

The Management and Alternative Therapies for Comorbid Sleep Disorders in Epilepsy

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Abstract: Background: There is a complex and interactive relationship between sleep and epilepsy. Sleep disorders are common in patients with epilepsy, and methods for managing sleep disorders in patients with epilepsy are limited.

Objective: This review addresses the relationship among sleep, sleep disorders, and epilepsy, focusing on the management of sleep disorders in epilepsy, including some complementary and alternative therapies.

Methods: The terms related to “sleep” and “epilepsy” were searched in “Pubmed” and “Cochrane Library”.

Results: Sleep stages differently affect both seizures and interictal epileptiform discharges. Seizures disrupt sleep architecture greatly, especially when occurring during sleep in the night. Insomnia and obstructive sleep apnea (OSA) are the most frequent types of comorbid sleep disorders in patients with epilepsy. Pharmacological agents with both anti-convulsant and sedative effects are the priorities for comorbid sleep disorders in epilepsy. Continuous positive airway pressure (CPAP) therapy is the most effective non-pharmacological method to improve OSA and reduce seizures. Complementary and alternative therapies such as Chinese traditional medicine, cognitive behavioral therapy, meditation, yoga, neurofeedback, and acupuncture may have benefits in reducing seizures and improving sleep quality simultaneously by alleviating stress and seizure triggers; however, evidence-based therapies are still deficient.

Conclusion: Management of sleep disorders in patients with epilepsy is challenging. Large-scale randomized controlled clinical trials are in demand to guide the treatments in the future.

Keywords: sleep disorders, epilepsy, insomnia, sleep-disordered breathing, parasomnia, management, complementary and alternative therapies.

1. INTRODUCTION

Epilepsy is a chronic brain disease characterized by hyper-synchronized excitatory neuronal discharges and recurrent clinical seizures. The interictal epileptiform discharges (IEDs) and seizures in patients with epilepsy may occur at different times within the 24h sleep-wake cycle. Following circadian rhythms, most epileptic seizures occur in a nocturnal or diurnal pattern [1]. Sleep disorders are frequent due to complex interactive correlations between sleep and epilepsy [2]. According to a questionnaire-based study, the prevalence

of subjective sleep disturbance (insomnia, sleep-related respiratory disorders, parasomnias, excessive daytime sleepiness) in patients with focal epilepsy is 38.6%, which is about twice as high as in the general population (18%) and have positive associations with great impairment of quality of life in patients with epilepsy [3]. The therapies are still in deficiency and management of sleep disorders in patients with epilepsy is challenging.

In this review, we addressed the relationships among sleep, sleep disorders, and epilepsy, focusing on the management of sleep disorders in epilepsy, including some complementary and alternative therapies. We searched the terms “sleep”, “sleep disorder”, “insomnia”, “sleep-disordered breathing”, “parasomnia”, and “epilepsy”, combined with “management”, “alternative medicine”, or “complementary therapy” in “Pubmed” and “Cochrane Library”.

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2. THE INTERACTIONS BETWEEN SLEEP AND EPILEPSY

Generally speaking, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep have distinct electrophysiological features that exert different influences on IEDs and seizures. NREM sleep represents a state of electroencephalographic (EEG) synchronization that promotes diffuse cortical synchronization and enhances interhemispheric impulses, while REM sleep is a desynchronized EEG state that has an inhibition of thalamocortical synchronization and tonic reduction of interhemispheric impulses [4]. Hence, NREM sleep is a seizure promoter and REM sleep is a seizure protector.

From another aspect, seizures disturb the sleep-wake cycle and cause the disruption of sleep architecture, especially when seizures occur in sleep, causing sleep fragments, reduction of REM sleep, and increase of N1 stage in NREM sleep, further resulting in decreased total sleep time and increased wake time [5, 6]. Studies indicate that seizures in patients occurring during sleep cause a reduction in REM sleep and an increase of N1 stage in NREM sleep, further resulting in decreased total sleep time and increased wake time [5]. Other macrostructural sleep anomalies include increased latency to sleep onset, an increase in the number and duration of awakenings after sleep onset, reduced sleep efficiency, reduced or abnormal k-complexes and sleep spindles, reduced or fragmented REM sleep, and increased stage shifts [7, 8]. As for microstructural sleep anomalies, frequent microarousals and a significant increase in cyclic alternating pattern time and rate are usually observed in patients with epilepsy [9]. In addition, medicinal issues related to antiseizure medicines (ASMs) exert multiple effects on sleep [10].

3. SLEEP DISORDERS IN PATIENTS WITH EPILEPSY

The major diagnostic sections of sleep disorders classified by the third edition of the International Classification of Sleep Disorders-3 (ICSD-3) are listed as follows: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and other sleep disorders [11]. The standard procedures of diagnosing sleep disorders in patients with epilepsy have been issued recently by the European Academy of Neurology and the European Sleep Research Society [12].

Insomnia is the commonest sleep disorder in patients with epilepsy. The prevalence of insomnia in adults with epilepsy is from 36-74%, whereas the prevalence of moderate to severe insomnia symptoms is about 15-51% [7, 13]. Poor sleep quality in patients with epilepsy is associated with frequency of seizures, fatigue, daytime sleepiness, and depression [14].

Sleep-disordered breathing (SDB) precipitates the occurrence of a group of disorders, including obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders [11]. The prevalence of OSA in patients with medically refractory epilepsy is about 30% [15, 16], and it is around

30-60% for children with epilepsy [17]. Among a large cohort of 416 patients with epilepsy referred for a sleep evaluation, 75% of them showed OSA [7]. The risk factors for OSA include older age, obesity, focal seizures, and long epilepsy duration [18]. CSA is relatively rare in patients with epilepsy, which is about 4% in 416 patients with epilepsy [7]. The Sleep Apnea scale of the Sleep Disorders Questionnaire (SASDQ) has been validated in epilepsy patients to screen OSA [19]. Sudden unexpected death in epilepsy (SUDEP) usually occurs in bed at night and is presumed to be closely correlated with sleep [20, 21], which might be caused by the OSA in these patients when there is no intervention by other people under that condition [22].

Parasomnias such as REM sleep behavioral disorder (RBD) are relatively frequently seen in elderly epilepsy patients, which are usually confounded with sleep-related hypermotor epilepsy (SHE) [23, 24]. A video-polysomnography recording compared 59 patients with disorder of arousal (DOA) with 30 patients with SHE and found that the total number of motor events was significantly lower in DOA (3.2 ± 2.4) than in SHE patients (6.9 ± 8.3 ; $p = 0.03$). Episodes occurred mostly during N3 in DOA and N2 in SHE, and the last major event outside N3 was highly suggestive for SHE. The last minor event in N3 was highly suggestive for DOA [25]. Frontal Lobe Epilepsy and Parasomnias (FLEP) scale has been developed to discriminate parasomnias from SHE [26].

The prevalence of sleepwalking and sleep paralysis is as high as 15.3% and 11.7% in a cohort of patients with genetic generalized epilepsy and their relatives, respectively, implying a shared genetic pathway [27]. A three-case series of the coexistence of juvenile myoclonic epilepsy and narcolepsy indicated shared genetic predisposition of HLA-DQB1*0602 between these two diseases; however, more evidences are required to demonstrate it [28]. The prevalence of restless leg syndrome (RLS) was between 18-35% and periodic limb movement disorder (PLMD) was 5% among patients with epilepsy who were referred to a sleep lab [15].

In some cases, sleep disturbances may be caused by ASMs. Xu *et al.* reported that in a total of 201 patients, 34% had sleep disturbances with focal seizures on at least 2 AEDs [29]. Vagus nerve stimulator (VNS) is a surrogate therapeutic method for drug-refractory epilepsy, which might be associated with OSA [30, 31]. Psychiatric comorbidities such as depression are significantly correlated with bad sleep quality [32], which may aggravate sleep disturbances in patients with epilepsy.

The mechanisms underlying sleep and epilepsy are not very clear yet. Feng *et al.* found that thalamic nuclei have divergent activity patterns, which may respectively participate in seizure propagation, impaired level of conscious arousal, and altered relay of information to the cortex during focal limbic seizures [33], and the disrupted thalamic-cortex network function may explain the high comorbidity of sleep disorders and epilepsy. The dysfunction of the hypothalamus may be involved in the pathophysiology of sleep disorders in epilepsy either as a close association between epileptiform activity and alterations in sleep architecture; this has been observed in a spontaneous epileptic rat model related to hypothalamic pathology [34].

4. THERAPEUTIC METHODS FOR SLEEP DISORDERS IN PATIENTS WITH EPILEPSY

4.1. Pharmacological Therapies

Different types of medicines, including sedative-hypnotics, antidepressants, and ASMs have been used to control insomnia in patients with epilepsy. Short-term use of drugs that do not interfere with seizure threshold is recommended [35]. Benzodiazepines (BZDs) can be used for patients with difficulties in initiation and maintenance of sleep, which may have a simultaneous anti-seizure effect. However, a long-term BZDs use may cause dependence and abuse and is associated with disrupted sleep structure [36]. Zolpidem and eszopiclone are non-BZDs hypnotics, which have a more quick and significant therapeutic efficiency than BZDs, but the side effects of enuresis, sleepwalking, confused arousals, chronic abuse, and withdrawal seizures should be taken into account [37]. Melatonin reduces mean sleep latency by 11 min ($p=0.02$) and mean wake after sleep onset (WASO) by 22 min ($p=0.04$) as compared to placebo in children with epilepsy [38]. Antidepressants, such as trazodone, may be beneficial if insomnia is caused by depression [39], but tricyclic drugs and selective serotonin reuptake inhibitors (SSRIs) have a high risk of inducing seizures, especially when used in high doses [40]; about 36% adverse effects of insomnia during treatment with escitalopram have been reported, especially in the first 3-4 weeks of treatment [41]. Some ASMs such as gabapentin and pregabalin have benefits for sleep, which improve sleep efficiency, increase slow-wave sleep and REM sleep, and improve daytime attention in patients with focal epilepsy and insomnia [42].

Cannabidiol (CBD) is a type of cannabis derivatives that exerts effect through CB1 and CB2 receptors. By opening K^+ channels and blocking Ca^{2+} channels, CB1 receptors reduce neuronal excitability and neurotransmitter release [43]. CBD has been used to control drop attacks in Dravet syndrome and Lennox-Gastaut syndrome [44]. The common adverse effects of CBD include pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia, and abnormal behavior [45]. Cannabis may have both beneficial and harmful effects on sleep. Studies suggest that cannabis has potential therapeutic benefits for insomnia, sleep apnea, and sleep disturbances secondary to chronic pain, multiple sclerosis, Parkinson's disease, and post-traumatic stress disorder, *etc.* However, cannabis withdrawal has a negative impact on sleep efficiency, total sleep time, WASO, REM sleep time, and leg movement activity [46].

In patients with RLS, iron-replacement therapy can be used if patients have an iron deficiency. Drugs such as dopaminergic agonists pramipexole, gabapentin, and pregabalin are helpful in patients with RLS [47].

Clonazepam and melatonin are effective to control the hyperkinetic symptoms associated with RBD [48]. Melatonin was demonstrated to have anticonvulsant activity in both animal models and children with refractory epilepsy [49, 50].

The wakefulness-promoting agents, modafinil (the agonist of adrenergic $\alpha 1$ and histaminergic H1 receptors) and Wakix (pitolisant, an inverse agonist of the histamine H3 receptor), not only have been used in treatments for cata-

plexy and hypersomnolence but also have the potential to exert antiepileptic effects [51-53].

5. NON-PHARMACOLOGICAL THERAPIES

Continuous positive airway pressure (CPAP) therapy is an effective method for OSA that improves oxygen saturation levels during sleep. Decreased spike rates have been found after 2-3 days of treatment with CPAP during slow-wave sleep, thus improving seizure burden in patients with the comorbidity of epilepsy and OSA [17]. However, CPAP treatment alone is ineffective for VNS-induced SDB. VNS parameters need to be adjusted as VNS-induced SDB events decrease in a dose-dependent manner [54].

A significant decrease in total sleep, an increase in REM sleep, and an intact slow-wave sleep have been observed after ketogenic diet therapy, having a positive correlation with improved quality of life in children with refractory epilepsy [55, 56].

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are non-invasive neuromodulating methods. Low-frequency repetitive TMS treatment has also been demonstrated to have an antiepileptic effect on patients with refractory focal seizures [57, 58]. TMS also has been used to treat sleep disorders, including OSA, sleep bruxism, RLS, narcolepsy, and primary insomnia, but the stimulating targets at brain regions are different based on their pathophysiological brain networks [59-61]. The therapeutic use of tDCS has been studied regarding pain, epilepsy, depression, movement disorders, *etc.* [62]. A recent randomized, double-blind, sham-controlled, and three-arm parallel, multicenter study in China demonstrated that 14 consecutive days of tDCS therapy significantly decreased seizure frequencies in patients with refractory focal epilepsy [63]. However, no consensus for tDCS to be used in sleep disorders exists, although a few studies have shown that it could regulate the total sleep time of healthy people [64, 65].

5.1. Complementary and Alternative Therapies

About 38% of all adults, 44% of adults from 50-59 years old, and 12% of children were using complementary and alternative medicines (CAM), as reported by the National Center for Complementary and Alternative Medicine (NCCAM), in 2007. At least 24% to 44% of patients use CAM specifically for treating epilepsy [66]. Methods of CAMs include Chinese traditional medicines, natural products, and non-pharmacological alternative methods, such as cognitive and behavioral techniques (CBT), mindfulness training, yoga and meditation, biofeedback, and acupuncture, *etc.* We have summarized some randomized clinical trials (RCTs) of CAM therapies for epilepsy and their probable effects on sleep, moods and cognition, simultaneously (Table 1).

6. BOTANICALS AND CHINESE HERBAL MEDICINES

There are a plenty of botanicals options that have been reported as a treatment for epilepsy, such as Dianxianning, St. John's wort, kava, rosenroot, ginkgo biloba, passiflora incarnata extract, huperzine A, xylaria nigripes, and sometimes a mixture of extracts, for example, Chai-Hu-Long-Ku-

Table 1. Randomized controlled trials on complementary and alternative therapies for epilepsy and with probable effects on sleep and moods.

Therapeutic Methods	The Number of Cases	Effects on Seizures	Effects on Sleep	Effects on Moods	Refs.
Xylaria nigripes	39(treatment): 42(placebo)	No increase in seizure frequency and severity	A decrease of PSQI score but with no statistical difference	Improved total effective rate of depression	[70]
Cognitive behavioral therapy	18(CBT): 19(control)	Decreased seizure frequency	Not mentioned	Improved depression and psychosocial function compared with baseline	[77]
Mindfulness-based therapy	30(MT):30(SS)	Reduction of seizure frequency	Not mentioned	Reduction in depressive and anxiety symptoms, and improvement in delayed memory	[82]
Yoga	10(yoga): 10(control)	Seizure freedom and improvement in EEG	Not mentioned	Not mentioned	[85]
Neurofeedback training	15(SMR): 16(SCP): 13(NFB)	No difference	Not mentioned	Improved cognition and quality of life	[88]

Abbreviations: CBT: cognitive behavior therapy; PSQI: Pittsburg Sleep Quality Index; MT: mindfulness-based therapy; SS: social support; EEG: electroencephalogram, SMR: sensorimotor rhythm; SCP: slow cortical potentials; NFB: sham neurofeedback.

Mu-Li-Tan (TW-001) [67, 68]. These drugs usually have sedative and antidepressant effects that may be beneficial for treating comorbid sleep disorders in epilepsy [68]. The pharmacological basis for these medicines may be related to the effects on GABA_A receptors, L-type Ca²⁺ channels, Na⁺ and K⁺ channels, and Ca²⁺-activated potassium channels [69], but their mechanisms still remain unclear.

There are currently no sufficient randomized clinical trials (RCTs) to supply evidence-based data for botanical options in the treatment of epilepsy and comorbidities [67]. In 2015, our double-blind, placebo-controlled, randomized, multi-center, superiority study observed that xylaria nigripes alleviated depressive symptoms and improved quality of life in patients with epilepsy after 12 weeks of treatment compared with the control group [70]. Xylaria nigripes could improve insomnia in 4 weeks compared with pre-treatment [71], and our study demonstrated no increase in seizure frequency and severity after treatment with xylaria nigripes [70]. Basic research indicates that xylaria nigripes may induce the activity of glutamate decarboxylase, which possesses neuro-protective, anti-oxidative and anti-inflammatory effects [72-74].

7. COGNITIVE BEHAVIORAL THERAPY (CBT)

CBT encourages patients to learn to identify maladaptive thought patterns and replace them with healthier cognitive and behavioral responses [75]. High-quality evidence strongly recommends CBT as the first-line treatment for chronic insomnia in adults of any age [76]. In a randomized study, seizure frequency was significantly reduced in the CBT group compared to a relaxation control, maintained at 3 months following treatment [77]. Quite a few evidences have demonstrated CBT to be effective to reduce anxiety and depressive symptoms in patients with epilepsy [78-80]. Therefore, CBT may be suitable to control insomnia comorbid

with epilepsy, probably by prompting healthy behavior change and improving mood problems [81].

8. RELAXATION THERAPIES

Relaxation therapies are methods that promote muscle relaxation, including meditation, yoga, neurofeedback, *etc.* [75]. Mindfulness is a form of mental meditation. A study showed that mindfulness-based therapy significantly improved the quality of life of patients with delayed memory, and reduced depressive and anxiety symptoms and seizure frequency, in an RCT of 60 patients with refractory epilepsy [82].

Yoga may induce relaxation, diminish stress, and influence the EEG and autonomic nervous system, thereby controlling seizures [83]. A meta-analysis taking into account 50 subjects with epilepsy from two trials revealed that yoga treatment might have possible beneficial effects on seizures control when compared with no intervention or sham yoga [84]. A recent RCT involving 20 children with epilepsy showed that seizure freedom and improvement in EEG were observed after 6 months of yoga add-on therapy [85]. Yoga may also be beneficial for improving sleep quality and insomnia *via* muscle relaxation [86]. However, yoga is not recommended for the treatment of insomnia in the recent European guidelines due to poor evidence [76].

EEG-based biofeedback, also called “neurofeedback”, involves an increase in amplitude and occurrence of the 12-15 Hz sensorimotor rhythms over central electrodes that may reflect a state of alertness and relaxation [87]. A meta-analysis showed that 82% of participants had >30% seizure reduction after neurofeedback therapy [75]. A recent RCT illustrated that sensorimotor rhythm neurofeedback training improved cognition in 44 children and adolescents with controlled focal epilepsy [88]. The effectiveness of neurofeedback in the treatment of chronic insomnia is still controver-

sial [89]. A double-blind, placebo-controlled study concluded that the efficacy of neurofeedback on primary insomnia exhibited no difference with unspecific placebos [90].

9. ACUPUNCTURE

The mechanism of acupuncture for treating diseases is still unknown, although a hypothesis has been proposed that it can correct the imbalance of energy in the body and maintain internal homeostasis [91]. Acupuncture has been demonstrated to have potential efficacy in animal models, and it has also been shown that low-frequency electroacupuncture (EA) stimulation of Feng-Chi acupoints improved epilepsy and epilepsy-induced sleep disruptions in the pilocarpine-induced rat epilepsy model [92], whereas 100 Hz EA of bilateral Feng-Chi acupoints exacerbated seizures and related sleep disturbances [93]. However, reviews indicate that acupuncture is not effective for treating epilepsy in both pediatrics and adults [91, 94]. There are some RCTs that have revealed that acupuncture improves primary insomnia, insomnia after stroke, and sleep disturbances in patients with traumatic brain injury and post-traumatic stress disorder, *etc.* [95-97], but it is not recommended for the treatment of insomnia in European guidelines may be due to its poor evidence [76].

In summary, most RCT studies on CAM therapies simply evaluated their effects on seizures and psychosocial functions, but not on sleep. Compared with conventional drugs, CAM therapies have the advantages of non-invasive or minor side effects. However, as the therapeutic targets of CAMs are not focused and specific, most of them are add-on therapies. The common limitations of CAM studies are that samples are too small to obtain unbiased and meaningful conclusions, and most studies did not evaluate the effects of CAMs on sleep disorders in patients with epilepsy. CBT is the first-line treatment for primary insomnia and it has benefits for epilepsy also; therefore, it is worthwhile to develop a large-scale RCT to demonstrate the effects of CBT on comorbid sleep disorders in patients with epilepsy.

CONCLUSION

There is an interactive complex relationship between sleep and epilepsy. Sleep states not only have an influence on seizures but also affect the distribution and frequency of IEDs. Epileptic seizures, especially seizures arising from sleep in the night, greatly disrupt sleep architecture. Comorbid sleep disorders are common in patients with epilepsy, among which insomnia and OSA are the most frequent types.

Certain types of ASMs such as gabapentin, pregabalin, and BDZs have benefits for sleep, and medicines for sleep disturbances, such as melatonin, may have anticonvulsant properties as well. The most effective non-pharmacological therapeutic method is CPAP for OSA, which may decrease the incidence and frequencies of nocturnal seizures in patients with epilepsy. Chinese traditional medicines may have therapeutic effects on epilepsy and improve sleep quality, but their effective components and pharmacological mechanisms are still unclear. Other non-pharmacological CAMs, including CBT, meditation, yoga, neurofeedback, and acu-

puncture, *etc.* may reduce seizures and sleep disturbances *via* alleviating stress and seizure frequency triggers; however, they are not supported as effective methods by the recent European guidelines. Large-scale RCTs are in demand to guide evidence-based treatments for the comorbidity of sleep disorders and epilepsy in the future.

LIST OF ABBREVIATIONS

ASMs	=	Antiseizure Medicines
BZDs	=	Benzodiazepines
CAM	=	Complementary and Alternative Medicines
CBD	=	Cannabidiol
CBT	=	Cognitive and behavioral techniques
CPAP	=	Continuous positive airway pressure
CSA	=	Central sleep apnea
DOA	=	Disorders of arousal
EA	=	Electroacupuncture
EEG	=	Electroencephalogram
IEDs	=	Interictal epileptiform discharges
NREM	=	Non-rapid eye movement
OSA	=	Obstructive sleep apnea
PLMD	=	Periodic limb movement disorder
RBD	=	Sleep behavioral disorder
RCTs	=	Randomized clinical trials
REM	=	Rapid eye movement
RLS	=	Restless leg syndrome
SDB	=	Sleep-disordered breathing
SHE	=	Sleep-related hypermotor epilepsy
SSRIs	=	Selective serotonin reuptake inhibitors
tDCS	=	Transcranial direct current stimulation
TMS	=	Transcranial magnetic stimulation
VNS	=	Vagus Nerve Stimulator
WASO	=	Wake After Sleep Onset

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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