



## Sleep and Epilepsy: A Summary of the 2011 Merritt-Putnam Symposium

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*Sleep itself is a mystery, and the problem of epilepsy is not simplified by having to consider the reciprocal relationship of sleep and seizures. Possibly investigators will need to unravel the mysteries of both in order fully to understand either.*

Lennox and Lennox, 1960

### Lennox and Lennox, 1960 (1)

Despite the long history of sleep and epilepsy research, the relationship between the two remains poorly understood (2, 3). An abundance of evidence suggests a bidirectional relationship between sleep and epilepsy, where sleep disorders are common comorbidities in individuals with epilepsy; and sleep, slow-wave sleep (SWS) in particular, may provide a physiological milieu for epileptiform activity. Sleep is also critical in post-encoding evolution including a range of sleep-dependent memory processes, from simple stabilization of memories to the discovery of insights. The chronobiology of sleep results in the need to understand the chronopharmacology of antiepileptic drug therapy in individuals with epilepsy. At the 2011 Merritt-Putnam Symposium, the dynamic symbiotic relationship between sleep and epilepsy was explored.

Objectives of the symposium were to 1) identify distinguishing clinical and EEG features of nocturnal seizures and parasomnias, which allow accurate diagnosis; 2) understand how sleep disturbances can exacerbate epilepsy and epilepsy can adversely alter sleep; 3) review common pathophysiological mechanisms between sleep and epilepsy; 4) recognize the consequences of nocturnal seizures and epileptiform discharges on cognition; and 5) learn to manage nocturnal seizures and epileptiform activity using current treatment options.

The symposium addressed one of the NIH research benchmarks: Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment (4). Specifically, the topics aimed to prevent or limit other adverse consequences occurring in people with epilepsy, identify the range and

frequency of sleep disorder subtypes associated with epilepsy, identify the influence of sleep disorders on the incidence of seizures, and identify the influence of sleep disorders on at least one comorbidity of epilepsy.

In this review, highlights of the conference are presented. In addition, slides from the individual talks are available at the American Epilepsy Society Web site (5).

### Differentiating Nocturnal Epilepsy From Parasomnias

Jennifer L. DeWolfe, DO

Clinicians are often presented with individuals who have nocturnal events that may result in diagnostic difficulties (6). These behaviors can include seizures, parasomnias, normal sleep phenomenon such as hypnic jerks, sleep-related movement disorders such as periodic limb movements, bruxism, somniloquy, sleep enuresis, post-arousal abnormal behaviors, and psychogenic events. Knowledge of the behavioral and EEG features of nonepileptic sleep disorders and nocturnal epilepsy are required to appropriately manage the patient.

Parasomnias—defined as undesirable behavioral, autonomic, and experiential phenomena such as emotions, perceptions, and dreaming that occur during entry into or during any stage of sleep, or partial to full arousals from sleep—are common in the general population. Parasomnias and epileptic seizures can coexist in the same subject, making a definitive diagnosis of these conditions particularly challenging (7). Table 1 provides a summary table of differentiating factors in epilepsy and seizures.

The most common parasomnias, non-rapid eye movement sleep (NREM) disorders of arousal, primarily occur during the first half of the night, arise from SWS, and rarely occur more than once per night (8, 9). NREM disorders of arousal occur frequently in children and typically are diagnosed by pediatricians (10). For



the most part, night terrors are self-limited, although they can sometimes persist into adulthood. In a typical night terror, the child is found in a sitting position, appears intensely fearful, and is screaming and crying. The child typically is not consolable but stops crying after a few minutes or longer and goes back to sleep. The child is amnesic for the event.

Other examples of NREM disorders of arousal include confusional arousals in which individuals awaken from SWS and are disoriented to their surroundings with slow speech, decreased responsiveness, and confused behavior (8, 9). The behaviors may be inappropriate and can be sexual or violent in nature. Unlike night terrors, the events can last for hours.

Sleepwalking manifestations are observed when the individual suddenly arouses from SWS with altered consciousness and performs behaviors ranging from walking (8, 9) to more complex activities including cooking, eating, dressing, urinating, and even driving. As with other NREM disorders of arousal, events may be induced by alcohol and medications (e.g., lithium, zolpidem, anticholinergics).

A key feature to the diagnosis of NREM disorders of arousal is that they usually occur as single events. The EEG during the event shows an arousal from SWS with diffuse intermixed theta, slow alpha, and possibly delta activity, demonstrating incomplete arousal. It is felt that NREM sleep disorders are due to physiological dysfunction in neuronal regulation of generalized cortical activation and sleep instability and that they are associated with increased fragmentation of SWS (8).

NREM parasomnias may be associated with other parasomnias, sleep disorders, and medical and psychiatric disorders, and they are often familial. Stress, sleep deprivation, and alcohol and drug abuse can be precipitating factors (8, 9).

Rapid eye movement sleep (REM) parasomnias include nightmares, REM sinus arrest, sleep paralysis, nocturnal groaning (catathrenia), and REM behavior disorder (RBD). People with RBD complain of “acting out dreams.” There is disruption of normal REM-associated atonia (paralysis) and impaired suppression of movement generators. The behaviors associated with RBD can be quite violent and self-injurious. Typically, individuals may describe vivid dream-related imagery if awoken during the behaviors, which may occur more than once a night. The disorder can be induced or worsened by alcohol or medications, including many antidepressants. The associated polysomnographic findings demonstrate REM

sleep with the absence of normal atonia and with increased motor activity consisting of a variety of abnormal behaviors in the absence of epileptiform activity. RBD incidence may be increased in a number of neurologic disorders and can be the harbinger of neurodegenerative disorders, especially the  $\alpha$ -synucleinopathies (11–17). Psychiatric disorders, epilepsy, and narcolepsy are common comorbidities.

The treatment of the parasomnias should include attention to safety factors and preventive measures. Individuals who get out of bed during the event should be encouraged to sleep on a mattress on the floor. Firearms and sharp objects should be removed from the bedroom and, in some cases, alarms placed on the doors. In the case of RBD, until the behaviors are controlled, the bed partner should sleep in another room. The patient should not be forcefully awakened, and if an event occurs, the patient should be guided back to bed gently. Maintaining a regular sleep–wake schedule and sufficient sleep time is important. Medications that precipitate attacks should be avoided. Benzodiazepines or imipramine can be used for NREM parasomnias, and benzodiazepines and melatonin for REM behavior disorder. Obstructive sleep apnea may be worsened with benzodiazepines, thus sleep apnea should be ruled out prior to starting these medications.

Individuals with epilepsy are at high risk for a number of sleep complaints and disorders including fatigue, parasomnias, insomnia, excessive sleepiness, and restless legs syndrome (18); disrupted sleep (19); and obstructive sleep apnea (18, 20). Poor sleep hygiene can disrupt sleep and contribute to insomnia and sleep deprivation (18, 19).

### **The Epilepsy–Sleep Connection: How Sleep Disorders Influence Management of Epilepsy and Epilepsy Treatments Impact Sleep**

*Beth Malow, MD, MS*

Sleep influences the expression of interictal epileptiform discharges (IEDs) and epileptic seizures. In turn, epilepsy and its treatments affect sleep. Sleep disorders are common in patients with epilepsy, and their treatment may impact favorably on seizure control. Deciphering the relationship of seizures to sleep may lead to improved knowledge of how seizures are initiated and to improved diagnosis and management of epilepsy.

**TABLE 1. Seizures vs Parasomnias**

<b>Seizures</b>	<b>Parasomnias</b>
Occur during sleep and wake	Only sleep related
May cluster in sleep	Usually 1 event a night (NREM) vs possible multiple events at night (RBD)
Adult and childhood onset	Childhood onset (NREM) vs adult onset (RBD)
Stereotyped	Usually not stereotyped
Usually brief	May be prolonged
Amnesia (complex partial or secondarily generalized seizure)	Amnesia typical (NREM) vs recall of associated dreams if awoken during behaviors (RBD)



There is a relationship between sleep state and IEDs (21–23). In temporal lobe epilepsy, most patients have increased IEDs in NREM sleep stages 3 and 4 compared with lighter NREM sleep and REM sleep. Sleep-modulated IEDs may have localizing and prognostic value. In individuals with tuberous sclerosis complex, REM sleep provokes the most lateralized IEDs compared with NREM and wakefulness (24). Lateralization of REM IEDs corresponds to the hemisphere of ictal EEG onset and the location of the largest tuber.

Seizures predominate during NREM sleep and are more likely to occur in lighter stages of NREM sleep (stages 1 and 2) (25, 26). NREM sleep activates frontal lobe seizures more than temporal lobe seizures (2, 27). Sleep time is a robust stimulus for seizure onset, especially in frontal lobe seizures, although clock time (time of day) can also play an important role. In a study of 1,008 seizures from 225 children (28), generalized seizures and those of temporal, frontal, parietal, and occipital lobe origin revealed specific circadian patterns. In addition, generalized and temporal lobe seizures occurred more frequently in wakefulness, while frontal and parietal seizures occurred more frequently in sleep, independent of day or night pattern. Auras, gelastic, dyscognitive, atonic, hypomotor, and myoclonic seizures, and epileptic spasms occurred more often in wakefulness, while tonic, tonic-clonic, automotor, and hypermotor seizures occurred more frequently in sleep. Clonic, atonic, myoclonic, and hypomotor seizures occurred more frequently during daytime. Hypermotor and automotor seizures occurred more frequently at night.

Epilepsy also affects sleep organization. Temporal lobe epilepsy disrupts sleep organization more than frontal lobe epilepsy and idiopathic generalized epilepsy, even in the absence of seizures (27, 29, 30). Individuals with epilepsy have 1) decreased sleep efficiency (time asleep/time in bed); 2) an increase in sleep-stage shifts; and 3) an increase in the number and duration of awakenings even during nights when there are no seizures.

Seizures themselves have profound effects on sleep architecture, even apart from the resulting arousals and awakenings (31). When comparing seizure-free nights and nights with seizures, it has been found that nighttime seizures reduce REM sleep and increase NREM stage-1 sleep, while decreasing daytime alertness. Daytime seizures also reduce REM sleep the following night.

Antiepileptic drugs also can impair sleep efficiency and sleep latency, and alter the time spent in various sleep stages (32–34). However, the interaction between the underlying epileptic state, seizures, and interictal EEG abnormalities is complex, making it difficult to determine the role antiepileptic drugs play in sleep. Unanswered questions are 1) whether antiepileptic drugs that reduce sleep-stage shifts, arousals, and awakenings are “better” than those that do not? 2) if they are better, then might these effects translate into improved daytime alertness, health-related quality of life, or even reduced seizure frequency? 3) does improving (or not suppressing) REM or SWS affect cognition?

Obstructive sleep apnea (OSA) is one of the most common sleep disorders, with as many as 24% of men and 9% of women in the general population affected (35, 36). However, a large percentage of individuals with moderate to severe sleep

apnea are undiagnosed (93% of women and 82% of men with moderate to severe sleep apnea are undiagnosed) (35). Sleep apnea is a risk factor for a myriad of medical conditions, including hypertension, heart disease, stroke, impaired glucose tolerance, and obesity. Sleep apnea also contributes to daytime sleepiness and impairs health-related quality of life.

Sleep apnea often coexists with epilepsy, and its treatment may improve seizure control, daytime sleepiness, or both (37–39). OSA may be even more prominent in patients with medically refractory epilepsy (20), although the reasons for this increased risk are not clear. Tracheostomy, continuous airway pressure (CPAP), and positional therapy have been used to improve seizure control and daytime alertness (40, 41). Facilitation of seizures by OSA may be due to sleep deprivation or sleep-related seizures due to frequent arousals leading to stage-shifts into and out of sleep. It is unlikely that the seizures are caused by hypoxemia, decreased cardiac output, or arrhythmias.

Finally, it is important to note that poor sleep hygiene increases the risk of seizures. Sleep and sleep deprivation have long been recognized to influence IEDs and seizures (42).

### Neurobiological Mechanisms Linking Sleep and Epilepsy

*John Huguenard, PhD*

The mechanisms underlying normal sleep appear to be closely related to the mechanisms responsible for seizures, particularly in the generation of spike-wave discharges (SWD). There is increasing evidence that thalamically generated thalamocortical oscillations (spindles) may have a similar network basis as hypersynchronous thalamocortical oscillations (SWD) (43).

Evidence for such a relationship comes from both animal and clinical studies. There is a close correlation between the time of sleep spindles and generalized SWD (44). Accordingly, SWD incidence in rat genetic absence models is similar to humans (45, 46). As in patients, in murine models of absence seizures, SWD occurs mainly during quiet wakefulness or SWS, but rarely during REM sleep or active wakefulness. In the feline penicillin generalized model, spindles have been shown to gradually transition to SWD as the systemic effect of penicillin is established (47). In addition, corticothalamic feedback is capable of transforming sparse, spindle-like *in vitro* oscillations to highly generalized and synchronous slow epileptiform SWD-related oscillations in physiologically intact thalamic circuits (48).

However, while intact thalamocortical networks are generally thought to be critical for both spindles and SWD, under some conditions isolated cortical islands can generate SWD, suggesting that the generation of slow cortical oscillatory responses *per se* does not require thalamic participation. In a seminal study, Marcus and Watson demonstrated that isolated cortical islands with an intact corpus callosum could generate SWD in cat cortex when a convulsant was applied bilaterally (49). Similarly, Steriade and Contreras (50) showed that following a unilateral left thalamectomy, application of bicuculline to the left cortex could result in slow, rhythmic, cortical activity resembling SWD. While these studies show that SWD activity can occur in isolation within cortical circuits, the experimental conditions were somewhat artificial, in that under normal conditions such cortical circuits are intimately and reciprocally



connected with corresponding thalamic circuits in such a way as to affect the ultimate expression of SWD.

While the minimal tissue substrate for SWD is the cortex, thalamocortical circuitry is involved in most pathological states in which SWD are generated, since inactivation of the thalamus, especially the reticular thalamic nucleus (see below) abolishes SWD in experimental models (51). The circuitry within the thalamus creates an intrinsic oscillatory unit whose function depends critically on reciprocal synaptic connectivity between excitatory thalamocortical relay neurons and inhibitory thalamic reticular neurons along with a robust postinhibitory rebound mechanism in relay neurons (52).

While the internal thalamic circuit has clear pacemaking functions, the ability of cortical or peripheral inputs to trigger such rhythmic activities is not completely understood. Cortical input to sensory thalamus is thought to mainly evoke feed-forward synaptic inhibition of thalamocortical (TC) cells via reticular thalamic nucleus (nRT) neurons, with the net effect of restricted thalamic output and shaping of sensory cortical drive. This relies on a stronger synaptic strength in the cortico-nRT pathway than in the cortico-TC pathway, allowing the feed-forward inhibition of TC cells to overcome direct cortico-TC excitation. Paz et al. (53) recently found a systemic and specific reduction in strength in *GluA4*-deficient, *Gria4*( $-/-$ ), mice of one excitatory synapse of the rhythmogenic cortico-thalamo-cortical system, the cortico-nRT projection. Thus, in these mice, cortical output becomes less effective in evoking feed-forward inhibition, leading to overexcitation of TC cells and triggering of robust thalamocortical network oscillation via the intact nRT-TC pathway. These results reveal a previously unknown mode of cortico-thalamo-cortical transmission, bypassing direct cortico-nRT excitation, and describing a mechanism for pathological oscillation generation. This bypass mode could also be dynamically activated under other circumstances, perhaps with particular spatiotemporal patterns of sensory input, explaining the sudden onset of SWD episodes in some patients.

### **Sleep, Memory, and Learning: The Impact of Epilepsy**

*Robert Stickgold, PhD*

There is strong evidence that at least one function of sleep is to consolidate recent memory traces into more permanent forms of long-term storage, thereby integrating key features of recent experience with existing memories (54). As a reflection of the importance of sleep in memory are studies in both animals (55) and humans (56, 57) that demonstrate sleep-deprivation after learning impairs performance.

Consolidation during sleep promotes both quantitative and qualitative changes of memory representations. Through specific patterns of neuromodulatory activity and electric field potential oscillations, SWS and REM sleep support system consolidation and synaptic consolidation, respectively. During SWS, at a time of low cholinergic activity, slow oscillations, spindles, and ripples coordinate the reactivation and redistribution of hippocampus-dependent memories to neocortical sites, whereas during REM sleep, local increases in plasticity-related immediate-early gene activity at a time of high cholinergic and theta activity appear to favor the subsequent synaptic consolidation of memories in the cortex (58).

Observations in animals and humans have led to the concept that sleep is critical for memory consolidation in that a memory trace is considered unstable until the first postexposure sleep period. SWS, characterized by high-amplitude slow oscillations (1–4 Hz) and sleep spindles (10–15 Hz), plays a critical role in learning and memory (59). Following training on many cognitive tasks, the amount of time spent in SWS early in the night, when slow oscillations are the strongest (60), is correlated with improved performance the next morning (56, 57). This improvement is region-specific: slow oscillations in sleep are the strongest in the regions activated during acquisition (61). Overnight improvement in performance in a visual-skill learning task was highly correlated with the amount of time spent in early night SWS (56, 57). Similarly, improvement on a motor task was correlated to a region-specific increase in slow oscillations (61). For declarative memory tasks, these oscillations are thought to allow the cortex to accept information transferred from the hippocampus. Through specific, coordinated neurophysiological events (slow waves, spindles, ripples), new information is integrated into the preexisting cortical networks. The content of this information is thought to be determined by the sequential firing of pyramidal neurons in the CA1 layer of the hippocampus, which can be observed as sharp waves in the local hippocampal EEG. The tagging of the appropriate synapses is thought to be achieved through the recurrent reactivation of the networks that relate to preceding behavior during learning (62). Evidence for this physiological phenomenon is the replay of place cells in the CA1 layer of the hippocampus during sleep (63).

The synaptic homeostasis hypothesis of sleep suggests a second mechanism for sleep-dependent memory consolidation. Experiences while awake selectively enhance corresponding synapses, leading to a global increase in synaptic strengths during wakefulness. Because unbridled daily increases of this nature would eventually produce an epileptic brain, a parallel synaptic downscaling process is needed. The synaptic homeostasis hypothesis proposes that this downscaling occurs during sleep, triggered by the slow oscillations of SWS. Such global downscaling could result in an increased signal-to-noise ratio in recently learned networks (64).

In normal individuals, both SWS and REM are required to consolidate experience-dependent neuronal changes into a form that supports improved task performance (56). For example, individuals performing a visual discrimination task show no improvement when tested after a night of sleep unless they obtained at least 6 hours of posttraining sleep prior to retesting, in which case, improvement was proportional to the amount of sleep in excess of 6 hours. For subjects averaging 8 hours of sleep, overnight improvement was proportional to the amount of SWS in the first quarter of the night, as well as the amount of REM sleep in the last quarter. A two-step process, modeling throughput as the product of the amount of early SWS and late REM, accounted for 80% of intersubject variance.

In addition to the role of sleep in improving procedural and declarative memories in humans, it appears that insight (defined as a mental restructuring that leads to a sudden gain of explicit knowledge allowing enhanced behavior) can be improved through sleep. In an intriguing study, subjects performed a cognitive task that required the learning of stimu-



lus-response sequences, in which they improved gradually by increasing response speed across task blocks (65). However, they could also improve abruptly after gaining insight into a hidden abstract rule underlying all sequences. Initial training establishing a task representation was followed by 8 hours of nocturnal sleep, nocturnal wakefulness, or daytime wakefulness. On subsequent retesting, more than twice as many subjects gained insight into the hidden rule after sleep as after wakefulness, regardless of time of day. It was concluded that sleep, by restructuring new memory representations, facilitates extraction of explicit knowledge and insightful behavior.

Impaired sleep-dependent improvement in motor procedural learning has been reported in patients with schizophrenia (66, 67). Manoach et al. (66) had patients with schizophrenia and matched controls perform a motor sequence task (MST) before and after a night of polysomnographically monitored sleep. Patients with schizophrenia showed no significant overnight task improvement, whereas controls showed significant improvement. While there were no group differences in overall sleep architecture, patients showed significant reductions in fast sigma frequency power (45%) and in spindle density (43%) during stage-2 sleep in the last quartile of the night (S2q4). Although spindle activity did not correlate with overnight improvement in either group, sleep duration in patients significantly correlated with the plateau level of overnight improvement seen at the end of the morning testing session, and SWS duration correlated with the delay in reaching this plateau. SWS and S2q4 each predicted the initial level of overnight improvement in schizophrenia, and their product explained 77% of the variance, suggesting that both sleep stages are necessary for consolidation. These sleep-dependent impairments may contribute substantially to generalized cognitive deficits in schizophrenia (68).

Additionally, Wamsley and colleagues (67) reported that patients with schizophrenia show dramatic reductions of both spindles and sleep-dependent memory consolidation. Compared with controls, patients with schizophrenia had marked reductions in the density (reduced 38% relative to control participants), number (reduced 36%), and coherence (reduced 19%) of sleep spindles but showed no abnormalities in the morphology of individual spindles or of sleep architecture. In patients, reduced spindle number and density predicted less overnight improvement on the MST. Reduced amplitude and sigma power of individual spindles also correlated with greater severity of positive symptoms. The observed sleep-spindle abnormalities implicated thalamocortical network dysfunction in schizophrenia.

The role of sleep in memory consolidation in epilepsy has not been well studied. In one study limited by small patient numbers, Deak et al. (69) studied patients with temporal lobe epilepsy and controls on a motor-sequence task known to undergo sleep-dependent enhancement in healthy subjects, and on a selective reminding test, a verbal memory task on which patients with temporal lobe epilepsy have shown impaired performance 24 hours after training. The investigators found that patients with temporal lobe epilepsy display greater forgetting on the selective reminding test compared with controls over 12 hours of daytime wakefulness, but not over a similar period including a night of sleep. The authors

suggested that sleep may provide protection against forgetting in individuals with temporal lobe epilepsy.

In a study of sleep-related declarative memory consolidation in four children with idiopathic focal epilepsy (70), recall performance of learned word pairs significantly decreased overnight, suggesting impairment in sleep-related declarative memory consolidation. In a population of healthy control children, recall of learned word pairs was increased after a night of sleep, but not after a daytime wakefulness period. Treatment of EEG abnormalities in one of the children resulted in improvement in sleep-induced memory consolidation, suggesting that IEDs in idiopathic focal epilepsies may disrupt the brain processes underlying sleep-related memory consolidation.

Our knowledge of the critical relationship between epilepsy and sleep-induced memory consolidation is very limited. This area of research has enormous potential for improving the well-being of individuals suffering from the comorbidity of epilepsy-related cognitive impairment.

### **Treatment of Nocturnal Seizures: Are We Still in the Dark?**

*Blaise Bourgeois, MD*

When considering how to most effectively treat patients with nocturnal seizures, it is necessary to consider the chronopharmacology of antiepileptic drugs. Chronopharmacology is the study of the interactions of biologic rhythms with medications and focuses on the biologic rhythm dependencies of medications and on the effect of timing pharmacotherapy on biologic time. Humans, like other organisms, have endogenous biological clocks that operate during the 24 hours and other time periods. High-amplitude circadian rhythms in disease pathophysiology give rise to day-night patterns in the onset and symptom exacerbation of many medical conditions. Chronopharmacokinetics deals with the study of the temporal changes in absorption, distribution, metabolism, and elimination of drugs, and thus takes into account the influence of time of administration on these different steps. Circadian time-dependent differences are seen in the pharmacokinetics of many classes of medications. Time variations in the intensities of symptoms or risk of disease, coupled with evidence of circadian rhythms that affect the pharmacokinetics, efficacy, and safety of medications constitute the rationale for chronotherapy.

Specific seizures/epilepsy syndromes with nocturnal predilection such as frontal lobe epilepsy, benign rolandic epilepsy, and Panayiotopoulos syndrome lend themselves to using chronotherapy. Understanding why these seizures occur predominately during sleep may provide insights into novel therapeutics.

While data in the area of chronotherapy in epilepsy is limited, the field is developing and there have been a number of interesting studies demonstrating the potential usefulness of chronotherapy. For example, animal studies show that there are circadian variations of pharmacokinetic parameters of carbamazepine. In rats, the maximum peak concentration and the maximum time to reach this peak was observed when carbamazepine was given at 4 pm and at 10 am, respectively; and the elimination half-life decreased from 15.15 hours after administration at 4 pm to 10.48 hours at 10 pm (71). The authors noted that the observed variations may be related to factors such as



daily fluctuations of absorption or binding of the drug, diurnal variations of metabolizing enzymes, and diurnal variations in hepatic blood flow.

In a study of mice housed under a light–dark (12-hour:12-hour) cycle, valproic acid (VPA) was administered at a constant rate using osmotic mini-pumps implanted subcutaneously (72). There was a significant circadian rhythm in plasma-VPA concentrations: higher values were obtained in the light phase, and lower values were found during the dark phase. A significant circadian rhythm also was shown for clearance of the drug: lower values were obtained in the light phase, and higher values were demonstrated in the dark phase. The authors also administered single doses of valproic acid intravenously and found circadian effects with a higher clearance, a larger volume of distribution, and a smaller area under the curve in mice injected with the drug at 1 pm than at 5 pm.

There have been a number of limited studies indicating that effectiveness of antiepileptic drugs can be enhanced by using chronotherapeutics. Yegnanarayan et al. (73) studied 103 patients with diurnal generalized tonic-clonic or secondarily generalized tonic-clonic seizures with subtherapeutic trough levels of phenytoin or carbamazepine. The patients were randomized to either dose-increment without a change in schedule or to no dose-increment but with two-thirds or more of the daily dose administered at 8 pm. In follow-up, more patients in the group with the high evening dose had therapeutic levels than the group with even dosing. In addition, the efficacy was greater in the group with high evening dosing.

The authors also randomized 62 patients with clinical toxicity and with levels in the toxic range into two groups: 1) dose reduction only, and 2) dose reduction with two-thirds or more of the daily dose administered at 8 pm. In follow-up, while there were no significant differences in drug-level reduction between the two groups, there was improved drug tolerance in the group with higher dosing in the evening. The authors concluded that administration of most or all of the dose of phenytoin and carbamazepine at 8 pm can improve the response of diurnally active epilepsy, achieve therapeutic levels in patients with subtherapeutic levels, and reduce toxicity in patients with toxic levels.

Higher evening antiepileptic drug doses have also been used to treat nocturnal and early-morning seizures. In a study of 17 patients, mostly children with predominantly nocturnal or early-morning seizures, the medication schedule was changed to a higher evening drug dose (mean, 66% of daily dose) without a change in the total daily dose (74). In follow-up, the mean seizure frequency per month decreased from 65.5 per month to 2.6 per month with a mean reduction in seizure frequency of 78.5%. A responder rate (>50% reduction) of 88.2% (15/17) was achieved and 64.7% (11/17) became seizure-free.

Pharmacokinetic modeling was carried out to assess the effect on nocturnal peak and trough levels of changing from even twice daily dosing to one-third of the dose in the morning and two-thirds of the dose in the evening on 1:2 differential dosing. Modeling shows that the pharmacokinetic impact of a higher evening dose is modest, the impact of a higher evening dose is lower for drugs with longer elimination half-lives, and the use of extended-release preparations low-

ers the pharmacokinetic impact of higher evening dosing on maximal concentration but not on trough concentrations. The positive clinical response, therefore, may not be due to higher nocturnal peaks alone.

There may be specific treatments for some nocturnal epilepsy syndromes. Mutations of gene coding for neuronal nicotinic acetylcholine receptors can result in a form of autosomal dominant nocturnal frontal lobe epilepsy. Willoughby et al. (75) used a nicotine patch treatment for a patient with a defined mutation for autosomal dominant nocturnal frontal lobe epilepsy whose seizures were refractory to standard antiepileptic therapy. In this *N*-of-one study, the patient responded remarkably well to the patch. Acetazolamide also has been shown to be effective in autosomal dominant nocturnal frontal lobe epilepsy (76).

Thus, while chronotherapy is a nascent therapy in epilepsy, it is emerging and likely to become more important in the future as the chronobiology of epilepsy is better understood.

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