

# Epilepsy and sleep

**Deepti Vibha\* ; Manjari Tripathi\*\***

Department of Neurology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi  
Department of Neurology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi

\*Assistant Professor & \*\*Associate Professor

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## Abstract

The relationship of epilepsy and sleep is widely known but the causative mechanism and its implications in diagnosis and management is still a matter of curiosity and research. The effect of epilepsy in disturbing normal sleep architecture and the effect of pre morbid sleep disturbances in worsening epilepsy show the close relationship between them. This review discusses how each one influences the other. Finally the epileptic syndromes which are typically described with sleep are discussed.

**Keywords:** epilepsy; sleep

## Introduction

There is a complex association of epilepsy with sleep. The relationship of epilepsy to sleep architecture and the influence of sleep in epilepsy and epileptiform discharges has an important bearing while dealing with patients with epilepsy. This review attempts to look at the mutual relationship as it is currently understood, looking at each aspect separately.

The review will be covered under the following headings (table 1).

### A. Effect of epilepsy on sleep

A variety of sleep architectural abnormalities have been reported in patients with epilepsy with disturbance especially in REM (Rapid Eye Movement) sleep (1).

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*Address for correspondence*

**Dr Manjari Tripathi**

Associate Professor  
NIH Fellow (UCLA) , Department of Neurology  
Room No 705, Neurosciences Centre  
All India Institute of Medical Sciences New Delhi,  
India, 110029. Tel: 26594494 / 26588248(O)  
FAX: 26588248/ 26588166

Excessive daytime sleepiness (EDS) occurs more commonly in patients with epilepsy. Whether it is in part due to the epileptic syndrome or an effect of AEDs is still an unresolved issue (2). Primary sleep disorders like obstructive sleep apnea (OSA) also affect vigilance, sleep quality, & quality of life in the people with epilepsy (3).

### 1. Effect on sleep organization

Seizures and antiepileptic drugs (AEDs) affect sleep macro architecture and may produce excessive daytime sleepiness (EDS) in patients with epilepsy. It has been shown that patients with epilepsy have disturbed, decreased and labile REM sleep (4), difficulty in sleep onset resulting in reduced total sleep time and sleep efficiency (5), delayed onset REM sleep (6) and increased number of nocturnal arousals and awakenings (1). These changes may be present even in the absence of seizures and AEDs (7). The findings suggest that sleep in the epileptic brain is inherently unstable. These effects are more pronounced after generalized motor and multiple focal seizures in a given night. Daytime seizures produce a decrease in REM sleep and prolonged sleep latency the night following the seizure and shorter mean sleep latency on the multiple sleep latency test (MSLT) the following day (8). Thus the instability of sleep promotes

Table 1: Outline of the review

A. Effect of epilepsy on sleep	B. Effect of sleep on epilepsy and epileptiform discharges	C. Specific syndromes of sleep and epilepsy	D. Parasomnia and epilepsy
1. Effect on sleep organization	1. Effect of sleep wake cycle on occurrence of seizures	1. Nocturnal Frontal Lobe Epilepsy (NFLE)	1. Differentiating parasomnia from seizure
2. Effect and frequency of sleep disorder symptoms in epilepsy	2. Effect of sleep on Interictal Epileptiform Discharges (IEDs) a) In partial epilepsy b) In generalized epilepsy	2. Juvenile Myoclonic Epilepsy (JME)	
3. Primary sleep disorders in epilepsy	3. Effect of sleep deprivation	3. Benign epilepsy with centro-temporal spikes (BECTS)	
4. Effect of anti epileptic drugs (AEDs) on sleep		4. Landau-Kleffner syndrome (LKS)	
5. Effect of epilepsy surgery and vagal nerve stimulation on sleep			

seizures, and seizures in turn fragment sleep, thus facilitating the epileptic process (9).

## **2. Effect and frequency of sleep disorder symptoms in epilepsy**

Patients with epilepsy are significantly more likely to report nocturnal and early morning awakenings even though their total hours slept was comparable to those of the controls. Poor sleep was reported among 37% of patients who had epilepsy (10). Epworth Sleepiness Scale scores of 10 or greater are observed in 11% to 28% of epilepsy patients (11). In order to have objective measurement of sleep problems, a study conducted on 30 patients who were on treatment for epilepsy showed mean sleep latency (MSL) to be 8.4 minutes, borderline by standard criteria and pathologic hypersomnia (MSL<5 minutes) in 10% of cases (12).

## **3. Primary sleep disorders in epilepsy**

OSA may be more common than suspected in patients who have epilepsy. In a study of 39 patients with epilepsy refractory to medical treatment who underwent polysomnography (PSG), one third were found to have OSAS that was moderate and severe in 13% of cases (13). Improved seizure control following treatment of OSAS with continuous positive airway pressure (CPAP), positional therapy, weight reduction, pharmacotherapy, tonsillectomy, and tracheostomy has been reported in both adults and children (14).

## **4. Effect of Anti Epileptic Drugs (AEDs) on sleep**

The exact evidence of effect of AEDs on sleep has been contaminated by methodologic variations across studies, including sample composition, dose, timing, and duration of treatment, failure to control for seizures and concomitant AEDs, and PSG methodology. The long term effects of AEDs on nocturnal sleep are shown in table 2 (15). Some of these effects are reversed with long-term treatment.

## **5. Effect of epilepsy surgery and vagal nerve stimulation on sleep**

The vagus nerve stimulator (VNS) is used for treatment of refractory seizures. As projections from the vagus nerve undoubtedly stimulate brainstem structures, some of which are related to sleep and alertness, it is possible that this device has independent effects on sleep and wakefulness (16). While some studies have found improved sleep macroarchitecture, increased delta power, normalization of previously dampened background sleep rhythms, and improved quality of sleep (17, 18), there is evidence to show that VNS may predispose to obstructive sleep apnea (OSA) by altering upper airway muscle tone or interfering with central respiratory mechanisms (19, 20). A sleep assessment including sleep history followed by diagnostic PSG in cases of suspected OSA should be performed before VNS implantation.

Table 2: Long term effects of AEDs on nocturnal sleep

AED	Sleep efficiency	Sleep latency	Stage 1	Stage 2	Slow wave	REM
Phenobarbitone	Increased	Decreased	Not known	Increased	No change	Decreased
Phenytoin	No change	Decreased	Increased	Increased	Decreased	No change
Primidone	Not known	Decreased	Not known	Not known	Not known	No change
Carbamazepine	No change	No change	No change	No change	No change	No change
Valproate	Not known	No change	Increased	Decreased	No change	No change
Ethosuximide	Not known	Not known	Increased	Not known	Decreased	Not known
Gabapentine	No change	No change	No change	No change	Increased	Increased
Lamotrigine	No change	No change	No change	Increased	Decreased	Increased
Topiramate	No change	Decreased	No change	No change	No change	No change
Levetiracetam	Not known	Not known	No change	No change	No change	No change
Topiramate	Not known	Not known	Not known	Not known	Not known	Not known
Pregabalin	Increased	Decreased	Not known	Not known	Not known	Not known
Zonisamide	Not known	Not known	Not known	Not known	Not known	Not known

## B. Effect of sleep on epilepsy and epileptiform discharges

### 1. Effect of sleep wake cycle on occurrence of seizures

Two patterns of sleep related epilepsy patterns emerged from early studies: (1) patients who had nocturnal seizures had peak seizure occurrence within the first 2 hours of sleep (between 9 PM and 10 PM) and 1 hour before awakening (between 4 AM and 5 AM); (2) diurnal seizure patients had a peak shortly after awakening (between 7 AM and 8 AM), a mid-afternoon increase (between 4 PM and 5 PM), and a peak in the evening (between 7 PM and 8 PM) (21). Later studies observed that patients who have frontal lobe epilepsies (FLE) typically arise from sleep, almost exclusively during non-rapid eye movement (NREM) sleep during an episode of seizure (22). Secondary generalization of partial seizures tends to occur more often during sleep (28%) compared with wakefulness (18%), and frontal lobe seizures tend not to secondarily generalize during sleep (23). Seizures of mesial temporal origin may be particularly vulnerable to circadian effects (24).

### 2. Effect of sleep on Interictal Epileptiform Discharges (IEDs)

Effect of sleep on the EEG in epilepsy has interested

epileptologists for long. Sleep and sleep-deprived electroencephalograms (EEGs) are commonly used diagnostically to increase the yield of epileptiform activity.

*a) In partial epilepsy:* Many studies have demonstrated that NREM sleep activates IEDs in partial epilepsies (25, 26). Also when more than one epileptic focus is seen during wakefulness or non-REM sleep, discharges persisting during REM sleep are more likely the site of onset for the patient's seizures (26, 27).

*b) In generalized epilepsy:* Generalized IEDs in IGE usually increase in NREM sleep (28). Typically, spike rates increase with sleep onset, continue to increase through NREM 3, diminish sharply in REM sleep, and increase sharply in the morning after awakening. During NREM sleep, generalized spike-wave discharges often become more disorganized, increase in amplitude, and slow in frequency, sometimes with the addition of polyspikes, whereas the morphology in REM sleep is similar to wakefulness (29).

### 3. Effect of sleep deprivation

Sleep deprivation has long been recognized as a seizure precipitant, reported by 25% of patients who have epilepsy, more often in those who have awakening epilepsy (30). Whether the IED activation produced by total sleep deprivation (TSD) is caused by sleep itself (greater

amounts of sleep recorded, sampling effects) or because TSD exerts an independent activating effect has been the subject of intense debate (24). In a study of 588 patients with TSD, IEDs appeared in the first 30 minutes in 46%, after 1 hour in 57%, after the second hour in 69%, after the third hour in 73%, and after the fourth hour in 75% of cases (31). Comparative studies largely confirm that TSD activates IEDs in 23% to 93% of patients who have definite or suspected seizures (15).

## C. Specific syndromes of sleep and epilepsy

### 1. Nocturnal Frontal Lobe Epilepsy (NFLE)

In a review of 100 consecutive cases of nocturnal frontal lobe epilepsy (32), 28% occurred in sleep stages 3 or 4, and only 3% during REM. Autosomal dominant nocturnal frontal lobe epilepsy is characterized by enuresis, sudden awakenings with dystonic or dyskinetic movements, complex behavior, and violent behavior in sleep (33). Even with ictal recordings, many or most patients do not show clear epileptic activity (32). All of these studies suggested that nocturnal frontal lobe epilepsies are frequently misdiagnosed but easily controlled with medication.

### 2. Juvenile Myoclonic Epilepsy (JME)

JME is characterized by generalized tonic-clonic seizures can occur independently or precede myoclonus. Both show a strong relationship to sleep deprivation and commonly occur after awakening (34). Patients can even control seizures through careful sleep hygiene, although this is rarely completely successful (35). Fortunately, control with drug treatment is typically complete (34).

### 3. Benign epilepsy with centrotemporal spikes (BECTS)

Seizures in BECTS occur predominantly or exclusively during sleep and consist of hemifacial twitching lasting usually for less than two minutes. The diagnosis is made by clinical description and an EEG is performed for confirmation. Characteristic centrotemporal spikes invariably increase with sleep, typically dramatically (36).

## 4. ESES (encephalopathy with status epilepticus during sleep)

ESES is an epileptic encephalopathy with heterogeneous clinical manifestations (cognitive, motor, and behavioral disturbances in different associations, and various seizure types) related to a peculiar EEG pattern characterized by paroxysmal activity significantly activated during slow sleep – that is, a condition of continuous spikes and waves, or status epilepticus, during sleep. The pathophysiologic mechanisms underlying this condition are still incompletely understood; recent data suggest that the abnormal epileptic EEG activity occurring during sleep might cause the typical clinical symptoms by interfering with sleep-related physiologic functions, and possibly neuroplasticity processes mediating higher cortical functions such as learning and memory consolidation (37).

## D. Parasomnia and epilepsy

### 1. Differentiating parasomnia from seizure

As already mentioned in the section of NFLE, the parasomnias may be frequently confused with seizure and vice versa. Although video Polysomnography (v-PSG) is considered as the gold standard, its availability is limited to few tertiary care centres and overnight recordings may be practical only if the episodes are frequent. Thus clinical differentiation is important to distinguish them. Parasomnias can be defined as abnormal movements or behaviors, occurring in sleep or during arousals from sleep, intermittent or episodic, or without disturbing the sleep architecture. Several parasomnias may be mistaken for seizures, especially complex partial seizures and NFLE. Somnambulism, night terror, confusional arousals, sleep enuresis and nightmares are more common in childhood while REM behavior disorder (RBD) tends to occur at a later age. All these events may be mistaken for seizure. Table 3 tabulates briefly the clinical features which differentiate seizures, especially NFLE from parasomnias. Derry et al (38) have proposed a Frontal Lobe Epilepsy and Parasomnias (FLEP) scale which has a sensitivity of 100% and specificity of 90%. It scores the patient on seven clinical criteria. A later study which used this scale found a lower sensitivity (71.4%) with a high specificity (100%) (39). Although the diagnostic power may vary in different

Table 3: Parasomnia and NFLE (Nocturnal frontal Lobe epilepsy)

Characteristic	Sleep walking	Confusional arousals	Sleep terrors	Nightmares	RBD	NFLE
Timing during sleep	First third	First third	First third	Second half	Second half	Any
Sleep stage at start	SWS	SWS	SWS	REM	REM	Any, esp. stage 2
Duration	2-30 min	5-40 min	1-10 min	3-20 min	3-20 minutes	<2 min
Agitation	None/mild	Moderate	Marked	Mild	Variable	Variable
Autonomic arousal	None/mild	Moderate	Severe	Mild	Variable	Variable
EEG abnormalities	No	No	No	No	No	Yes
Amnesia	Yes	Yes	Yes	No	No	Yes
Post event confusion	Usual	Usual	Usual	Very rare	Very rare	Usual
Age	Usually < 10 years				≥ 50 years	Usually childhood or adolescence
Family history	60-90%				Usually absent	dH40%
Attacks per night (mean)	1 or 2				1-2	3 or more
Episode frequency/month	<1-4				Variable	20-40
Clinical course (over years)	Tends to disappear by adolescence				Variable, can increase with age	Often stable with increasing age
Stereotypy	Variable from attack to attack					High degree of stereotypy

centres, it nevertheless emphasizes that comprehensive clinical history would decrease the need of v-PSG and should always precede referral to tertiary care centers.

## Conclusion

The intricate relationship of epilepsy and sleep has been and still is a topic of interest and research. The relationship is not only complicated by the administration of AEDs which have independent effect on the sleep architecture but also interventions like epilepsy surgery and vagal nerve stimulation. Not only this, sleep instability can promote seizures, thus forming a vicious cycle. The knowledge of these intricacies would help us classify and manage patients better.

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