




Proceedings of the Sleep and Epilepsy Workshop: Section 2 Comorbidities: Sleep Related Comorbidities of Epilepsy

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Abstract

Epilepsy is a chronic disease with multiple, complex comorbidities. Bidirectional relationships exist among seizures, sleep, circadian rhythms, and diseases within and outside of the central nervous system. Seizures fragment sleep and can contribute to development of sleep disorders, which in turn leads to worse overall health and more seizures. Moreover, treatment options are often limited by interactions with anti-seizure medications. Advances in the fields of epilepsy and in sleep medicine have been made separately, and therefore treating patients with these comorbidities necessitates interdisciplinary approach. The focus of this section of the Sleep and Epilepsy Workgroup was to identify methods of collaboration and outline investigational, educational, and treatment priorities to mutually advance what we consider a combined field.

Keywords

sleep, epilepsy, comorbidities, insomnia, circadian rhythm

Introduction

The lifelong nature of epilepsy as a chronic disease¹ invariably exposes patients to multiple factors that impair sleep. In turn, poor sleep worsens any disease, including epilepsy.^{2,3}

Comorbidities of epilepsy are diverse and severe. Patients with epilepsy (PWE) with unaddressed comorbidities, regardless of epilepsy status, can experience worse quality of life and higher mortality. Each comorbidity requires specialized expertise, but



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the experts in these multiple fields may have limited interactions with each other.

Sleep Loss, Insomnia, and Epilepsy Comorbidities

Insufficient sleep has negative consequences for nearly all physiological functions. The effects of sleep deprivation or insomnia, whether acute or chronic, matter to patients with or without epilepsy. Although all individuals can be negatively affected by poor or insufficient sleep, we don't know whether PWE may be particularly susceptible to deleterious effects of sleep disturbances. As reviewed in part 1,⁴ however, PWE may have less ability to compensate for comorbid risks than those without, and the consequences of sleep disturbances may severely worsen seizure control. Outside of seizure control or direct effects of epilepsy, the problems of sleep deprivation or insomnia fall into the 4 major areas outlined below.

Neuropsychiatric and Cognitive Consequences of Sleep Loss

Mood disorders are a common consequence of sleep loss.⁵⁻⁷ Many psychiatric disorders have sleep problems as the defining features, in the diagnostic criteria, which makes it difficult to separate sleep problems from other psychiatric conditions. For example, the following disorders include sleep alteration as part of the diagnostic criteria: bipolar disorder, generalized anxiety disorder, acute stress disorder, post-traumatic stress disorder (PTSD), separation anxiety disorder, and major depressive disorder. Not only can sleep disorders be inherent in many psychiatric diagnoses but sleep disturbances also exacerbate psychiatric disorders, and conversely, psychiatric disorders worsen sleep quality; treatments for one show evidence of improvement for the other.⁸

Major depression can serve as the template of these interrelationships. The incidence of sleep problems in depression is 90%; in fact, sleep alterations are in the diagnostic criteria. Depressed patients may have sleep-onset insomnia, sleep-maintenance insomnia, terminal insomnia (obligate early awakening), vivid nightmares, or subjective daytime sleepiness. Sleep deprivation is a significant and independent risk factor for suicide. Although hypersomnia (and its often-difficult-to-distinguish, activity-limiting fatigue) is a common complaint, objective measures such as mean sleep latency on multiple sleep latency test are normal. Polysomnography classically demonstrates poor sleep depth (inadequate N3 or slow-wave sleep), poor sleep continuity (long sleep-onset latency, low sleep efficiency), and high rapid eye movement (REM) sleep pressure (shortened REM latency and increased REM duration).^{8,9,10} Despite these relationships, a paradoxical relationship between depression and acute sleep deprivation is well known. Acute sleep deprivation transiently improves mood in 45% to 72% of those with depression.¹¹ The mechanism is unknown, but hypotheses include stress hormone activation or a "reset" of circadian rhythms via CLOCK gene transcription, or changes in medial prefrontal cortex, ventral anterior cingulate cortex, or the dopaminergic system.^{12,13}

In general, treatment of insomnia in these disorders improves psychiatric outcomes. Relationships between psychiatric disorders and insomnia are probably dynamic. For example, hypotheses in relationships between PTSD and insomnia propose that acute sleep deprivation during trauma exposure may be adaptive for survival, and subacute insomnia post-trauma may protect from consolidating the traumatic memory. However, chronic post-traumatic insomnia may contribute to the development of PTSD.^{8,14}

Sleep disturbances also accompany thought disorders. Patients with schizophrenia experience shorter sleep time and decreased slow-wave sleep. Most sleep problems, however, can be considered iatrogenic; weight gain from antipsychotics use can lead to increased sleep-disordered breathing (a problem that is undervalued in epilepsy).^{8,15}

Sleep disturbances are a prominent comorbidity of the dementias. Insomnia increases the risk of Alzheimer dementia (AD) specifically, but sleep-disordered breathing is associated with a higher incidence of dementias regardless of cause. Up to 2 of 3 patients with AD have sleep problems, including sundowning and other severe behavioral problems. In Lewy body dementia, 60% to 95% of patients experience excessive daytime sleepiness, insomnia, or REM sleep behavioral disturbances.^{16,17} Although PWE also experience high rates of insomnia,⁴ since the behavioral consequences may be less dramatic, attention to disturbed sleep patterns of patients and their caregivers may yield important improvements to daytime function.

Although somewhat outside of the scope of presentations during the workshop, the participants noted that parasomnias, because of an enhanced incidence in psychiatric disease, place patients at risk for misdiagnosis of seizures.¹⁸

Circadian Rhythm Disorders

"Circadian" in most neurological literature is meant as a synonym for "something that happens every 24 hours," whereas the biological definition requires that a circadian rhythm be a self-sustaining, endogenously maintained rhythm. Although sleep occurs in a 24-hour pattern, its daily occurrence is the cumulative effect of homeostatic sleep debt and the circadian timing system.^{19,20} A line of research that may yield important findings is the effect of a misalignment between an individual's biological time for optimal sleep (also known as the sleep phase of the circadian cycle) and social requirements or disease-provoked shifts in the phase of sleep, the circadian rhythm sleep-wake disorders.²¹ Most are familiar with jet lag. Another common, but often unrecognized, disorder is delayed sleep-wake phase disorder, in which an individual's sleep phase is later than socially dictated. This disorder is often seen in young individuals whose "night owl" preference for late activity—sometimes masquerading as insomnia—collides with social requirements for morning awakening, resulting in daytime hypersomnia. The acknowledgment that recognition and treatment of circadian disorders is not widespread lead to the recently formed International Association of Circadian Clinics, increased familiarity with which epilepsy research may benefit.

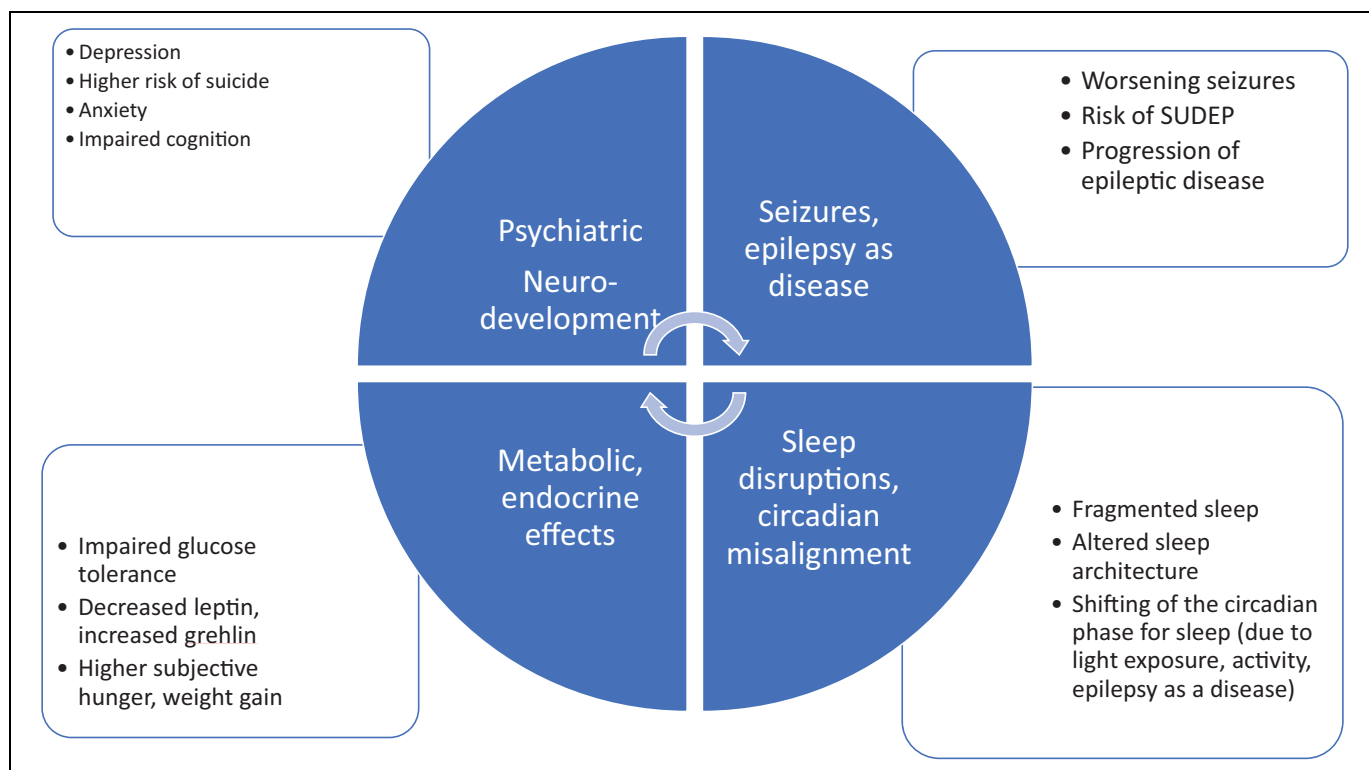


Figure 1. Schematic of the multilateral relationships among sleep, circadian rhythms, and epilepsy divided into major domains of comorbidities.

For instance, the epilepsy field may learn from examples resulting from endocrine and metabolism research. Circadian rhythms, as opposed to ineffective “catching up” on missed sleep, dictate metabolism and energy expenditure.^{22,23} Circadian misalignment has been linked to obesity, hypertension, glucose uptake, stress hormone release, and cardiovascular death.²⁴⁻²⁷ Sufficient sleep, synchronized to the appropriate circadian phase (or “biological night”) is important for hormonal homeostasis and function. Classic examples are the diminished nocturnal secretion of growth hormone, as well as impaired cortisol secretion with circadian misalignment.^{28,29}

Alteration in rhythmic endocrine function, whether mediated by circadian or other biological rhythms, may be particularly applicable to evaluating comorbidities in women with epilepsy, as treatment considerations have to include planned conception, pregnancy, and lactation.³⁰ Therefore, understanding the relationship of the circadian function and epilepsy may lead to breakthrough discoveries relating to improvement in seizure control, treating the comorbidities of epilepsy, and modifying the risk of Sudden Death in Epilepsy Patients (SUDEP).

The Developing Brain and Pediatric Considerations

Appropriate sleep has profound consequences in the developing brain; what is not well characterized are the consequences of disturbed sleep in the pediatric epilepsy patient.

The effects of sleep deprivation in children affect 4 important domains: (1) emotional functioning with increased anxiety and depression and insomnia; (2) cognitive functioning with poor attention, dropping school grades, and higher school dropouts; (3) behavioral issues including aggression, acting out, oppositional behavior, irritability, and low morale; and (4) daytime sleepiness with dozing off in class.³¹ Developmental consequences of acute sleep loss in children as revealed by functional neuroimaging include alterations in the frontoparietal, insular, and medial frontal cortex regions.³² Such alterations have unclear effects in the child with epilepsy who may have altered sleep on the basis of epilepsy or due to common causes of sleep deprivation such as prolonged digital media use,

The National Sleep Foundation has recently published a final report on the normal sleep requirements across childhood into adolescence.³³ Although both the American Academy of Pediatrics and the American Academy of Sleep Medicine strongly recommend later school times to promote longer sleep and account for the adolescent propensity for delayed sleep phase preference, implementation has been limited.^{34,35} The widespread social and technical pressures affecting normal children need to be evaluated in those with epilepsy as an at-risk population.

In summary, epilepsy has complex, bidirectional interactions between sleep and circadian phase, sleep disorders, and consequent comorbidities (Figure 1). These interactions are complex and require a multidisciplinary team approach for

both investigations and treatment. Therefore, the most urgent need would be to bring together this team.

Major Investigational and Treatment Priorities

Based on our discussions and the presented evidence, our multidisciplinary workgroup identified the following consensus priorities:

1. *Standard settings*: Agreements on standards on basic definitions (what constitutes “meaningful” sleep loss, experimental models, appropriate surveys, sleep-related outcomes, and physiological measures) and surrogate markers are required in the sleep-epilepsy community. The multidisciplinary, diverse backgrounds of sleep, epilepsy, circadian, and other specialists require common ground. This mutual work will lead to establishment of sleep-epilepsy phenotypes for modeling and more in-depth research.
2. *Standardized evaluation*: Specific standards are required to set minimum criteria of sleep and circadian data analysis, monitoring technologies, and clinical tools such as sleep surveys and quality of life measures pertaining to sleep.
3. *Caregivers*: Not much data exist on how disturbed sleep affects the caregivers in PWE. We expect that the morbidity load is high for both the patient and the patient’s family. Therefore, we need to better understand and manage the consequences for the patient’s family.
4. *Education*: Needs include cross education among diverse fields involved in sleep and epilepsy research, as well as education for families, patients, general practitioners, and epileptologists.
5. *Interaction*: Formal venues offering networking, education, academic advancement, and research networks would knit together a diverse group of clinicians, researchers, and advocates. Formal periodic interactions among our multiple fields would enable us to achieve commonality and high standards.

In conclusion, good sleep is essential for the overall health of each individual and is particularly important for PWE. It is necessary for the normal growth and development of the developing brain. It helps daytime cognitive functioning, memory consolidation, and improved attention span. Sleep loss leads to not only poor neurocognitive functioning but also mood disturbances, drowsy driving-related accidents, metabolic disturbances, and a higher risk of suicide as well as cardiac death. Improved sleep leads to improved seizure control and overall improved quality of life. Addressing the major funding priorities will lead to higher quality research studies, a better understanding of the complex sleep-epilepsy phenotypes, improvement of clinical care, and better function of the patient’s families. Sleep epilepsy education is paramount for achieving these goals.


Declaration of Conflicting Interests

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