



Review article

The relationship between sleep and epilepsy: Evidence from clinical trials and animal models

Gabriela Matos ^a, Monica L. Andersen ^{b,*}, Angela Cristina do Valle ^a, Sergio Tufik ^b

^a Department of Pathology, Faculdade de Medicina, Universidade de São Paulo (USP), Av. Doutor Arnaldo, 455, Cerqueira César 01246-903, São Paulo, SP, Brazil

^b Department of Psychobiology, Universidade Federal de São Paulo (UNIFESP), R. Napoleão de Barros, 925, V. Clementino 04024-002, São Paulo, SP, Brazil

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ABSTRACT

Interactions between sleep and epilepsy have been widely documented. Sleep can modulate epileptic phenomena, and epilepsy and seizures disorganize the macro- and micro-architecture of sleep. In turn, sleep deprivation exerts a strong influence on the occurrence of seizures and interictal epileptiform discharges. Recently, sleep disturbances occurring in conjunction with epilepsy have been suggested to lead to a worsening of the quality of life for patients with epilepsy. In addition, data from animal models clarify many gaps in this relationship. In this brief review, we present an outline of the interactions between sleep and epilepsy based on a thorough review of the existing literature.

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1. Introduction

The relationship between sleep and epilepsy is complex and clinically relevant. A better understanding of the many gaps that permeate this relationship would contribute to the development of

more effective therapeutic approaches that could result in a better quality of life for patients with epilepsy. This review covers the basic mechanisms between sleep and epilepsy, summarizes the contribution of animal models to the knowledge about sleep and epilepsy, highlights the differences in this relationship according to the type of seizure, demonstrates the controversial effects of sleep deprivation on epilepsy, and presents the recent data on Obstructive Sleep Apnea Syndrome (OSAS) in patients with epilepsy.

* Corresponding author. Tel.: +55 11 2149 0155; fax: +55 11 5572 5092.

E-mail address: mandersen@psicobio.epm.br (M.L. Andersen).

2. History

After systematic clinical observations in hospitalized patients with spontaneous recurrent seizures, Aristotle and Hippocrates pointed to the close correlation between sleep and epilepsy [1]. The studies concerning this relationship were only resumed after the 19th century, with the advent of modern epileptology [2]. In 1885, Gowers [3] identified two periods of susceptibility for night seizures, with the first occurring during the beginning of the night and the second at the end of the sleep cycles. He also demonstrated that 21% of observed seizures occurred predominately at night, 42% during the day and 37% during both periods. In 1929, Langdon-Down and Brain [4] described three peaks for the occurrence of seizures with a daytime prevalence: the first, with the most frequent occurrence, was soon after awakening, the second was in the late afternoon, and the third was in the evening. Still, research into this theme was based solely on clinical observations made in patients who were hospitalized. Clinical studies investigating the pathophysiological aspects common to sleep and epilepsy were only possible due to the invention of the electroencephalograph by Hans Berger in 1929 [5,6]. The seminal study establishing a relation between sleep and epilepsy was conducted by Gibbs and Gibbs [7]. They described the unquestionable link between sleep and interictal epileptiform discharge (IED). The analysis revealed a significant increase in the frequency of IED during sleep (63%) as compared to during a waking state (19%) in 174 patients who suffered generalized seizures, suggesting that there is the potential for a sleep facilitating effect during the paroxysmal events.

Janz [8] classifies epilepsy into three groups: epilepsies upon awakening, sleep epilepsies and diffuse epilepsies. Janz also suggested that the distribution of the seizures depended on the etiology concomitant with the age of onset. The etiology of epilepsies upon awakening was predominantly cryptogenic (a presumably organic basis) or idiopathic (genetically transmitted) and occurred more often in children and adolescents. Sleep epilepsies most often presented a known etiology (symptomatic origin), and age did not correlate significantly because the lesions to the nervous system could occur at any phase of life [6]. Diffuse epilepsy, in turn, presented with a higher incidence in patients with a known etiology, although Janz suggested the predominance of this type of epilepsy during the first years of life.

It should be highlighted that the international classification of epilepsy has been constantly revised and reformulated throughout the years in view of the technological and scientific advances inherent in intellectual advancement, especially in recent decades. In the early 1990s, epilepsies were classified according to criteria that included, among other factors, the age of the patient and the etiology of the disease [9]. Recently, other criteria have been proposed for this classification [10,11].

3. Neurobiological aspects of epilepsy and sleep

Epilepsy is a chronic disease characterized by spontaneous recurrent seizures in the absence of any metabolic intoxication or fever. Epilepsy affects about 1 to 3% of the population worldwide and can be seen across all age groups as well as at varying levels of severity. Seizures vary from brief attention lapses or muscle jerks to severe and prolonged convulsions. The frequency of this event also varies, from less than one per year to several per day [12]. Each epileptic syndrome is composed of a typical pattern of seizures, which can be characterized electrophysiologically as a result of excessive and synchronic discharges within a unique neuronal population (partial or focal seizure) or involve both brain hemispheres (generalized). Partial seizures are classified as simple or complex, with the latter accompanied by an alteration of consciousness [13]. Any type of partial seizure may secondarily generalize to a tonic-clonic seizure, which is characterized by the complete loss of consciousness [14].

Sleep, a complex and cyclical physiological state that occupies one-third of the human life span, is capable of modulating epileptic seizures in some types of epilepsy [15]. Although generally viewed as a passive condition, sleep is actually a highly active and dynamic process [16]. Since Aserinsky and Kleitmann recognized eye movements during sleep, sleep has been divided into two distinct stages: *non-rapid eye movement* (NREM) and *rapid eye movement* (REM) stages [17]. NREM sleep is subdivided into four stages according to the soundness, or “depth,” of sleep. Stage 1 is characterized by low voltage waves of mixed frequencies, followed by the intrusion of phased patterns called sleep spindles and the K complex that characterizes stage 2. The presence of slow high voltage waves is characteristic of phases 3 and 4, and the phased patterns described previously may appear in the third phase of NREM sleep. REM sleep is characterized by mixed frequencies and a low voltage potential. Although muscular tonus is reduced in the NREM phase, there is tonic inhibition of motoneurons in the REM phase. In a healthy adult, sleep alternates between the NREM stages (S1–S4) and REM sleep every 90 min and this 90-minute cycle is repeated four to six times per night [18]. Recently, the American Academy of Sleep Medicine (AASM), after a review of the original sleep scoring manual, proposed new rules for sleep scoring (reviewed in [19]). Because most sleep studies described in this review were analyzed according to Rechtschaffen and Kales [18], we adopted the standard criteria.

4. Animal models

The majority of studies concerning the relationship between sleep and epilepsy are based upon clinical trials. Consequently, the potential existence of any bias that might, in some way, influence the physiological response (e.g., antiepileptic medication, stress, anxiety, or even inherent habits of each patient) should be noted. For this reason, experimental research is of the utmost importance. Animal models may be used to isolate some of those biases and thus clarify some of the uncertainties in the relationship between sleep and epilepsy.

An interesting study comparing patients with mesial temporal lobe epilepsy with an experimental rat model of the same syndrome [20] demonstrated that the patients and rats presented a similar distribution of seizures along the light–dark cycle. In both humans and rats, seizures were more prevalent during the light period than the dark, and the peak number of seizures occurred in the late afternoon. According to the authors, this similarity between the species is hard to explain, considering that humans and rats have different activity rhythms (diurnal and nocturnal, respectively). Thus, Quigg et al. suggested that sleep may not be the only factor facilitating the occurrence of seizures [20].

Some studies have demonstrated an alteration in the sleep pattern of rats with spontaneous recurrent seizures. Male adult rats following pilocarpine-induced temporal lobe epilepsy [21,22] presented significant reduction of REM sleep during the afternoon period [23], concomitantly with decrease of sleep cycles throughout the light–dark cycle after 60 days of status epilepticus [23]. Possible dysfunction in the regulation of the cyclicity of sleep–wake cycle was suggested to explain this altered sleep pattern [23]. Corroborating of this important finding, Bastlund et al. [24] found a significant reduction in REM sleep in the morning after 15 weeks of the status epilepticus procedure, even in the absence of antiepileptic medication, in rats with complex partial seizures induced by hippocampal electrical stimuli [25]. The authors suggest that lesions in the dorsomedial hypothalamus and spontaneous recurrent seizures may be responsible for this abnormal sleep architecture.

In a genetic model of absence epilepsy (WAG/Rij strain), alterations in the organization of sleep were found in drug-free, naïve rats. The adult epileptic group had a longer lasting sleep cycle compared to that of non-epileptic animals [26]. More specifically, there was an increase of NREM sleep concomitant with a reduction of REM sleep twice during the day, at the beginning and the end of the light period.

There is evidence, however, that the distribution of the sleep phases is related to the age of the animals and to variations in the light/dark phase. In this same study, older animals (six months of age) had a reduction in NREM sleep, which occurred only at the end of the light period when sleep is predominant in rodents. This phase of the day is characterized by a significant increase of spike-wave discharges in older rats, and this factor could explain the alterations that were found in this specific group.

There are a few studies concerning the possible effects of sleep deprivation upon epilepsy. WAG/Rij animal model rats were submitted to sleep deprivation for 12 h. In the first 4 h of the experiment, researchers observed a significant increase in spike-wave discharges, and these discharges fell to baseline values in the subsequent hours [27]. According to the authors, the first hours of sleep deprivation increase drowsiness, resulting in the more prominent number of spike-wave discharges. On the other hand, during the subsequent hours following sleep deprivation, the predisposition of sleep is increased, with the rats falling asleep more quickly, which, in turn, reduced the quantity of intermediate phases. For this reason, the number of spike-wave discharges in epileptic rats submitted to sleep deprivation was decreased.

In summary, these experimental models demonstrated some reciprocal effects between sleep and epilepsy, suggesting that the epilepsy and seizures (without antiepileptic medication) alter the pattern of sleep and possibly other physiological systems (circadian timing system, hypothalamic-pituitary-adrenal axis, and core body temperature). These alterations correlated with the occurrence of seizures (reviewed in [28]). Nevertheless, more studies focusing in subjacent mechanisms are needed to explain this interaction.

5. Effects of sleep on epilepsy

Although sleep exerts a strong influence on seizure occurrence, the detrimental effects from sleep on epilepsy depend on the type of epileptic syndrome [9,29]. In children, Patry et al. [30] described a pattern of continuous spike waves during NREM sleep called “electrical status epilepticus during the slow sleep” [30,31]. The electroencephalogram (EEG) was characterized by significant activation of continuous epileptiform discharges during sleep, usually during the NREM stage. In addition, benign childhood epilepsy with centrotemporal spikes (the most frequent epilepsy in childhood) has generalized tonic-clonic seizures commonly related to sleep [32]. In adults, study has demonstrated that partial seizures from the frontal lobe occur more frequently and are more strongly related to sleep than those with a temporal lobe origin [33]. On the other hand, epilepsy with grand mal on awakening presents with generalized seizures more frequently upon awakening (not only in the morning, but at any time of the day) and in the evening [34]. Seizures from patients affected by mesial temporal lobe epilepsy occur more often during the light period than the dark period [20]. Collectively, these studies have indicated that sleep-wake cycle, not circadian variation, influences seizures (reviewed in [35]).

Clinical and experimental evidence points to the effects that sleep can have on subsequent epileptic episodes, by either facilitating or inhibiting the episodes, depending on whether the sleep phase is NREM or REM, respectively [36–40]. Generalized synchrony present in the NREM phase could enhance the propagation of post-synaptic responses (including epileptogenic discharges), concomitant with the muscular tonus that would facilitate the stereotypical movement that is observed during most seizures. Conversely, the REM phase would make such muscular events less likely to occur, as a result of the pattern of asynchronous discharges between neurons and the profound inhibition of motoneurons [41].

There are over 40 kinds of seizures and more than 30 types of epilepsy, which are classified according to the age of onset and related conditions [11]. In order to strengthen our comprehension of the

effects of sleep on epilepsy, the more common syndromes are divided into two general areas: epilepsies with primarily focal paroxysmal events and primarily generalized seizures.

5.1. Partial seizures

Crespel et al. [42] have demonstrated that the prevalence of seizures during sleep was 66.11% in patients with frontal lobe epilepsy. Polysomnography revealed that these events occurred during NREM sleep (phase 2), which was similar to the pattern seen in seizures during sleep in patients with temporal lobe epilepsy. REM sleep was associated with a reduction in the number of seizures [42,43], leading to the hypothesis that this phase of sleep could act as an endogenous anti-epileptogenic system (reviewed in [40]). In fact, the facilitating or protective effect of sleep on epilepsy seems to be determined by seizure type, etiology and clinical signs (reviewed in [29]), including the origin and age of onset of seizures.

5.1.1. Epileptogenic sites

In 133 epileptic patients, Herman et al. [43] examined the distribution profile of partial seizures with 5 distinct epileptogenic sites in the central nervous system. Forty-three percent of all partial seizures began during sleep. Sleep seizures occurred during the initial stages (mainly phase 2) of sleep but were rare in slow-wave sleep (phases 3 and 4). In addition, no seizures occurred during REM sleep. Epilepsies from the mesial and neocortical temporal lobe, parietal-occipital lobe, and temporal lobe were prevalent during wakefulness, and only those forms of epilepsy that originate in the frontal lobe occurred more often during sleep. These results indicate that synchronized and facilitating effects for the appearance of seizures exist and, further, that these effects are dependent on the origin of the seizures.

Despite differences in the distribution of seizures along the sleep-wake cycle among epilepsy types, Bazil and Walzack [44] demonstrated that adult patients with epilepsy have distinct periods for the secondary generalization of focal seizures within the different epileptogenic foci. Seizures of the frontal lobe become equally generalized in the sleep/wake phases, but those of the temporal lobe presented significant secondary generalization in the NREM sleep phase (45%). Complex partial seizures were more frequent during NREM phases 1 and 2 than during the REM phase, suggesting that the pathophysiological mechanisms common to NREM sleep and secondary generalization phenomena act in distinct manners for each type of epilepsy. In other words, structures involved in the propagation of the seizure of the temporal lobe are more activated during the initial phases of sleep than the structures involved in frontal lobe epilepsy. Based upon data from animal models [45–49], the authors suggested that brainstem reticular formation and the thalamus are involved in the discharges of secondary generalization of partial seizures.

In the nineties, an important epilepsy type, autosomal dominant nocturnal frontal lobe epilepsy, was described [50,51]. In this idiopathic syndrome, digital video-EEG analysis revealed partial seizures with frontal lobe seizure semiology [51], and an associated missense mutation was found within the gene encoding the alpha 4 subunit of the nicotinic acetylcholine receptor [52]. Although the altered expression of receptors may be related to the prevalence of seizures from the frontal lobe during sleep in this kind of epilepsy; autosomal dominant nocturnal frontal lobe epilepsy is characterized by genetic heterogeneity, and the missense mutation was not present in one group of patients with epilepsy from Europe [15,53].

5.1.2. Age of onset and seizure diurnal distribution

There is evidence that the distribution of seizures is also related to the age of onset. An extensive study conducted in patients with epilepsy (76 children and 100 adults) revealed the majority of seizures and partial seizures in both children and adults occurred

between the end of the morning and during the afternoon over the course of a 24-hour period [54]. Furthermore, the prevalence of seizures with an extra-temporal origin in children (particularly for frontal lobe epilepsy) and with a temporal origin in adults during the same period was demonstrated. There was a significant reduction in the number of seizures overall and in complex partial seizures during the entire night in both children and adults. In the pediatric group, the tonic partial seizures were significantly reduced during the last part of the night. With respect to the epileptogenic foci of seizures, night seizures with an extra-temporal and a temporal origin were reduced for children and those with only a temporal origin were reduced for adults with partial seizures. Seizures with an extra-temporal origin, especially those caused by frontal lobe epilepsy, occurred during the daytime period in children, whereas, in adults having the same clinical state, those seizures occur predominately during the nighttime period. Corroborating these data, pediatric patients had a significant reduction of seizures from frontal lobe epilepsy at nighttime, while adults with the same conditions experienced the majority of seizures during sleep [33]. In all age groups, EEG analysis [54] revealed a higher number of seizures during phases 1 and 2 of NREM sleep followed by phases 3 and 4, with the fewest partial seizures occurring during the REM phase. Taken together, all these findings indicate a clear distribution of seizures across the 24 hours of the day, with age and origin of the epileptic focus determining the predominant period for seizure activity. The mechanisms underlying this distinct distribution require further clarification [54].

5.2. Generalized seizures

Lennox–Gastaut syndrome is characterized as a typically infantile epilepsy, detected in children between 2 and 8 years of age, and it affects boys more often than girls. The etiology is predominantly idiopathic, though the disease has a cryptogenic origin in 30% of the cases. The seizures vary and include tonic, atonic and atypical absence. The paroxysmal phenomena occur preferably during NREM sleep [55]. A polysomnographic study of 206 seizures in patients with Lennox–Gastaut syndrome identified some of the alterations in the micro-structure of sleep [56]. The majority of seizures occurred during stages 3 and 4, while fewer seizures occurred during the REM sleep stage, suggesting that the synchrony of sleep may facilitate the epileptogenic potential in this specific syndrome.

Non-convulsive generalized seizures are characterized by brief moments of immobility and unresponsiveness toward the environment. These features are typical of absence epilepsy, an idiopathic disease that occurs predominantly during the drowsiness stage and the first phases of NREM sleep but is rare during REM sleep [57]. One hypothesis postulated that the same mechanism responsible for the generation of sleep spindles also gives origin to the spike–wave complex [58,59].

Juvenile myoclonic epilepsy is the most common form of idiopathic generalized epilepsy and is diagnosed in adolescence or early adulthood, predominantly between the ages of 12 and 18 years. Generalized tonic–clonic seizures occur after myoclonic jerks in most cases [60]. Myoclonic and tonic–clonic seizures are observed soon after awakening from an all-night sleep or a nap, and the number of spikes increases both at sleep onset and upon awakening [61].

In most idiopathic epilepsies, generalized seizures occurred during light NREM sleep and transition phases. Studies on feline epilepsy models have suggested the mechanisms of the sleep–wake cycle involved in triggering generalized seizures [37,62,63], including the propagation of generalized seizures by background EEG synchronization, phasic events (K complexes and spindles) and reduced muscle tone [37,62].

6. Effects of epilepsy on sleep

In addition to the particular effects of sleep upon each type of epilepsy, studies have also shown that the quantitative and qualitative

profile of the sleep cycle is dependent on the type of seizure and the origin of the epileptic focus. Patients with epilepsy of the frontal lobe presented with a sleep organization comparable to that of control subjects, though their sleep micro-structure was affected by the occurrence of seizures [33]. In the same study, a second group composed of individuals who had epilepsy of the temporal lobe experienced significant sleep fragmentation, sleep efficiency below normal levels, an increase in the number of awakenings and abnormalities in the micro-architecture of sleep. Awakenings preceded by K complexes concomitant with alterations in the morphology of sleep spindles were characteristic of the groups in this analysis, especially in patients with temporal lobe epilepsy. Taken together, these data suggest that chronic sleep deprivation as a result of sleep fragmentation in this type of epilepsy could cause the specific distribution of the seizures, especially those during the daytime period [33].

Epilepsy *per se* alters the sleep architecture of patients with temporal lobe seizures. Polysomnographic recordings showed that seizures occurring on the previous day caused a significant reduction in the duration of REM sleep, even in the absence of seizures during the nighttime period, but had no effect on other measures, such as sleep efficiency and drowsiness [44]. In contrast, ictal events occurring within the same period led to more conspicuous alterations; in addition to the post-seizure reduction in REM sleep, there was also an increase in daytime somnolence, a reduction of phases 2 and 4 of NREM sleep and an increase in REM sleep latency [44]. This latency was even more significant when the seizure occurred before the first REM episode. In addition, night seizures decreased sleep efficiency, with this alteration becoming more significant when the seizure occurred before the first REM episode. The authors suggest that factors including the occurrence of seizures, altered sleep architecture, the specific regulation centers of the sleep–wake cycle that are affected and psychological factors could be possible contributors to REM sleep reduction.

The literature contains conflicting data with regard to absence seizures. One investigation examining 10 patients with generalized seizures, most of whom had absence seizures, showed a significant reduction of phase 4 of NREM sleep in addition to a reduction of sleep efficiency, even in the absence of epileptic seizures [64]. The authors suggest that such alterations may be attributed to the epilepsy itself or to the use of antiepileptic medication. In contrast, other studies did not find any alteration in sleep parameters in patients with absence epilepsy [57,65].

Sleep alterations were also reported in Lennox–Gastaut syndrome. In an investigation on sleep architecture, Eisensehr et al. [56] found significant reductions in the REM phase and stage 2 of NREM, concomitantly with an increase in stage 3 of NREM. Because there was no reduction in the use of this medication, the use of antiepileptic medication could explain these findings.

7. Sleep deprivation and epilepsy

Several studies have suggested that sleep deprivation facilitates the appearance of IED. The activation percentage of IED in adult epileptic patients varies between studies, from 30% to 57% [66–68], and depends on the population observed as well as the duration of the polysomnography. Although the facilitating effects caused by sleep deprivation are obvious, IED also occurred during the vigil phase preceding sleep [69]. A study conducted in 30 patients with generalized idiopathic and focal epilepsy revealed a significant increase in cortical excitability in both groups after sleep deprivation [70]. In this study, the alteration in excitability was more evident in patients with generalized seizures, but these changes in excitability increased only in the ipsilateral hemisphere of the focal seizures in the focal seizure group.

On the other hand, there is controversy regarding the facilitation of epileptic seizures by sleep deprivation. A clinical study examining over 400 patients with epilepsy indicated that stress and fatigue as well as sleep deprivation are precipitating factors for seizure onset,

suggesting that these factors interact with each other to culminate in the pathophysiological epileptic event [71]. Corroborating the findings that sleep deprivation *per se* would not exert a significant effect on the occurrence of partial seizures, a recent study revealed that sleep deprivation did not alter the frequency of focal seizures in patients of the same age and sex and having the same epileptogenic focal site. These data indicate that only sleep deprivation would not facilitate the occurrence of epileptic seizures once the setting was changed, such that it was free of external factors, especially the daily stress to which the patients were subjected [72].

In primarily generalized seizures, especially in younger individuals, sleep deprivation facilitates the occurrence of paroxysmal events [6,73], as in the case of juvenile myoclonic epilepsy. In such individuals, the ictal events may be triggered by sleep deprivation and subsequent awakening [74]. In another study, approximately 28% of the patients who have idiopathic generalized seizures indicated that sleep deprivation was the main triggering cause of epileptic seizures [71].

8. Obstructive Sleep Apnea Syndrome and epilepsy

Sleep disturbances may be associated with epilepsy, and these disturbances may contribute to a worsening quality of life for the epileptic patient [75]. An extensive investigation conducted via questionnaires revealed that sleep disturbances were twice as common (38.6%) in the 486 adult patients with partial epilepsy when compared to the 492 non-epileptics (18%) [76].

Obstructive Sleep Apnea Syndrome (OSAS) afflicts 33% of partial epileptic patients who are refractive to treatment [77]. OSAS is characterized by recurrent episodes of breathing interruption (apnea) or a reduction in air flow during breathing, which, in turn, lead to a reduction of blood oxygenation and with micro-arousals. Most conventional antiepileptic medications may worsen OSAS because they affect the respiratory centers, reduce the threshold for awakening and induce weight gain [78].

Many studies have found a co-existence of OSAS with epilepsy. Investigating the existence of sleep disorders in 63 adults with epilepsy by polysomnography, Malow et al. [79] determined that 71% of these patients were diagnosed with OSAS. Corroborating such findings, another work demonstrated that 5% of adult patients with OSAS ($n=577$) were diagnosed with epilepsy, suggesting a tight correlation between the two diseases [80].

Sleep disturbances also affect younger patients, including children. A study examining 40 children who had generalized and focal seizures revealed that 42.5% had some respiratory disturbance during sleep, particularly OSAS (20%). Pediatric epilepsy patients with OSAS had an increased body mass, augmented sleep latency and a higher rate of oxygen desaturation when compared to the control group [81]. Another interesting study, which was conducted in adult epilepsy patients over 50 years-old, showed a worsening of OSAS in individuals with poorer control of the seizures, as compared to epileptic patients with an absence of paroxysmal events [82]. Taken together, these results indicate a strong relationship between epilepsy and OSAS, in which the sleep fragmentation and chronic sleep deprivation caused by OSAS may facilitate the appearance of IEDs and the occurrence of seizures. This important relationship deserves more investigation because approximately 7.5% to 17% of the population with epilepsy dies without any clear cause, where this may be associated with uncontrolled seizures [83–85]. The pathological mechanisms responsible for this phenomenon, known as Sudden Expected Death in Epilepsy (SUDEP), are not well understood [86]. Frequently, those patients affected by SUDEP were found in the prone position in their own bed. Avoidance of the major risks factors, as seizure control can be used to prevent SUDEP (reviewed in [87]). Further studies are warranted to address the pathophysiological process involved in this complex phenomenon.

The most common treatment for OSAS is the application of a continuous positive air pressure (CPAP) device. Not only does the

CPAP improve daytime somnolence and quality of life, it also allows for better control of seizures [75]. Evidence has suggested that CPAP be used as a co-treatment for some cases of epilepsy. Vaughn et al. [88] demonstrated that four of eight adult epileptic patients submitted to long-term CPAP treatment experienced a reduction in the frequency of seizures. Three of these patients became seizure-free, and the fourth had a 95% reduction in the number of seizures. In another study that was conducted in 28 adult epileptic patients submitted to CPAP treatment, 15 patients presented good compliance with the equipment, and the majority had better control of their seizures and increased alertness [79].

More recently, an investigation conducted in epileptic children and adults showed improvements in epileptic seizures (at least a 45% reduction in the number of the paroxysmal events) in those patients (1 child and 3 adults) who adhered to the CPAP correctly throughout the entire experimental period [89]. Corroborating these data, a recent extensive study conducted in adult epileptic subjects revealed a 50% reduction in seizures in approximately 28% of patients submitted to CPAP treatment [90]. Although this reduction was not significant when compared to the SHAM group due to the sample size being too small to be compatible with high powered statistical tests, the value of this study was in its characterization of a research model focused on epileptic patients utilizing CPAP.

Thus, the low quality of life of patients with epilepsy may be attributable, in part, to the chronic sleep deprivation to which these individuals are frequently exposed. The combination of the continuous use of antiepileptic medication, the epileptic condition *per se*, ictal events and the presence of sleep disturbances may culminate in this condition that, unfortunately, still prevails in most patients with epilepsy.

9. Final considerations

Although the relationship between sleep and epilepsy was initially recognized centuries ago, specific investigations into their potential connection were only resumed in recent decades. Since that time, much has been learned about this interaction, yet much more remains to be found. This missing information has the potential to significantly improve the daily routine of patients with epilepsy. The literature has described excellent animal models of epilepsy over the years; nevertheless few studies have focused on the physiological mechanisms underlying this association. Presently, the sleep disturbances associated with epilepsy are recommended for concurrent treatment in an attempt to reduce the frequency of epileptic seizures. Additional studies are still needed to investigate the involvement of other factors such as gender, age, the type of epilepsy and the regular habits of each individual subject.

Recognizing the common pathophysiological mechanisms (by means of experimental and clinical studies) of both phenomena – sleep and epilepsy – continues to be the only manner to improve the quality of life for those affected by spontaneous recurrent seizures.

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