

Epilepsy and sleep

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The relationship between epilepsy and sleep is complex as seizures may be exacerbated by sleep deprivation and some seizures mainly occur during sleep. Further, there is a possibility of nocturnal seizures being misdiagnosed as parasomnia and vice versa. Finally, sleep disorders may aggravate epilepsy and epilepsy may aggravate certain sleep disorders.

Normal sleep physiology and relationship to seizures

Sleep consists of active brain states during which many biological processes occur, such as synaptic plasticity and memory consolidation¹. Using electroencephalography (EEG) sleep can be broadly divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM can be subdivided into light (stages I/II) and deep (stage III, previously split into stages III/IV) sleep. These sleep states cycle over 90 minutes throughout the night. Deep sleep mainly occurs during the first part of the night, and towards morning there is more REM sleep (Figure 1). The transition between wakefulness and sleep and between different sleep stages is often gradual and the mechanisms controlling these transitions are poorly understood.

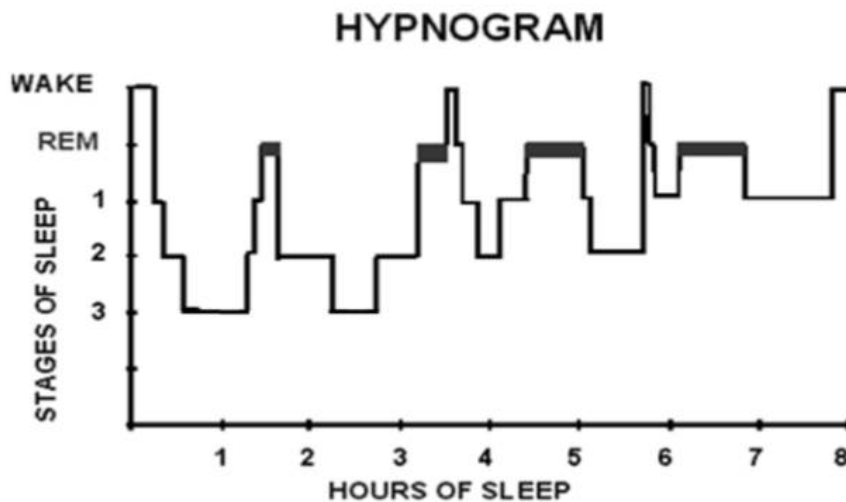


Figure 1. Normal hypnogram. Note that there is more deep sleep in the first parts of the night and more REM sleep towards morning.

It has been clear for many years that some patients with epilepsy have seizures mainly during sleep^{2,3}. Particularly frontal lobe seizures often occur from both daytime and night-time sleep. However, if temporal lobe seizures occur during sleep, the seizures are more likely to secondarily generalise⁴. There may also be diurnal variation of certain types of epileptic syndromes such as juvenile myoclonic epilepsy or epilepsy with generalised tonic-clonic seizures on awakening⁵. Both benign (such as benign focal epilepsy with centrottemporal spikes [BECTS]) and severe epilepsy syndromes (such as Landau-Kleffner and Lennox-Gastaut syndrome with electrical status epilepticus during sleep [ESES]) show a predilection for sleep.

Thalamocortical rhythms are activated during NREM sleep giving rise to sleep spindles. Similar circuits are involved in the generation of spike-wave discharges in primary generalised epilepsy, providing a possible explanation for the promotion of spike-wave discharges seen during NREM sleep⁶.

Inter-ictal epileptiform discharges (IED) are facilitated following sleep deprivation, even in the absence of sleep during the EEG recordings⁷. The reasons for this remain unclear but it has been suggested that the increase in spike-wave activity seen after sleep deprivation may be due to more frequent fluctuations in vigilance levels both during wakefulness and sleep⁸. Using transcranial magnetic stimulation (TMS), increased cortical excitability has been shown in epilepsy patients after sleep deprivation. This has not been the case for control subjects or at least not to the same extent. Interestingly, changes have been seen bilaterally in patients with generalised epilepsies but only ipsilateral to seizure onset zone in patients with focal epilepsies^{9,10}. Changes may reflect reduced intracortical inhibition, as the most likely mechanism for an increase in excitability at the stimulation intervals used is reduced GABA activity

The propensity for IED as well as seizures also varies throughout the night and IED are more commonly seen during NREM sleep than REM sleep¹¹⁻¹³. Epileptic seizures can occur at any stage of NREM sleep but are more frequent during changes between sleep stages and lighter stages than deep sleep. Seizures rarely occur during REM sleep⁴.

Interaction between sleep disorders, antiepileptic drugs and epilepsy

Excessive daytime sleepiness (EDS) is common in patients with epilepsy and is often attributed to antiepileptic medication. Tiredness is often a dose-related side effect of many antiepileptic drugs (AEDs). AEDs may, however, also interfere with the normal sleep pattern. AEDs have different effects on sleep (summarised in Table 1) and some also have different long- and short-term effects. For example, carbamazepine initially reduces and fragments REM sleep but this effect is reversed after a month of treatment. GABAergic drugs (such as phenobarbitone and benzodiazepines) prolong NREM sleep and shorten REM sleep and gabapentin and pregabalin have been shown to increase slow-wave sleep (SWS) and have even been suggested as a treatment option for primary insomnia¹⁴.

Seizures and frequent IED can also disrupt sleep architecture, causing more unstable sleep in both partial and generalised epilepsies. Patients with epilepsy may have increased sleep latency and number of awakenings during the night, as well as reduction or fragmentation of REM sleep. Reduced amount of REM sleep has been seen after both daytime and nocturnal temporal lobe seizures¹⁵. The effect was most pronounced when seizures occurred during sleep but also significant when seizures occurred on the previous day. Disrupted sleep may hence contribute to the prolonged recovery time that some patients report following seizures. Polysomnography of patients with juvenile myoclonic epilepsy (JME) have also shown reduced sleep efficiency and increased sleep latency, unrelated to seizures as well¹⁶.

Obstructive sleep apnoea (OSA) is more common in patients with epilepsy than in the general population and may be related to severity of epilepsy. The risk factors for OSA are however the same as in the general population (male gender, obesity, age). OSA may fragment sleep as well as cause sleep deprivation that may have detrimental effect on seizure control. In older adults with late onset seizures or worsening of seizure control, OSA has been associated with seizure exacerbation¹⁷. Several studies have also shown an improvement of seizure control after treatment of concomitant OSA¹⁸⁻²¹.

Table 1. Effect of antiepileptic drugs on sleep.

	Effect on sleep						Effects on sleep disorders	
	Sleep efficiency	Sleep latency	Stage I	Stage II	Stage III	REM	Improves/ treats	Worsens
Phenobarbitone	↑	↓	-	↑	0	↓	Sleep onset insomnia	OSA
Phenytoin	0	↓	↑	↑	↓	0 or ↓	None known	None known
Carbamazepine	0	0	0	0	0	0	RLS	RLS
Valproate	-	0	↑	↓	0	0	None known	OSA*
Ethosuximide	-	-	↑	-	↓	-	None known	None known
Gabapentin	0	0	0	0	↑	↑	RLS	OSA*
Lamotrigine	0	0 [†]	0	↑	↓	↑	None known	None known
Topiramate	0	↓	0	0	0	0	OSA*	None known
Tiagabine	-	-	-	-	↑	-	Insomnia	None known
Levetiracetam	-	-	-	-	↑	-	None known	None known
Pregabalin	↑	-	-	-	↑	-	None known	OSA*

0, no change; -, not reported; ↑, increase; ↓, reduction; OSA, obstructive sleep apnoea; REM, rapid eye movement; RLS, restless leg syndrome

*Due to change in weight

[†]Lamotrigine may be associated with insomnia (clinical observation but rarely reported in the literature)

Epilepsy and AEDs may also aggravate OSA. AEDs could reduce respiratory drive and upper airway tone and some drugs are also associated with weight gain. Identification and treatment of both epilepsy and OSA is hence important to optimise patient outcome.

Differential diagnosis of paroxysmal nocturnal events

Paroxysmal nocturnal events often represent a differential diagnostic challenge for the clinician. Patient recall is often poor and the bed partner is often the person instigating contact with medical professionals. Despite this, there may still be a limited history as events occur during the night when it is dark, and the witness may be asleep at the onset and miss part of the events. The witness may also not be alert enough to provide a good description of the events. However, there may be no witness account at all for individuals who sleep alone. 'Routine investigations' such as EEG are often normal and hence not helpful for the differential diagnosis.

There are, however, some clinical features that may help in differentiating nocturnal events:

1. Timing of events during sleep, i.e. soon after sleep onset or later towards morning?
2. How often during the night, i.e. how many events each night?
3. Frequency of events, i.e. do events occur every night, once per week, once per month, less frequently and does the frequency vary over time?
4. Lifetime duration, i.e. at what age did events start and has there been any change in frequency/severity over time?

Frontal lobe epilepsy

1. Can occur throughout night but most likely in transition periods and NREM light sleep
2. May occur several times per night, often in clusters (may be unrecognised)
3. Frequency varies
4. Age at onset variable, often childhood or teens.

Three main types of nocturnal frontal lobe seizures have been described: paroxysmal arousals, nocturnal paroxysmal dystonia and episodic nocturnal wanderings²².

Paroxysmal arousals consist of brief, sudden eye opening, head raising or sitting up in bed, a frightened expression and, sometimes, vocalisation. Nocturnal paroxysmal dystonia involves dystonic posturing and hypermotor (complex motor) phenomena. Episodic nocturnal wanderings are longer in duration (1–3 minutes), with associated stereotyped dystonic movements²². People with nocturnal frontal lobe epilepsy (NFLE) will commonly have more than one of these seizure types. Daytime inter-ictal EEG shows epileptiform abnormalities in up to one-third of cases; this increases to 50% of nocturnal EEGs. Ictal EEG is often unhelpful with no clear changes or only myogenic artefacts. Occasionally there may be subtle features such as electrodecrement or rhythmic frontal slow.

If seizures are very brief, it can be particularly difficult to obtain correct diagnosis. However, distinguishing on the basis of frequency, time of night and stage of sleep can be particularly useful, as mentioned above. Furthermore, there are semiological features that can help distinguish between epilepsy and parasomnia. Importantly, brevity, sitting, standing/walking, preceding arousal or fearful emotional behaviour are not good differentiators. Stereotypy and dystonic posturing are more common features in seizures, while yawning, waxing and waning, prolonged duration (over two minutes) and indistinct offset are more common in parasomnias¹⁹. This last feature is quite a notable difference between seizures and NREM parasomnias on video. Derry and co-workers have devised a scoring system (the frontal lobe epilepsy and parasomnia or FLEP scale) and more recently also a diagnostic decision tree to facilitate differentiation of seizures and parasomnia^{23,24} (Table 2).

Parasomnias

Parasomnias are abnormal events occurring in association with sleep that are classified according to the sleep stage from which they occur. NREM parasomnias occur from deep NREM sleep (stage III) and REM sleep behaviour disorders (RBD) occur during REM sleep.

NREM parasomnia

1. Occurs in the first third of the night
2. 1–3 episodes per night
3. Frequency varies
4. Onset in childhood.

NREM parasomnias are often most difficult to differentiate from nocturnal epileptic seizures. As for nocturnal frontal lobe seizures, there are also three main types of NREM parasomnia: confusional arousal, night terrors (pavor nocturnis) and sleep walking (somnambulism). There are however more uncommon types, such as sleep eating and sleep sex. There is often a family history of NREM parasomnias that can be of any type, not necessarily the same for all affected family members. Symptoms are often exacerbated by sleep deprivation, fever and stress. For some patients alcohol may be a trigger but this has been disputed²⁵. Other sleep disorders causing sleep deprivation (such as obstructive sleep apnoea and periodic limb movements of sleep) may also exacerbate NREM parasomnias.

Table 2. Frontal lobe epilepsy and parasomnia (FLEP) scale.

Clinical feature		Score
Age at onset		
What age did the patient have their first event?	<55 years	0
	≥55 years	-1
Duration		
What is the duration of a typical event?	<2 min	+1
	2–10 min	0
	>10 min	-2
Clustering		
What is the typical number of events to occur in a single night?	1 or 2	0
	3–5	+1
	>5	+2
Timing		
At what time of night do the events most commonly occur?	Within 30 minutes of sleep onset	+1
	Other times (including if no clear pattern identified)	0
Symptoms		
Are events associated with definite aura?	Yes	+2
	No	0
Does the patient wander outside the bedroom during the events?	Yes	-2
	No (or uncertain)	0
Does the patient perform complex, directed behaviours (e.g. picking up objects, dressing) during event?	Yes	-2
	No (or uncertain)	0
Is there a clear history of prominent dystonic posturing, tonic limb extension or cramping during events?	Yes	+1
	No (or uncertain)	0
Stereotypy		
Are the events stereotyped or variable in nature?	Highly stereotyped	+1
	Some variability/uncertain	0
	Highly variable	-1
Recall		
Does the patient recall the events?	Yes, lucid recall	+1
	No or vague recollection only	0
Vocalisation		
Does the patient speak during the event and if so, is there subsequent recollection of speech?	No	0
	Yes, sounds only or single words	0
	Yes, coherent speech with incomplete of no recall	-2
	Yes, coherent speech with recall	+2
Total score		

Scores: ≤0 very unlikely to have epilepsy; >3 very likely to have epilepsy; +1 to +3 relatively high chance of epilepsy and further investigation would be required in these individuals

Patients may be amnesic for events but often describe dream-like experiences such as seeing spiders, feeling chased, and house/walls collapsing on them. These events are not as narrative as dreams associated with REM sleep. Events may also be related to daytime frustrations or incidents. The bed partner may describe fearfulness or confusion and patients may get out of bed with these events. These conditions are most common in children (up to 20% of children sleep walk). Symptoms may also occur in adults, up to 2–3% are said to have events at least once a year. There is often a history of NREM parasomnias in childhood but NREM parasomnias may also start in adulthood.

The similarities between features seen during NFLE and NREM parasomnias have prompted the hypothesis that the disorders may have a common pathogenic background²⁷. Central pattern generators (CPGs) are neuronal networks activating specific sequences of motor responses. These are usually controlled by the cortex, but temporary loss of this control, either by sleep or epilepsy, facilitated by arousal, can result in the emergence of stereotyped inborn fixed action patterns seen in both NFLE and NREM parasomnias²⁷⁻²⁹. Such ‘release phenomena’ include oroalimentary automatisms, bruxism, pedalling activity, wanderings, and emotional responses (ictal fear, sleep terrors)³⁰. There does also appear to be an unusually high proportion of patients with NFLE reporting a history of parasomnia, up to 34%²². A recent study also found a higher proportion of relatives with parasomnias in relatives of patients with frontal lobe epilepsy compared to relatives of normal control subjects³¹.

Treatment of NREM parasomnias is mainly non-pharmacological, including sleep hygiene and avoiding triggers. Patients can be reassured that the parasomnias themselves are benign but safety aspects (such as ensuring doors and windows are properly closed and locked and that objects with which patients can hurt themselves or partners are locked away) are important to avoid injury to patient or bed partner. In more severe cases pharmacological treatment may be indicated. There are no randomised controlled treatment trials of NREM parasomnias but there are case series reporting efficacy of both long-acting benzodiazepines (clonazepam) and antidepressants (for example paroxetine or clomipramine).

REM sleep behaviour disorder (RBD)

1. Occurs during second half of night
2. 1–2 episodes per night (but often smaller movements more frequently during REM sleep)
3. Frequency varies (but usually most if not every night)
4. Mean age at onset 50–55 years.

Normally there is muscle atonia during REM sleep to ensure we do not act out our dreams. In REM sleep behaviour disorder (RBD) there is loss of this normal atonia during REM sleep. For a diagnosis of RBD there must also be a history of or observed motor activity during REM sleep. There will often be vivid dreams with some recall, but patients are usually unaware of events. Movements are often reported to be violent and may injure the bed partner. However, during polysomnography, a wide range of movements and behaviours can be seen and it is possible that it is the violent movements that wake the bed partner up and is hence reported. Onset is often later in life and in a large proportion of cases (30–90% depending on study and duration of follow-up), RBD is symptomatic of an underlying neurodegenerative disorder such as dementia, Parkinson’s disease, multiple system atrophy or cerebrovascular disease³²⁻³⁴. RBD may pre-date the onset neurodegenerative disorder. It has been suggested that the risk of developing Parkinson’s disease is related to the severity of loss of REM atonia on polysomnography³⁵. RBD may also be secondary to withdrawal from alcohol or sedative drugs or precipitated by drugs including tricyclic antidepressants, SSRIs or other types of antidepressants (mirtazapine). It may also be seen in younger patients with other sleep disorders such as narcolepsy. In these patients there does not appear to be

any increased risk of developing neurodegenerative disorders and the underlying mechanisms for the RBD may be different.

Treatment includes withdrawal of drugs that may contribute and safety precautions, as for the NREM parasomnias (see above). Even though patients with RBD rarely leave the bed, there is a risk of falling out of bed if movements are violent. Protecting the bed partner is important and sometimes sleeping in separate beds is warranted. RBD often responds well to low doses of clonazepam (0.5–2 mg). Again, there are no randomised controlled trials. More recently, melatonin has been shown to be an effective treatment of RBD, often in higher doses, up to 12 or even 15 mg³⁶.

Sleep-wake transition disorders

The most common of these are hypnic or myoclonic jerks that occur on going to sleep or waking. The jerks are benign in nature and do not require any treatment apart from reassurance of their harmlessness.

Rhythmic movement disorders are less common sleep wake transition disorders:

1. Occur at wake-sleep transition
2. Many times per night
3. Every night
4. Usually in children or adults with learning disability but can occur in adults of normal intelligence.

Rhythmic movement disorders are characterised by repetitive movements occurring immediately prior to sleep onset and can continue into light sleep. The most dramatic type is head banging (jactatio nocturna) but other movements, such as body rocking, can also be seen. Movements often start in infancy or childhood and persistence of movements beyond the age of ten is often associated with learning disability or autism. Movements can however also continue in adults of normal intelligence. Patients are usually aware of movements. It has been suggested that it might represent a learnt behaviour and it is often difficult to treat. Protection of the patient, i.e. padding of bedhead or a helmet, may be required in severe cases. Benzodiazepines, tricyclic antidepressants or gabapentine can be tried but responses are usually disappointing.

Periodic limb movements of sleep (PLMS)

1. Occur in the early part of the night/throughout
2. Series of ≥ 4 in any sleep stage, up to hundreds per hour
3. Every night
4. Idiopathic form rare under the age of 40 years.

Periodic limb movements of sleep (PLMS) can occur in association with restless leg syndrome (RLS) or separately. Many people with RLS also have PLMS but the converse is not true and most people with PLMS do not have RLS. Periodic limb movements often consist of typical dorsiflexion of toes and ankle but may also affect the knee, hip or arms. Movements are repetitive, occurring every 5–90 seconds. Movements can occur during all stages of sleep, including REM sleep. PLMS may occur in up to 50% of people over 50 years of age and are sometimes associated with daytime movements. The periodic limb movement index (PLMI) averaging the number of movements per hour may be helpful to ascertain severity of symptoms. Less than five per hour is likely to be normal in younger people but this cut-off may be too low a limit in older patients. Movements are only clinically insignificant if associated with daytime symptoms such as excessive daytime sleepiness (periodic limb movement disorder – PLMD).

PLMS can be familial, but can also be secondary and associated with iron deficiency, pregnancy, peripheral neuropathy, neurodegenerative diseases and, rarely, spinal cord lesions. Antidepressant drugs (SSRIs and tricyclics), neuroleptics, lithium, caffeine and alcohol may also be associated with PLMS. Patients should have iron and ferritin levels checked and supplements provided if levels are low or within the lower end of the reference interval if ferritin <50 µg/litre). Treatment may be required if symptoms are severe and there are frequent arousals. In the first instance, any medication contributing to the symptoms should be discontinued if possible. Other treatment options are symptomatic and include dopamine agonists (ropinirole or pramipexole), anticonvulsants (gabapentin, pregabalin, carbamazepine), benzodiazepines (clonazepam) or opiates (tramadol).

Narcolepsy

Narcolepsy is a well-defined chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally, in particular REM sleep. Features of REM sleep intrude into wakefulness and other stages of sleep. Patients with narcolepsy hence not only have difficulties staying awake but also staying asleep.

There is a classical tetrad of symptoms:

1. Excessive daytime somnolence (EDS)
2. Cataplexy
3. Hypnagogic or hypnopompic hallucinations
4. Sleep paralysis.

Only 10–15% of patients have the full tetrad. EDS, often in combination with sleep paralysis and/or hallucinations, is the presenting symptom in around 90%. The sleepiness is continuous but will intermittently worsen, resulting in an uncontrollable urge to sleep even in inappropriate situations, and often interferes with normal activities. Even a brief nap is often refreshing. Around 60–70% of patients have cataplexy that can develop years after the initial presentation, usually within in 3–5 years. Episodes with cataplexy may be mistaken for seizures. Cataplexy is a sudden decrease in voluntary muscle tone (especially jaw, neck and limbs) that is usually precipitated by strong emotions such as laughter, anger or surprise. Usually events are often partial, only involving for example the face, head and neck muscles and manifest as drooping of face muscles, jaw dropping, or head nodding. If severe, limbs may be involved and patients may fall (complete attack). Consciousness is preserved throughout but if episodes last longer than two minutes, patients may go into REM sleep. Sleep paralysis and hallucinations are not specific for narcolepsy but can occur in other sleep disorders and can also occur in people without sleep disorders, particularly following sleep deprivation. Hypnagogic denotes events associated with sleep onset and hypnopompic events associated with sleep offset. There may also be episodes with automatic behaviour or micro sleeps/sleep attacks that occasionally can be mistaken for epileptic seizures or post ictal behaviour.

Narcolepsy is diagnosed using polysomnography and the multiple sleep latency test (MSLT). There is a strong association with HLA type, suggesting that narcolepsy is an autoimmune disorder. Approximately 90% of patients who have narcolepsy with cataplexy have the HLA allele HLA DQB1*0602. However, this is also frequently found in the general population (around 25%) and is therefore in general not helpful for diagnosis. Genetic factors may also be involved but to date no specific gene for narcolepsy has been identified in humans. Loss of hypocretin (orexin)-producing neurones in the hypothalamus has been shown in patients with narcolepsy with cataplexy and it is likely that narcolepsy is due to hypocretin (orexin) deficiency^{30,31}. Low levels of hypocretin have been shown in patients who have narcolepsy with cataplexy but for patients with narcolepsy without cataplexy, levels are similar to control subjects^{32,33} and in this group of patients, CSF analyses are less helpful for the diagnosis.

Treatment of narcolepsy includes sleep hygiene and planned daytime naps, preferably no longer than 15 minutes. EDS is also treated with stimulants; modafinil or amphetamine derivatives (dexamphetamine or methylphenidate). Cataplexy and other REM sleep phenomena (sleep paralysis and hallucinations) usually respond well to treatment with antidepressants, for example fluoxetine, clomipramine or venlafaxine. Sodium oxybate taken in the evening to consolidate overnight sleep can be an effective treatment of both EDS and cataplexy but due to the high cost (permission needs to be sought from local authorities) usage in the UK is so far limited.

Summary

There are multiple links between epilepsy and sleep. Sleep and sleep deprivation may influence IED and seizures. Primary sleep disorders such as OSA may worsen epilepsy and treatment of these sleep disorders can lead to improved seizure control. Seizures may interfere with night-time sleep structure and cause EDS. Correctly diagnosing paroxysmal nocturnal events remains a challenge even using video-EEG telemetry. Identification and treatment of both sleep disorders and epilepsy is important for optimal patient care.

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