep laboratory for overnight polysomnography. Fifty-four percent had sleep apnea, and 32% had periodic limb movements during sleep (6 requiring medication). Of the 36 patients who were prescribed therapy based on the evaluation, 6 had significant improvement in seizures.

These studies stress the increased prevalence of sleep disorders—particularly obstructive sleep apnea—in the epilepsy population and the underuse of thorough and methodical workup and polysomnography in these patients to characterize the nature of sleep disturbances.

2.4. Effects of seizures on sleep

Intuitively, nocturnal seizures disrupt sleep structure. Most cause at least a brief awakening, and normal sleep is unlikely during a postictal state. It may seem that such disruption could be relatively minor, but even brief seizures can result in prolonged alterations in sleep structure. Many studies have shown improvement in sleep with treatment of nocturnal seizures [9–11]. In particular, most have shown improvement in sleep efficiency, decreased arousals, and increases in rapid eye movement (REM) sleep, although it is sometimes difficult to distinguish effects of anticonvulsants from effects of seizures. Patients with partial seizures have been shown to have relatively normal sleep on seizure-free nights except for slightly decreased sleep efficiency with temporal lobe epilepsy [12]. However, evidence also exists suggesting that in newly diagnosed patients with epilepsy, even on nights when patients do not experience seizures, sleep architecture is fragmented [9,13]. Although the work of Touchon et al. [9,13] has not been replicated, it lends support to the notion that the presence of epilepsy itself—not just the occurrence of seizures or the effects of AEDs—predisposes to sleep disruption.

The effects of individual temporal lobe seizures on sleep structure have been studied in patients in an epilepsy monitoring unit. Patients were recorded with polysomnography under baseline conditions (seizure-free) and following complex partial or secondarily generalized seizures [14]. With daytime seizures, there was a significant decrease in REM the following night (12% vs 18% for baseline) without significant changes in other sleep stages or in sleep efficiency. When seizures occurred early in the night, this decrease in REM was more pronounced (7% vs 16%) and there were increases in stage I sleep and decreases in sleep efficiency. These effects were even more pronounced when seizures occurred early in the night (Fig. 1).

Therefore, seizures can have a profound effect on sleep lasting much longer than the apparent postictal period. This helps to explain a commonly seen clinical

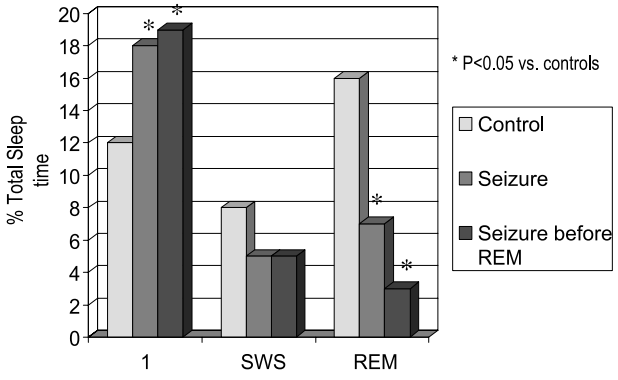

Fig. 1. Effects of seizures on sleep. Compared with seizure-free nights, patients with seizures during overnight polysomnography had significant decreases in REM and increases in stage I sleep. If a seizure occurred before the first REM period, effects were even more pronounced. Slow wave sleep (SWS) includes stages III and IV. Adapted from Bazil et al. [14].

phenomenon: patients who have only nocturnal seizures but who report difficulty concentrating or even total inability to work on the days following a seizure.

3. Effect of sleep, sleep deprivation, and sleep disruption on the occurrence of seizures

The amount of baseline rhythmicity occurring in the brain differs considerably between the states of sleep and wakefulness. It is, therefore, not surprising that various seizure types begin preferentially in specific sleep states. Crespel et al. [12] specifically examined the occurrence of frontal and temporal lobe seizures in 30 patients, using 5 days of continuous video EEG monitoring. Sixty-one percent of frontal seizures began during sleep, compared with only 11% of temporal lobe seizures. In a larger study, Bazil and Walczak [15] retrospectively studied more than 1000 seizures in 188 consecutive patients to look at patterns of onset in relationship to sleep. A similar, prospective study, restricted to patients with partial seizures, was performed later [16]. Both studies showed that, overall, 20% of seizures occurred during sleep. Both studies showed that most seizures during sleep began during stage II, with few occurring during slow wave sleep (stages III/IV) and few or none during REM sleep. Frontal lobe seizures began during sleep more often than temporal lobe seizures, a finding that is appreciated clinically. Both studies also showed that temporal lobe seizures were more likely to secondarily generalize when they began during sleep, while frontal lobe seizures were not. This intriguing finding suggests differences in the pathways of spread in partial epilepsy, which could have implications for treatment if the phenomena were better understood. Seizures that occur only during sleep may represent an important, distinct class and have a unique underlying pathophysiology, as these have a particularly good prognosis [17,18].

Sleep deprivation has long been thought to increase the risk of seizures, which is clinically readily apparent in a few syndromes, such as juvenile myoclonic epilepsy. However, a controlled study of patients with refractory partial epilepsy failed to show an effect [19]. Seventeen patients were sleep deprived on alternate nights, and 13 received 8 hours of sleep per night. There was no difference in the number of seizures or time to first seizure. This brings into question the common practice of sleep deprivation as an investigational tool in epilepsy monitoring units. However, empirical evidence strongly supports the contention that sleep deprivation probably does increase the risk of seizures in most patients in the outpatient setting, particularly when the deprivation is chronic. This can be due to sleep disorders (as described in Section 2.3), can be caused by outside influences, such as poor sleep hygiene, or can be voluntary; patients, like many in the general population, simply restrict themselves to an inadequate sleep time because of time constraints on other aspects of their lives. Any of these influences can result in increased seizures, further disrupting the already limited sleep time. A cycle of sleep disruption and intractable epilepsy can result, and seizures will not be controlled until the sleep disruption is also resolved, often providing clinicians with a formidable challenge to determine the nature of sleep disruption and to make the appropriate interventions to correct it.

Finally, certain circadian rhythms may influence seizures independently of sleep. Both rats with a model of limbic epilepsy and humans with medial temporal seizures have increased seizures during daylight, an effect not seen with human extratemporal seizures [20]. This is likely independent of sleep, of course, because rats are primarily nocturnal and humans diurnal. Humans with intractable temporal lobe epilepsy show abnormal secretion of melatonin, a sleep-related hormone with a characteristic circadian pattern [21]. Exogenous melatonin has been shown to help control seizures in a few small studies [22,23], raising the possibility that it may be useful in the treatment of some patients.

4. Other effects of sleep disruption on patients with epilepsy

In addition to the influence of seizure occurrence, patients with epilepsy are probably even more susceptible to the cognitive and functional consequences of sleep disruption than are the general population. The most obvious aspect of this is daytime drowsiness, which may, in part, be related to some domains of cognitive impairment. This is not a trivial problem, as daytime drowsiness contributes to increases in accidents and, particularly in the case of motor vehicles, to fatalities. Patients with uncontrolled seizures do not drive. But many with exclusively nocturnal events, and some who experience occasional daytime seizures, do drive, and the impact of daytime drowsiness on vigilance and psychomotor function must be recognized. Even patients with fully controlled seizures can still have disrupted sleep due to coincident sleep disorders (see Section 2) or to the influence of AEDs (discussed in Section 5). Thus, the potential for cognitive and functional impairment among these patients should also be recognized. Good seizure control should not mask the possibility that clinically relevant sleep disruption and its consequences may be significant in this population.

Sleep disruption can also have an influence on memory. Although the exact function of sleep remains unclear, there is growing evidence that sleep and REM or slow wave sleep in particular are required for optimal cognitive function. Sleep loss has been clearly documented to affect both cognitive and procedural skills.

This has been extensively studied in health care workers [24–26]. There is also growing evidence that chronic sleep restriction by as little as 2 hours per night can severely impair neurobehavioral functions in normal individuals [5]. Although the influence of sleep disruption on memory in patients with epilepsy has not been well studied, there is no reason (empiric or pathophysiologic) to believe that impairment of some memory functions should not occur in patients with epilepsy and disrupted sleep.

Both REM and slow wave sleep (stages III/IV) are considered to be "essential sleep," and subjects who are deprived of sleep (at least in the short term) will "rebound" or make up most of the REM and slow wave sleep that are lost. However, very little stage I or II sleep is regained [27]. Although the function of REM sleep remains speculative, there is considerable information suggesting that increased REM is correlated with enhanced learning of certain tasks in healthy normal volunteers, which may be correlated with function [28–30]. Additionally, enhancement of REM sleep occurs with drugs that have demonstrated efficacy in Alzheimer's disease [31,32], and REM enhancement associated with donepezil correlates with improved memory in normal individuals [32]. Increased slow wave sleep has also been correlated with certain types of learning in one human study [28], and it appears that memory processing in humans requires the involvement of slow wave sleep [33].

Patients with epilepsy frequently complain of impaired cognitive functioning, including memory impairment [34]. It may be that part of the cognitive impairment is due not to seizures or medications directly but to detrimental effects that these (and any coexisting sleep disorders) have on essential sleep, with adverse consequences for daytime functioning. Many of these patients undoubtedly suffer chronic sleep disruption due to one or more causes. The nature and impact of cognitive impairment in epilepsy are more extensively discussed in the article by Motamedi and Meador in this supplement [35].

5. Effects of anticonvulsant medications

A caveat to reviewing the effects of AEDs on sleep structure is that although there have been many studies, effect sizes are variable and are often not well defined. Large, prospective, well-designed studies are lacking in this area, despite our knowledge that AEDs can influence sleep. Early studies of the older AEDs showed an increase in sleep stability with all agents. In retrospect, much of this effect was likely due to a reduction in seizure activity, rather than an independent, beneficial effect of the drugs on sleep itself. More recently, the effects of anticonvulsant drugs have been studied independently of seizures, showing different effects (both detrimental and beneficial) of various AEDs. A summary of what is known of the effects of older and newer AEDs on various aspects of sleep, based on the available literature, is provided in Table 1 [36,37].

Benzodiazepines and barbiturates are used less commonly for chronic treatment of seizure disorders, but they have the most convincing evidence for detrimental effects on sleep. While both classes of medications reduce sleep latency, they also decrease the amount of REM sleep [38,39]. The effects of other anticonvulsant drugs are somewhat variable across studies, but a few conclusions can be drawn. Phenytoin may increase light sleep and decrease sleep efficiency, and some studies show decreased REM sleep [38,40–43]. Findings for carbamazepine are more variable, but there also seems to be a reduction in REM sleep [40], particularly with acute treatment [44,45]. There is some debate over whether the effects of short-term carbamazepine treatment on REM sleep also occur with chronic treatment.

Table 1
Summary of AED effects on sleep

AED	Sleep latency	Sleep efficiency	Stage I	SWS	REM	Daytime drowsiness
Barbiturates	+[a]	NE	NE	NE	–	–
Benzodiazepines	+	NE	NE	–	–	–
Carbamazepine	NE	NE	NE	NE	–	–
Phenytoin	+	NE	–	NE	–	–
Valproic acid	NE	NE	–	NE	NE	–
Felbamate	?	?	?	?	?	+
Gabapentin	NE	NE	NE	+	+/NE	?
Lamotrigine	NE	NE	NE	–/NE	+/NE	?
Levetiracetam	?	?	NE	NE	NE	?
Tiagabine	NE	+	NE	+	NE	?
Topiramate	?	?	?	?	?	?
Zonisamide	?	?	?	?	?	?
Pregabalin	+	+	?	+	?	–/NE

Note. Some of these results represent small studies, and the effect may not occur in all patients. Daytime drowsiness may be transient with some agents and more persistent with others. This table is based on Refs. [36,37].

[a] +, improves; –, worsens; NE, no effect; ?, unknown.

Studies of newer agents suggest fewer detrimental effects on sleep, but there still exist many gaps in our knowledge base. Lamotrigine has been shown to have no effect on sleep in one study [44], but another showed decreases in slow wave sleep [46]. Gabapentin has no detrimental effects on sleep, and it seems to enhance slow wave sleep in patients with epilepsy [43,44] and in normal volunteers [47,48]. Furthermore, limited studies suggest that gabapentin may be useful in the treatment of one common sleep disorder, restless leg syndrome [49]. Carbamazepine and lamotrigine have also been used successfully in the treatment of this disorder. Bell et al. [50] studied the effects on sleep of levetiracetam as monotherapy in normal volunteers and as add-on treatment to carbamazepine in epilepsy patients. No effect on number of awakenings, sleep efficiency, or amount of slow wave or REM sleep was seen in either group. There was, however, a subjective perception of fewer awakenings, more restful sleep, and decreased alertness on awakening in both groups. The effects of zonisamide, oxcarbazepine, and topiramate on sleep and sleep disorders are not known. Patients taking anticonvulsants known to disrupt sleep (phenobarbital, phenytoin, carbamazepine, or valproic acid) have increased drowsiness compared with epilepsy patients who are not taking anticonvulsants [51].

There is evidence that a new AED in development, pregabalin, significantly enhances slow wave sleep in normal volunteers, in contrast to alprazolam, which was shown to suppress slow wave sleep [37]. The clinical relevance of the differences among agents in their effects on sleep structure remains to be fully elucidated. Nonetheless, until such time as we have more information specific to the subpopulations of epilepsy patients we treat with AEDs, physicians must be cognizant of the possibility that they may beneficially or detrimentally impact sleep and that they may confound or help underlying, independent sleep disorders.

6. Conclusions

Attention to sleep in patients with epilepsy has important implications for diagnosis, seizure control, and quality of life. It is clear that independent sleep disorders frequently coexist with epilepsy and that seizures themselves cause sleep disturbance. The common complaint of daytime drowsiness can no longer be dismissed in patients with epilepsy, in whom sleep studies and diagnosis can clearly improve both seizure control and sleep. Any patient with persistent daytime drowsiness should, therefore, be considered for study by polysomnography or video EEG polysomnography.

Whether sleep disruption is caused by seizures, by AEDs, or by a coexisting sleep disorder, an adverse impact on daily functioning is likely. Decreased sleep efficiency and increased arousals result in daytime drowsiness and are associated with seizures and with some AEDs. Chronic sleep deprivation, such as could occur with any of these, clearly has adverse consequences for neurocognitive performance. More interesting, and potentially more important, are the specific effects of epilepsy itself, seizures, and AED treatment on "essential sleep"—slow wave and REM sleep. Although the exact role of essential sleep in daily functioning and well-being is not completely understood, there is growing evidence that these sleep stages may be essential for consolidation of certain types of memory, which ultimately impacts functioning. If this is true, sleep disruption in epilepsy may also play a role in the memory complaints that are so prevalent among epilepsy patients. This hypothesis will have to await further study. In any case, it is clear that sleep quality plays an important role in both seizure control and quality of life. Attention to seizures that may disrupt sleep, to possible concurrent sleep disorders, and to choice of AED treatment is, therefore, critical to the total care of patients with epilepsy.

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