Sleep-Related Epilepsy

Mar Carreño, MD, PhD[1],[*]
Santiago Fernández, MD[2]

Address
[*],[1]Epilepsy Unit, Hospital Clínic, C/Villarroel, 170. 08036, Barcelona, Spain
Email: mcarreno@clinic.ub.es
[2]Department of Neurology, Hospital Platón, Barcelona, Spain

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Opinion statement

Sleep has a strong influence on interictal epileptiform discharges and on epileptic seizures. Interictal epileptiform discharges are activated by sleep deprivation and sleep, and some epilepsies occur almost exclusively during sleep. Treatment of sleep-related epilepsy should take in account the type of epileptic syndrome, the type of seizures, the patient characteristics, and also the pharmacokinetics of the drug. Proper characterization of the epilepsy is essential to choose appropriate antiepileptic drugs. Drugs effective in focal epilepsy may be used to treat benign genetic focal epilepsies such as rolandic epilepsy and other focal (frontal or not) sleep epilepsies. These include both classical (such as carbamazepine) and new (such as levetiracetam and lacosamide) antiepileptic drugs. Drug-resistant cases should be evaluated for epilepsy surgery, which may be efficacious in this setting. Valproate, lamotrigine, topiramate, levetiracetam, and perampanel are effective against generalized tonic-clonic seizures in genetic generalized epilepsies, which frequently happen on awakening. Risks of valproate should be considered before prescribing it to women of childbearing age. Specific syndromes such as ESES require specific treatment such as a combination of high dose steroids, benzodiazepines, levetiracetam, and even surgery when an epileptogenic lesion is present. Sleep disorders that may worsen epilepsy such as obstructive sleep apnea or insomnia should be adequately treated to improve seizure frequency. Adequate control of seizures during sleep (especially generalized tonic-clonic seizures) decreases risk of sudden unexpected death in epilepsy (SUDEP).

Introduction

The fact that sleep has effects on epilepsy has been observed since the nineteenth century (1). Early studies observed that a significant number of seizures occur during sleep or during awakening, and this observation has been confirmed to the present day. Thus, there are some epilepsies in which seizures appear mainly or exclusively in this state (pure sleep epilepsy). Epilepsies whose seizures occur

during awakening have been called "awake epilepsy". Sleep has also a strong influence on seizure frequency and types and electroencephalogram abnormalities.

In this article, we will review the effects of sleep on epilepsy in general and on specific epileptic syndromes. We will also discuss the most appropriate treatment strategies for sleep-related seizures.

Effect of sleep on epilepsy

Effects of sleep on seizures and interictal epileptiform discharges (IEDs)

Sleep has an influence on seizures. It is accepted that non-REM sleep (NREM) is a facilitator of seizure activity, while REM sleep is a suppressor (2, 3). In NREM stage, epileptiform discharges increase in frequency and spreading. This phenomenon occurs as we move towards a deeper state of sleep, and presents in both generalized and focal epilepsies (4, 5), but seizures usually appears in stage 2 sleep (2, 3). One possible explanation of the increase of interictal discharges during NREM sleep is the progressive neuronal synchronizations that occur in deep sleep stages.

In REM sleep, both the frequency and the spread of interictal epileptiform discharges (IEDs) decrease. The extent and lateralization of IEDS is useful to localize the epileptogenic foci in refractory temporal lobe epilepsy (4, 6). In a recent study in children with generalized discharges in scalp EEG and normal/subtle changes in the MRI evaluated for epilepsy surgery, IEDs during REM helped to lateralize the epileptogenic hemisphere and proceed to surgery (7•). There is also a very low rate of seizures arising from REM sleep (3).

Sleep deprivation has long been recognized as a seizure precipitant, especially in patients with awakening epilepsies. This influence is not understood, but there is some evidence that sleep deprivation increases neuronal excitability (8). In a recent prospective study of a cohort of 104 patients, this was the second most frequent (71 % of cases) triggering factor for seizures, with the patients with generalized epilepsy being specially sensitive (9). Many other studies have also reported that sleep deprivation can precipitate EEG epileptiform discharges (10, 11), even in the absence of sleep during recordings (12). Comparative studies show that it activates epileptiform discharges in 23 to 93 % of patients with definite or suspected seizures (13).

Sleep deprivation has been used as a procedure for EEG activation. There is only one prospective study to show a specific effect on EEG. The authors reported 85 patients with suspected epilepsy to routine EEG, sleep-deprived EEG, and EEG during drug-induced sleep in a random order, and reported that sleep-deprived EEG was significantly more likely to show IEDs (14). In another recent study (15•), sleep-deprived EEG was more able to induce IEDs than routine EEG both in focal and generalized epilepsies. Using a sleep-deprived EEG as the first protocol in young patients with suspected epilepsy could reduce the number of EEGs requested in this population. Most authors advocate that the activating effect of IEDs of sleep-deprived EEG is a specific effect of deprivation, and not only sleep (16•, 17••).

Effect of sleep on epilepsy syndromes

There are a variety of epilepsies that are clearly related with sleep. These epilepsies are mainly the following:

West syndrome

This syndrome is characterized by infantile spasms and hypsarrhythmia on EEG, and usually starts between 3 and 12 months of age. The spasms are brief and usually occur in clusters. Seizures most commonly occur shortly after awakening. The characteristic high amplitude hypsarrhythmic EEG pattern is seen prominently in early NREM sleep [18] and, even more, can appear only in sleep [19]. Recently, it has been shown that hypsarrhythmia impairs the physiological overnight decrease of slow waves in NREM sleep [20].

Lennox-Gastaut syndrome

This syndrome is characterized by the presence of tonic seizures, atypical absences, and tonic-clonic seizures. Typically, tonic seizures predominate during NREM sleep.

Benign epilepsy with centrotemporal spikes (BECTS)

This is the most frequent epilepsy in children [21]. The onset is between 3 and 13 years, with remission before the age of 16 years [22]. Seizures are characterized by hemifacial clonic and lateral clonic deviation of mouth and tongue with salivary flow. Approximately 70 % of seizures occur during sleep, early after falling asleep, or shortly before awakening. The syndrome, also known as benign rolandic epilepsy, is generally self-remitting, and prognosis is excellent. Interictal EEG is characterized by high-voltage centrotemporal spikes. Amplitude and frequency of IEDs increases during sleep.

Panayiotopoulos syndrome

It is another benign age-related genetic focal epilepsy. Almost two thirds of seizures occur while the patient is asleep. Seizures are characterized by nausea, emesis, other autonomic features, loss of consciousness, and eye and head deviation. Half of the seizures end up as a hemiconvulsion or generalized convulsion. Interictal EEG shows focal or multifocal spikes that appear or increase in frequency during sleep. Most frequent spikes are recorded from the occipital regions but also from other locations such as the centrotemporal area or the midline. Even irregular generalized spike and wave discharges may be seen. A few cases display no interictal epileptiform activity [23].

Prognosis is excellent and more than 75 % of patients achieve complete remission without treatment, within 1–2 years from onset [24].

Electrical status epilepticus during slow sleep (ESES)

It is an epileptic encephalopathy defined by the following features: (a) a continuous EEG activity consistent in spike-wave discharges during slow sleep; (b) frequent seizures; and (c) global cognitive regression [25••]. The association with seizures and cognitive impairment has been made since early reports [26]. Another term that has been used is "continuous spike-wave discharges during sleep" (CSWS). ESES results from the association of various seizures

types, partial or generalized, occurring during sleep, and atypical absences during the awake state. The EEG pattern consists of continuous or almost continuous diffuse spike waves during non-REM sleep. It is an age-related syndrome with seizure onset between 2 months and 12 years, and a peak at 2–4 years (27). This could be due to the fact that childhood is the period in which slow waves are most prominent and synaptic density higher (28, 29). The absence of tonic seizures differentiates it from Lennox-Gastaut Syndrome. ESES is associated with cognitive and behavioral impairment, producing regression that can be acute or subacute (30).

About half of patients with ESES have malformations or cortical lesions (31). Pre or perinatal thalamic lesions have been associated with the ESES. Mutations have also been described in gene GRIN2A (32•, 33•). The pathophysiologic mechanism that triggers ESES is unknown. Cognitive impairment has attributed to the influence of continuous epileptiform activity during sleep, which does not allow adequate consolidation of memory during sleep (34). Processing of cortical information is disrupted by epileptiform activity (35). Similarly, some studies have established a correlation between neurocognitive deficits and the brain regions where EEG abnormalities are more frequent and dense (30, 36, 37). Two similar syndromes to ESES are also characterized by a specific increase in spike-wave during sleep: Landau-Kleffner syndrome, also known as acquired epileptic aphasia. Aphasia is due to hearing agnosia. Age of onset is between 3 and 9 years. Typically, there is an acute or gradual language regression, often with seizures. Sleep EEG may show continuous spikes and waves in NREM sleep (38). Spike and waves can be unilateral, lateralized, or diffuse (39, 40). There are no associated lesions on MRI and aphasia improves if the EEG normalizes, but language and cognitive deficits can persist.

The second variant is atypical benign partial epilepsy. These patients meet the criteria for benign partial epilepsy, but they have the continuous spike and wave EEG pattern during sleep. Besides focal motor seizures, atypical absences, myoclonic, and tonic seizures may occur (41). Cognition is preserved, but if mental retardation is present, the term "pseudo-Lennox-Gastaut" is used. EEG patterns and outcomes are similar to ESES.

Some authors consider these genetic or idiopathic focal epilepsies as a continuum, in which the rolandic epilepsy represents the mildest form, and ESES with this variants the most serious form (17••). To emphasize this hypothesis, mutations of the GRIN2A gene in BECTS, ESES, and Landau-Kleffner syndrome have been described (32•, 42, 43•). GRIN2A encodes the GLuN2A subunit of the NMDA receptor, that has important roles in synaptogenesis and synaptic plasticity (43•). According to some studies, these epilepsies may be associated with these mutations up to 10–20 % of cases (44, 45).

Genetic generalized epilepsies

Juvenile myoclonus epilepsy (JME)

It is also an age-related epilepsy and is clearly associated to sleep. Seizures occur after awakening from sleep or in the evening relaxation period and are facilitated by sleep deprivation and sudden arousal. JME is characterized by the presence of short myoclonic jerks, generally in the morning after awakening, without altered level of consciousness. The upper extremities

are especially affected. The myoclonus may evolve to a generalized tonic-clonic seizure. Recently it was established that the presence of myoclonus is a requisite for the diagnosis of JME (46•). Absences and praxis-induced seizures can occur (47). The EEG shows spikes and widespread polyspikes and diffuse spike and wave at 2.5–3.5 Hz, increased at sleep onset and on awakening, but less frequent in NREM and REM sleep and during the awake state (48). Because sometimes the routine EEG is normal, it is recommended to perform a prolonged EEG with sleep deprivation. Epileptiform discharges on awakening are considered a marker of JME and other genetic or idiopathic generalized epilepsies (49).

Epilepsy with tonic-clonic seizures on awakening

This syndrome may occur independently or as a part of other idiopathic generalized epilepsy syndromes, as JME. Seizures occur after awakening or during evening relaxation (50).

Nocturnal frontal lobe epilepsy (NFLE)

This is a frontal lobe epilepsy in which more than 90 % of attacks occur during sleep (51). NFLE is an heterogeneous disease as idiopathic, sporadic, familial, or symptomatic forms exist (51–53).

The genetic form of NFLE is heterogeneous with autosomal dominant inheritance (ADNFLE). Most frequent mutations involve genes coding for subunits of the heteromeric neuronal nicotinic receptors (nAChRs). However, these mutations account for around 12 % of cases (54•). ADNLFE is very similar to sporadic NFLE, but some mutations are frequently associated with specific psychiatric symptoms. ADNLFE was the first epilepsy in which genetic basis was detected (52). Recently, a recessive form due to mutation in PRIMA1 gene has been described. PRIMA1 is a transmembrane protein which anchors acetylcholinesterase to neuron membranes, and the mutation causes increase in cholinergic responses (55•).

The most frequent etiology of symptomatic forms is type II focal cortical dysplasia (56).

NFLE usually begins before 20 years of age, with different types of seizures: (1) short-lasting stereotyped movements involving the limbs, axial musculature, or head (57, 58); (2) paroxysmal arousals that are sudden and brief (5–10 s), sometimes accompanied by stereotyped movements, vocalizations, frightened expression, or fear (51); and (3) major attacks, (20–30 s in duration), with tonic or dystonic posturing, or complex movements such as pelvic thrusting, pedaling, or more violent movements of limbs (51, 52, 57). Almost all seizures occur during NREM sleep. NFLE has been studied with special interest for its resemblance to NREM parasomnias (sleepwalking and night terrors). Nocturnal PSG with synchronized audiovisual recording is often normal in NFLE. If the diagnosis is unclear, the use of sphenoidal electrodes to record epileptiform activity can be helpful (59).

Other focal nocturnal epilepsies

Sleep-related complex motor seizures are not necessarily frontal in all occasions. They may also originate from the temporal lobe (60, 61), the insula (62), and

the posterior regions (63). In these cases, auras can help to differentiate them from NFLE (64).

A nocturnal temporal lobe epilepsy has been described, but is uncommon (65).

Primary sleep disturbances and epilepsy

Excessive daytime sleepiness is the most common sleep complaint in patients with epilepsy (66•). The origin is multifactorial, the most common being an adverse effect of antiepileptic drugs (AED) and sleep disorders that frequently coexist with epilepsy, such as insufficient nighttime sleep and obstructive sleep apnea (OSA) (67). Excessive daytime sleepiness affects negatively the quality of life of patients with epilepsy.

Obstructive sleep apnea is a primary sleep disorder, and is one of the most frequent in patients with epilepsy. The prevalence of OSA in patients with epilepsy exceeds that of the general population and is even more frequent in patients with drug-resistant epilepsy (68). Risk factors are the same than in general population: older age, male sex, and increased body mass index (69). A recent study found that, in a regression model, only age, dental problems, and standardized AED dose are predictors of OSA (66•). The pathophysiology of OSA in patients with epilepsy however still remains unknown. Total load of AEDs (especially of some such as benzodiazepines) may decrease upper airway tone; in addition, the epileptic discharges and/or seizures could alter upper airway control during sleep. However, this hypothesis remains untested (66•). The Sleep Apnea Scale of the Sleep Disorders Questionnaire has shown validity as a screening instrument for the diagnosis of OSA in adults with epilepsy (70). OSA causes sleep deprivation because it results in fragmented sleep. OSA has been associated with poor control of seizures (69, 71).

Association between NREM sleep parasomnias (sleepwalking and night terrors) and NFLE is unclear, because both conditions are often difficult to distinguish on clinical grounds and PSG findings may be unclear.

REM sleep behavior disorder (RBD) is a parasomnia characterized by abnormal and often violent motor behaviors and complex vocalizations in which patients seem to enact their dreams while in REM sleep (72••). RBD can be misdiagnosed as sleep-related epilepsy. In addition, elderly patients with epilepsy may have RBD (73).

Sudden unexpected death in epilepsy (SUDEP)

Premature death among patients with epilepsy is higher than in the general population, and SUDEP is the most common cause of this mortality. This is defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in an individual with epilepsy, with or without evidence of a seizure, and excluding documented status epilepticus, in which the autopsy does not reveal a toxicological or anatomic cause of death (74). Recent studies estimate 7000 deaths per year in Europe and USA (75) due to SUDEP. The risk of sudden unexpected death is considered to be 24–40 times higher than general population (76, 77). The cause of SUDEP is unknown, but several risk factors have been reported: poor seizure control, frequent tonic-clonic seizures, and long-standing epilepsy (78, 79). Deaths are typically

unwitnessed, and associated with prone position (80), especially in individuals 40 or younger (81). Nocturnal seizures seem to be an independent risk factor for SUDEP: in a study of 154 patients who died of SUDEP, it was primarily a sleep-related (in 58 % of patients) and unwitnessed (86 %) event (82•). Several studies point out that SUDEP usually happens during sleep (83–87). Postmortem, half of the patients are found to have subtherapeutic levels of AEDs and most display evidence of a recent seizure (tongue injury, petechial hemorrhages in the skin, superior vena cava distribution, or conjunctiva) (74).

One study aimed to assess if NFLE could be a risk factor for SUDEP that included 103 patients showed that the incidence of SUDEP was not higher than the rates previously reported in prevalent epilepsy populations (88•), perhaps because of the low incidence of GTC seizures in this type of epilepsy. Some hypotheses that could explain the relationship between SUDEP and sleep are the autonomic changes that occur during sleep, both physiologically and those produced by seizures and the presence of other sleep disorders such as OSA (89).

SUDEPs reported in epilepsy monitoring units show combined cardiac and respiratory failure after a generalized tonic-clonic seizure (90••). Prolonged postictal generalized EEG suppression has been described in all observed cases of SUDEP in monitoring units (90••). This pattern correlates with respiratory depression and autonomic dysfunction (91, 92). To improve the knowledge about SUDEP in order to establish preventing strategies and diminish SUDEP incidence, a new multicenter collaborative research consortium is ongoing (75).

Night supervision, use of monitoring devices, treatment of sleep comorbidities (89, 90••), or avoiding prone position (81) could reduce the occurrence of this dreadful complication of epilepsy.

Treatment of sleep-related epilepsies and sleep-related seizures (Table 1)

Specific literature on treatment of sleep-related epilepsy is scarce. Possible reasons include the fact that pure sleep epilepsies are relatively uncommon and for the rest, which combine diurnal and nocturnal seizures in variable proportions, differential responses of diurnal and nocturnal seizures are often not studied or reported. Efficacy of antiepileptic drugs is assumed to be similar in sleep or a wake seizures, when that may not be necessarily the case.

In addition, objective measurement of nocturnal seizures is difficult due to the need to perform PSG to exclude subtle seizures which may not be noticed by the patient or the caregiver. This fact limits the possibility to perform randomized controlled studies. We will review the current treatment strategies in the types of epilepsies presenting mainly during sleep.

Genetic focal epilepsies

In general, no antiepileptic treatment is recommended in patients with benign epilepsy with centrotemporal spikes (rolandic epilepsy) and infrequent nocturnal seizures without secondary generalization, and the same may be applied to Panayotopoulos syndrome or idiopathic occipital lobe epilepsy. The extent of EEG abnormalities does not correlate with seizure frequency or prognosis,

Table 1. Treatment of epileptic syndromes related with sleep

Epileptic syndrome	Treatment and observations
All syndromes	Avoid precipitating factors, such as sleep deprivation and alcohol intake.
	Stress importance of being compliant with medications. Use chronopharmacology to guide dose and timing of antiepileptic drugs
Benign epilepsy with Centrotemporal Spikes (BECTS)	No treatment if few seizures and well tolerated
	If frequent seizures, secondary generalization, high family anxiety: LEV, sulthiame, VPA, CBZ, and OXC (atypical evolutions in some patients?)
Panayiotopoulos Syndrome	No treatment if few seizures and well tolerated
	If treatment needed: same than BECTs
	Rectal diazepam for prolonged seizures
Electrical status epilepticus during slow sleep (ESES)	Steroids, high dose BZDs (CLB), LEV, VPA, ETX, LTG, sulthiame, ketogenic diet, and surgery
Genetic generalized epilepsies	VPA, LEV, LTG, TPM, ZNS, and PER
	Women of childbearing age: LEV, LTG (may aggravate myoclonic seizures)
Nocturnal frontal and other focal epilepsies	CBZ, OXC, TPM, ZNS, LCM, nicotinic patches (ADFLE)
	If drug resistant, consider presurgical evaluation

VGB vigabatrine, *VPA* valproate, *LEV* levetiracetam, *CBZ* carbamacepine, *OXC* oxcarbamacepine, *LTG* lamotrigine, *TPM* topiramate, *ZNS* zonisamide, *PER* perampanel, *BZD* benzodiazepines, *ETX* ethosuximide, *CLB* clobazam, *LCM* lacosamide, *GTCS* generalized tonic-clonic seizures, *ADFLE* autosomal dominant frontal lobe epilepsy

and so it should not be used to take treatment decisions. Antiepileptic drugs may be considered in case of frequent seizures, occasional generalization, or extreme family anxiety. During many years, carbamazepine has been the drug of choice in rolandic epilepsy. Another option is oxcarbazepine (93). Valproate may be used in the minority of patients (around 10–20 %) who fail carbamazepine (94). There have been some reports associating carbamazepine to atypical negative evolutions, increasing the frequency of epileptiform discharges and producing temporary cognitive symptoms, although evidence is inconclusive (95–97). Sulthiame has been reported to be effective (98), even more than carbamazepine (99), decreasing epileptiform activity and improving cognition (100).

Levetiracetam monotherapy is also effective and well tolerated in patients with rolandic epilepsy who need treatment, (101). It seems to be as efficacious as valproic acid to control seizures (102•).

Continuous spike and wave during sleep (ESES)

In this pediatric syndrome with epileptic discharges highly activated by sleep, treatment is directed to reduce epileptiform discharges during sleep, as this may translate into cognitive improvement. However, there is no standard regimen and different combinations are used in different centers, as no controlled clinical trials have been conducted to establish the efficacy of various AEDs. For this reason, evidence to guide therapeutic decisions is only class III (open-label uncontrolled trials) or class IV (case reports or expert opinion).

High dose benzodiazepines (usually clobazam) and corticosteroids have been used to diminish EEG abnormalities and improve cognition and behavior, which has been shown to be associated with the duration of ESES (103). Drowsiness associated to benzodiazepines may limit their usefulness in this

particular syndrome. Corticosteroids are reserved for drug-resistant cases associated to cognitive regression because of the side effect profile. In a series of 44 patients with ESES treated with oral hydrocortisone (initial dose 5 mg/kg/day in the first month) with a progressive weaning and a total duration of corticosteroid treatment of 21 months, 75 % of patients responded in the first 3 months but only 45 % were long-term responders (104). High dose valproate (associated to ethosuximide in those patients initially not responding) has been reported to improve EEG pattern in more than 50 % of patients (105). Other possible alternative treatments are sulthiame and lamotrigine.

Of the new drugs, add on therapy with levetiracetam has been shown to improve EEG or cognition in more than 50 % of the patients, although some of the initial responders may later relapse. A better response has been described in those patients with ESES and underlying structural lesions (106, 107). Another options for patients who are resistant to conventional AEDs and corticosteroids is the ketogenic diet, which may cause some improvement in the EEG in a minority of patients (108).

Multiple subpial transections, a surgical procedure which is sometimes performed to treat language regression in Landau-Kleffner syndrome, may have some positive effect over cognition and behavior in patients with ESES. (109••). If the patient displays a clear-cut lesion in the MRI and the presurgical evaluation is concordant, other surgical procedures such as hemispherectomy or focal resections may be considered.

A recent study performed a pooled analysis of 112 articles including 950 treatments in 575 patients (110). Antiepileptic drugs were associated with improvement (i.e., cognition or decrease of EEG discharges) in 49 % of patients, benzodiazepines in 68 %, and steroids ($n = 166$) in 81 %. Surgery resulted in improvement in 90 % of patients. In a subgroup analysis of patients who were consecutively reported, the authors found improvement in a smaller proportion treated with AEDs (34 %), benzodiazepines (59 %), and steroids (75 %), whereas the improvement percentage after surgery was preserved (93 %). Possible predictors of improved outcome were treatment category, normal development before ESES onset, and the absence of structural abnormalities (110).

Lennox-Gastaut syndrome

Tonic seizures during sleep which are a hallmark of Lennox-Gastaut syndrome and occur in over 90 % of patients. Tonic status during sleep is a very difficult to treat severe complication of this syndrome, and sometimes it is the result of treating other seizure types with high doses of intravenous benzodiazepines (111, 112).

Genetic generalized epilepsies

In general, seizures in idiopathic or genetic generalized epilepsies occur on awakening. In particular, the syndromes of juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures (GTC) on awakening. Seizures occur more frequently after nights of sleep deprivation and alcohol intake. As these types of syndromes are seen preferentially in young patients, it is mandatory to stress the importance of therapeutic compliance, to recommend lifestyle with regular wake-sleep rhythm and to avoid sudden awakenings.

Valproic acid is still the most effective drug against the different types of seizures seen in idiopathic generalized epilepsies. However, careful assessment of risk-benefit ratio is required when valproate is prescribed to women of childbearing age, given its teratogenic potential and the negative impact on the psychosocial development of children exposed in utero to this drug (113••).

Other drugs that may be used in this population are lamotrigine (may exacerbate myoclonus in some patients) (114), topiramate (effective in GTC seizures) (115), levetiracetam (effective in myoclonic and GTC seizures) (116, 117), zonisamide (evidence in absences, myoclonus, and GTC shown in small open series only) (118), and perampanel (efficacy in GTC) (119, 120•).

Some antiepileptic drugs should not be used in these types of epilepsy because they either do not work or exacerbate seizure types other than GTC seizures, that is, absence and myoclonic seizures. These include carbamazepine, oxcarbazepine, phenytoin, gabapentin, and tiagabine (119).

Pharmacokinetics of the drug may be used to adjust the time of maximum expected concentration to the habitual time of seizure occurrence. Extended-release formulations may be used to delay time of maximum serum concentration of the drug. An occasional extra dose of a benzodiazepine can be used at bedtime if the patient has been sleep-deprived.

Only a minority of patients with idiopathic or genetic generalized epilepsy will present with generalized tonic-clonic seizures restricted exclusively to sleep. In these cases a frontal origin of the seizures should be ruled out.

Frontal and other focal sleep epilepsies

Antiepileptic drugs

The majority of pure sleep epilepsies are focal epilepsies (121), frequently non-lesional and often with a relatively benign outcome and good response to antiepileptic drugs. Focal seizures occurring mainly during sleep are usually frontal in origin, although other seizure onset zones may be possible. Nocturnal temporal lobe epilepsy is uncommon.

Treatment should be done with drugs which are effective in focal epilepsies.

Carbamazepine, oxcarbazepine, and topiramate are useful drugs in patients with frontal and other focal sleep epilepsies (51, 122–125).

Specific treatments such as acetazolamide can be used in the 30 % of patients with the genetic autosomal dominant frontal lobe epilepsy who do not respond to carbamazepine (52).

Some studies have shown potential usefulness of nicotine patches in some patients (126). Among new antiepileptic drugs, lacosamide seems to be also efficacious in patients with focal epilepsy and nocturnal seizures, with up to 65 % of patients with nocturnal drug-resistant seizures experiencing more than 50 % of seizure reduction in a retrospective study (127).

Surgical treatment of focal sleep-related epilepsy

Focal sleep epilepsy may be drug resistant. When the patient has failed two trials of appropriately given AEDs, he is considered to have drug-resistant epilepsy and surgical options should be considered taking into account the individual features of the epilepsy and the patient.

In a recent study (128•), the outcome of 95 patients with refractory sleep epilepsy who underwent presurgical evaluation and focal resection was analyzed. Most patients (61 %) had frontal lobe epilepsy, as expected, but up to 39 % underwent extrafrontal resection because of presumed seizure onset outside the frontal lobes. Most patients (almost 80 %) had a lesion in the MRI and the majority required invasive studies. 76 % of the patients, after a mean follow up of 82 months, were seizure free. Positive MRI findings, no need for invasive monitoring, complete removal of the epileptogenic zone, and cortical dysplasia type II in the pathology were associated with a good outcome. Cortical dysplasia type I was associated with seizure recurrence. The authors concluded that drug-resistant focal sleep epilepsy is cured with surgery in up to two thirds of cases including those not arising from the frontal lobe (128•).

Chronopharmacology in sleep epilepsies

Basic principles of chronopharmacology can be applied to treatment of sleep-related epilepsy. In a pilot trial (129), 18 patients with nocturnal or early-morning seizures refractory to conventional AED therapy were prospectively enrolled in a differential dosing trial. Patients were treated with a schedule in which the evening dose was twice the morning dose, keeping the total dose of medication constant. Of the 18 patients treated by this dosing strategy, 11 patients became seizure free following a mean follow up time of 5.3 months, and 4 patients had a 75–90 % reduction of seizures. This study suggested that chronotherapy can provide improved seizure control compared with conventional therapy in selected patients.

If seizures tend to occur during the transition from wakefulness to sleep, immediate release formulations can be more effective than extended-release ones, who would be more efficacious in seizures happening later at night or during sleep-wakefulness transition.

Treatment of factors that may worsen sleep-related epilepsy

Several studies have shown that OSA treatment with CPAP decreases interictal epileptiform activity and improves seizure control (130–132). Surgical treatment of OSA in children is also associated with decrease in seizure frequency, especially in those with elevated body mass index scores and younger age at time of surgery (133•). Based on these findings, some authors propose the implementation of OSA screening in adult epilepsy clinics, especially in patients with poor seizure control (66•, 134).

Insomnia is frequent in adults with epilepsy, being present in up to 40–55 % of patients (135, 136). It is correlated with number of AEDs and higher scores on depression scales. In patients with epilepsy and insomnia, melatonin can be used. However, its effect on seizure frequency is unclear. One study reported improvement in seizure frequency (137•), while other randomized placebo-controlled studies reported better sleep but no change in interictal epileptiform discharges or seizure

frequency (138●). More research will be needed to evaluate the efficacy of melatonin for epilepsy.

Effect of epilepsy treatments on sleep

A different range of effects of antiepileptic drugs on sleep architecture have been described, including reduced sleep onset latency (phenobarbital, phenytoin, gabapentin), reduced arousals from sleep (phenobarbital, gabapentin), increase in slow-wave sleep (pregabalin, carbamazepine, and gabapentin), decrease in slow-wave sleep (levetiracetam, ethosuximide), and increase (ethosuximide, gabapentin) or decrease (phenobarbital, phenytoin) in REM sleep (139, 140). Several non-pharmacological epilepsy treatments for drug-resistant epilepsy (ketogenic diet, successful epilepsy surgery, and vagal nerve stimulator) have been reported to improve sleep quality. However it is unclear how much of this effect is due to improvement in seizure frequency.

Some epilepsy treatments, however, may have a negative impact on sleep disorders. In some patients, vagal nerve stimulator may worsen OSA (141). This complication can be treated with changes in the operational parameters of the device or with the use of CPAP.

Compliance with Ethical Standards

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
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- ••   Of major importance

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