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Effects of Antiepileptic Drugs on Sleep Structure

Are All Drugs Equal?

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Contents

Abstract

Good-quality sleep is an important and frequently overlooked component of general health, but it is particularly essential to patients with epilepsy. Their sleep can be affected by seizures, concurrent sleep disorders and seizure treatment. Worsening sleep can result not only in poor daytime functioning but also potentially in worsening epilepsy. The effects of antiepileptic drugs (AEDs) on sleep are of particular concern. Some agents have detrimental effects on sleep, particularly benzodiazepines and barbiturates but also phenytoin and, possibly, carbamazepine. Others, especially gabapentin, seem to actually improve sleep quality. Much research in this area is confounded by the effects of seizures and concurrent conditions on sleep, making it difficult to isolate the direct effects of AEDs on sleep. But because AEDs have independent effects on sleep quality, the choice of an appropriate agent not only determines whether seizures are completely controlled but also whether the patient performs optimally on a daily basis.

Disorders of sleep are a significant public health problem throughout the world, contributing to lost productivity and an overall inability to function at maximum potential for countless individuals. In patients with epilepsy, insufficient or ineffective sleep can additionally contribute to worsening of seizures, which in turn can further impair sleep. Sleep disorders are therefore part of a complex interplay in patients with epilepsy, and consideration of sleep is crucial to the total care of any patient with epilepsy. Several reviews of this topic have been published recently.[1-4]

The interactions between sleep and epilepsy take place on many levels. Certain syndromes (such as awakening grand mal epilepsy and benign rolandic epilepsy of childhood) demonstrate a specific relationship between seizures and particular sleep states (see section 1.1). Seizures themselves are known to disrupt sleep when not fully controlled, particularly when they occur during sleep (see sections 1.2 and 1.3). Most patients with epilepsy take antiepileptic drugs (AEDs), and these have several influences on sleep (see section 2). Interictal discharges can be affected by AEDs, which can (at least theoretically) affect sleep. AEDs have as their primary goal the complete control of seizures, which (when attained) eliminates the detrimental effects of seizures on sleep. Finally, AEDs may have independent neuromodulatory effects, which can either improve or worsen various aspects of sleep. As there are many potentially appropriate AEDs for most patients, familiarity with possible effects on sleep is important in the recommendation of the best agent for each individual.

This article begins with a brief review of relevant aspects of the sleep/epilepsy interaction. Specific aspects of each agent will then be reviewed, followed by discussion of an approach to choosing and using sleep-friendly AEDs.

1. Interactions Between Sleep and Epilepsy

The relationship between sleep and epilepsy exists on several levels: the influence of sleep and sleep stage on various seizure syndromes; the effects of sleep and sleep deprivation on interictal epileptiform discharges; and the effects of uncontrolled epileptic seizures on sleep. Understanding these relationships is critical in the interpretation of the influences of AEDs on sleep.

1.1 Influences of Sleep on Various Seizure Syndromes

Sleep has influences on most types of epilepsy, but in a few syndromes the effects are dramatic. In the syndromes of awakening grand mal epilepsy and juvenile myoclonic epilepsy, seizures are largely or completely confined to immediately following nocturnal sleep or daytime naps. In other syndromes, such as benign rolandic epilepsy, most seizures occur during sleep.[2] Frontal lobe partial seizures tend to occur more frequently during sleep, whereas temporal lobe seizures occur roughly equally while patients are awake and asleep but are more likely to evolve into secondarily generalised seizures when starting during sleep.[5] Sleep deprivation is widely thought to increase the frequency of partial seizures; however, a well controlled study of patients with refractory seizures in an epilepsy monitoring unit failed to confirm this.[6]

These relationships can be important in the diagnosis of the epilepsy syndrome and in the counselling of patients as to the relationship of their seizures to the sleep-wake cycle and to sleep hygiene.

1.2 Effects of Interictal Discharges on Sleep

Sleep and sleep deprivation are known to increase interictal epileptiform discharges.[7,8] For focal discharges, the greatest frequency is in slow-wave sleep.[9] All types of epileptiform discharges decrease dramatically during rapid eye movement (REM) sleep.

It is possible that certain epileptic discharges result in sleep disturbance. In theory, the abnormal electrical discharge could result in microarousals.[3] If these are frequent, clinically measurable changes would be seen in sleep and could be reversed with agents that decrease interictal discharges. At least one study, however, showed that an AED (gabapentin) actually increases interictal discharges in pa-

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tients while improving sleep structure (decreasing the number of awakenings, decreasing stage 1 and increasing slow-wave and REM sleep).[10] Therefore, agents that are known to decrease interictal activity (such as valproic acid, lamotrigine and clonazepam)[11-14] will not necessarily improve sleep.

1.3 Effects of Uncontrolled Seizures on Sleep

Epileptic seizures also have profound effects on sleep. Nocturnal complex partial and secondarily generalised seizures may cause only a brief arousal but are followed by sleep that is less efficient, with significant decreases in REM and possibly slow-wave sleep.[15] Even daytime seizures can cause decreases in REM sleep the following night.[15] No specific studies have looked at the possible influence of simple partial or subclinical seizures on sleep; however, these effects (if any) are likely to be considerably less than those of larger seizures.

Patients with epilepsy commonly report daytime drowsiness,[16] and nocturnal seizures, recognised or unrecognised, can be a cause along with medications and coexisting sleep disorders. Optimising sleep in patients with epilepsy therefore begins with the best possible control of complex partial and secondarily generalised seizures.

2. Effects of Specific Antiepileptic Drugs (AEDs) on Sleep

Studies of effects of AEDs on sleep must be viewed with some caution. There are typically several potential confounding factors, the most important of which is probably seizure control. Because seizures themselves are known to adversely affect sleep, seizure reduction by AEDs can improve sleep in several ways including increased sleep efficiency and increased slow-wave and REM sleep.[17] These are not, however, direct effects of the agent. Additionally, many studies are performed using AEDs as add-on therapy, with potential for pharmacokinetic and pharmacodynamic interactions with other AEDs, which may affect the results. Most studies do not have a control arm, and many different doses of medication may have been studied under different conditions. Despite these limitations, there is a fair amount known about specific AEDs and their effects on sleep, particularly for the older agents.

Many of the AEDs seem to affect REM and/or slow-wave sleep. Both are considered to be ‘essential sleep’, and subjects who are deprived of sleep (at least in the short term) will ‘rebound’ or make up most of the REM and slow-wave sleep that was lost. Very little stage 1 or 2 sleep is regained.[18] Although the function of REM sleep remains speculative, there is considerable information suggesting that increased REM sleep is correlated with enhanced learning of certain tasks.[19-21] Additionally, enhancement of REM sleep occurs with drugs useful in Alzheimer’s disease,[22,23] and REM sleep enhancement due to donepezil correlates with improved memory in healthy individuals.[24] Increased slow-wave sleep has also been correlated with certain types of learning in one human study.[19] This is an exciting area of sleep research, and understanding of this relationship may help to explain cognitive difficulties seen in many patients with epilepsy.

Table I contains a summary of the effects of AEDs on sleep.

2.1 Barbiturates

Sedative-hypnotic drugs, including barbiturates, are commonly used to induce sleep. However, some (particularly phenobarbital [phenobarbitone] and primidone) are also used for the treatment of epilepsy. These agents decrease sleep latency and increase sleep continuity[25] and therefore could be beneficial in patients who have trouble falling asleep or who have frequent nocturnal awakenings. There are, however, potential detrimental effects as well. Daytime somnolence typically increases with barbiturate use,[25,26] and long-term barbiturate treatment can actually lead to insomnia[27] and drug dependence. The CNS depressant effect can worsen obstructive sleep apnoea.[28] Additionally, barbiturates have been shown to depress REM sleep.[29-31] Although patients may fall asleep more easily, their sleep may therefore be impaired overall when these agents are used.

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Table I. Summary of the effects of antiepileptic drugs (AEDs) on sleep (see text for references)[a]

AED	Sleep latency	Sleep efficiency	Stage 1 sleep	SW sleep	REM sleep	Daytime drowsiness
Older AEDs						
Barbiturates	↓	NE	NE	NE	↓	↑
Benzodiazepines	↓	NE	NE	↓	↓	↑
Carbamazepine	NE	NE	NE	NE	↓[b]	↑
Phenytoin	↓	NE	↑	NE	↓	↑
Valproic acid	NE	NE	↑	NE	NE	↑
Newer AEDs						
Felbamate	?	?	?	?	?	↓
Gabapentin	NE	NE	↓	↑	↑/NE	?
Lamotrigine	NE	NE	NE	↓	↑/NE	?
Levetiracetam	?	NE	NE	NE	NE/↑	?
Oxcarbazepine	?	?	?	?	?	?
Tiagabine	NE	↑	NE	↑	NE	?
Topiramate	?	?	?	?	?	?
Vigabatrin	?	?	?	?	?	↑
Zonisamide	?	?	?	?	?	?

a Note that some of these results represent small studies, and the effect may not occur in all patients.

b With short-term use only.

NE = no effect; **REM** = rapid eye movement; **SW** = slow-wave; ↓ indicates decreases; ↑ indicates increases; **?** indicates effects unknown.

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2.2 Benzodiazepines

Benzodiazepines are frequently used for the acute treatment of seizure exacerbations; however, some (clonazepam, clorazepate and clobazam) are also used long term for seizure treatment. Clobazam is not currently available in the US. These drugs have many effects similar to barbiturates, including decreased sleep latency and REM sleep and increased sleep continuity and daytime somnolence.[25,31] Benzodiazepines also decrease slow-wave sleep, particularly with long-term use,[27] and (like barbiturates) can worsen obstructive sleep apnoea.[32] In most patients, adverse effects on sleep tend to outweigh perceived improvement due to decreased sleep latency.

2.3 Phenytoin

Like benzodiazepines, phenytoin has also been shown to decrease sleep latency,[33] although it is not typically prescribed independently for this purpose. Therefore, in patients who have difficulty falling asleep, this effect could be beneficial. As with sedative-hypnotics, however, there are potential detrimental effects. Some patients show an increase in light sleep,[33,34] a measure of mild sleep disruption, and phenytoin may cause increased nocturnal awakenings.[34] Phenytoin has been shown in a number of studies to reduce REM sleep.[29,34-37] Thus, as with benzodiazepines and barbiturates, patients may get to sleep faster but have less effective sleep overall. One study also suggested increased daytime drowsiness with phenytoin.[26]

2.4 Carbamazepine

The results of studies looking for effects of carbamazepine on sleep have been variable. Patients have been reported to experience an improvement in disordered sleep when carbamazepine is used to treat affective disorders[38] or epilepsy,[39] although in these cases it is possible that improved sleep was a result of improvement in the underlying condition. Another study actually showed increased arousals with carbamazepine treatment.[34] A number of studies have shown adverse effects on REM sleep, particularly decreased density without a change in percentage REM sleep.[40,41] In other studies, carbamazepine did reduce REM percentage when used

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acutely[1,42] and in the longer term,[34] but decreased REM sleep may not be present when carbamazepine is used over the long term.[1,43] Daytime somnolence has been reported in studies of carbamazepine.[26,43] In one study, control patients showed increased drowsiness as measured by multiple sleep latency testing, but this disappeared with long-term treatment.[43] The same study showed no effects in patients with epilepsy. Another showed drowsiness, compared with healthy control individuals, in patients with epilepsy who were treated with carbamazepine long term; in this case, the effect persisted.[44]

Thus, in most patients, the effects of carbamazepine on sleep are minimal. In some patients, however, there may be detrimental effects (decreased REM sleep and/or mild daytime somnolence).

2.5 Valproate

Most studies of valproate[35,45] have shown no significant effects of its use on sleep. One study, however, showed that patients with epilepsy who were treated with valproate monotherapy experienced an increase in stage 1 sleep compared with similar patients who were taking no drug.[37] This suggests that, in some cases, valproate can cause mild sleep disruption. No studies have shown significant effects of valproate on slow-wave or REM sleep. There may be increased daytime drowsiness in patients with epilepsy who are treated with valproate.[26]

2.6 Gabapentin

In an add-on study of patients with epilepsy, gabapentin increased REM sleep.[1] Additionally, gabapentin improved sleep by reducing the number of awakenings and the amount of stage 1 sleep compared with baseline. These patients had a low amount of REM sleep at baseline, probably due to concurrent AEDs, and the result may reflect a partial correction of this deficit. Another add-on study of gabapentin in patients with epilepsy confirmed increased REM sleep, decreased awakenings and decreased stage 1 sleep but also showed a significant increase in slow-wave sleep.[10] In studies of healthy volunteers, gabapentin as monotherapy increased slow-wave sleep;[46,47] a study in patients with epilepsy showed similar results.[37] No effects were seen on other sleep parameters. Although its effects are generally mild, gabapentin demonstrates the most evidence for sleep improvement, particularly through decreased awakenings and increased slow-wave sleep. The effects of gabapentin on daytime drowsiness have not been studied.

2.7 Lamotrigine

Lamotrigine was also examined in the add-on trial of patients with epilepsy as described for gabapentin in section 2.6.[1] An increase in REM sleep was seen compared with the baseline condition, along with a decrease in phase shifts and a decrease in slow-wave sleep. Because the patients showed low amounts of REM sleep at baseline (probably because of the concurrent AEDs), the effect on REM sleep could be a result of a reversal of the detrimental effects of other agents. In a more rigorously controlled add-on study, also in patients with epilepsy, Foldvary et al.[48] showed that the addition of lamotrigine caused no significant change in percentage REM sleep but a decrease in slow-wave sleep. No other differences were seen.

Lamotrigine is therefore unlikely to have detrimental effects on sleep, with the possible exception of decreased slow-wave sleep. Clinically, some patients report an alerting effect; in these cases, the drug should be administered early in the day or, in the absence of enzyme-inducing drugs, as a single morning dose. The effect of lamotrigine on daytime drowsiness has not been specifically studied.

2.8 Tiagabine

A single double-blind study of tiagabine (5mg at bedtime) or placebo in ten healthy elderly (mean age 68 years) subjects was conducted.[49] As expected, when receiving placebo this population showed relatively low sleep efficiency, frequent arousals and small amounts of slow-wave sleep. With tiagabine, there were significant increases in sleep efficiency and slow-wave sleep, with other parameters unchanged (including number of arousals). It is not clear whether this effect would generalise to young-

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er subjects or patients with epilepsy. The effect of tiagabine on daytime drowsiness has not been specifically studied.

2.9 Levetiracetam

Bell et al.[50] studied levetiracetam as monotherapy in healthy volunteers and as add-on (to carbamazepine) therapy in patients with epilepsy. No effects on the number of awakenings, sleep efficiency or amount of slow-wave or REM sleep was seen in either group. There was, however, a subjective perception of fewer awakenings, more restful sleep and decreased alertness on awakening in both groups. In another small study, levetiracetam monotherapy was evaluated in patients with epilepsy compared with similar patients who were taking no AEDs.[51] No effect was seen on sleep efficiency or stage 1, stage 2 or slow-wave sleep. Interestingly, the percentage of REM sleep was increased compared with similar patients who were taking no drug. REM sleep latency was also shortened, although this was not statistically significant.

2.10 Other Agents

Sleep studies of felbamate, oxcarbazepine, zonisamide and topiramate have not been published. Felbamate has a well known alerting effect[52] and therefore in many patients must be administered early in the day to avoid the induction of insomnia. Vigabatrin increases daytime drowsiness,[44] but effects on sleep parameters have not been published. Anecdotally, some patients experience an alerting effect with zonisamide. Oxcarbazepine, although structurally similar to carbamazepine, may or may not have similar effects on sleep.

3. AEDs and Comorbid Sleep Disorders

Sleep disorders are common in the general population; therefore, concurrent sleep disorders frequently occur in patients with epilepsy (table II). Attention to these conditions can therefore be helpful in the choice of AED, as many of these drugs can be useful in other disorders.

Table II. Use of antiepileptic drugs (AEDs) in sleep disorders and comorbid conditions that can affect sleep

Condition	Potentially useful AED(s)	Potentially harmful AED(s)
Insomnia	Barbiturates, benzodiazepines, gabapentin, tiagabine	Felbamate
Restless legs/PLMS	Gabapentin, carbamazepine, benzodiazepines	
Obstructive sleep apnoea		Benzodiazepines, barbiturates
Depression	Lamotrigine	
Anxiety	Benzodiazepines	
Migraine	Valproic acid, gabapentin, topiramate	
Neuropathic pain	Carbamazepine, gabapentin, lamotrigine, topiramate	

PLMS = periodic limb movements of sleep.

Insomnia occurs in up to 19% of the general population[53] and, by inference, occurs in at least as many patients with epilepsy. Causes are many, including concurrent medical disorders, drugs and inadequate sleep hygiene. Drugs such as barbiturates (phenobarbital, primidone) and benzodiazepines (clonazepam, clorazepate, clobazam) can be helpful in patients who have difficulty falling asleep. In these cases, the drug should be primarily or exclusively (all are long acting) administered at bedtime. Drugs that increase slow-wave sleep (gabapentin and tiagabine) would not be useful in helping patients to fall asleep but could help consolidate sleep for patients with frequent or early awakenings. Insomnia is an adverse effect of felbamate and therefore this drug could exacerbate sleep problems in these patients.

Depression is a common cause of insomnia, and patients with insomnia have approximately four times the risk of depression compared with the general population.[54,55] Studies suggest that lamotrigine may improve depression in patients with epilepsy compared with topiramate[56] and valproic acid.[57] Lamotrigine may therefore be a good choice in patients with insomnia associated with mild depression.

Patients with underlying anxiety disorders often have difficulty with sleep, particularly initiation of

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sleep. These individuals may benefit from long-acting benzodiazepines, several of which (including clonazepam and clorazepate) are indicated for both anxiety and seizures. Alprazolam is commonly used for anxiety but is not particularly effective for epilepsy.

Restless legs syndrome and periodic limb movements in sleep are also common, occurring in between 2.5% and 15% of the population, although the prevalence of periodic limb movements may be up to 44% in the elderly.[58-63] Carbamazepine and gabapentin have been shown to be effective in restless legs syndrome[64,65] and gabapentin in periodic limb movements.[66] Clonazepam has also been used. Treatment with these agents should be considered in patients with epilepsy who have either of these disorders.

Perhaps the most important sleep disorder in patients with epilepsy is sleep apnoea. Like insomnia and periodic limb movements, sleep apnoea is common (at least 3% but possibly as high as 24% in middle-aged men).[67] In addition to the daytime somnolence and increased cardiovascular risk that all patients with this disorder experience, patients with epilepsy are also at risk for seizure exacerbations and even intractability.[68,69] In these cases, seizures in susceptible individuals may be triggered by hypoxia during apnoeic episodes. All patients with possible sleep apnoea need to be evaluated with polysomnography, and the most effective treatment is usually continuous positive airway pressure.[70] AEDs can, however, have an influence on this condition. Sleep apnoea can be worsened by sedative-hypnotic medications, including barbiturates and benzodiazepines.[32,71] These agents can further destabilise the upper airway and impair arousal, resulting in increased oxygen desaturation. There is a theoretical role for agents that improve slow-wave sleep, as there is relative stability of breathing in this stage; however, there is no published evidence of improvement in obstructive sleep apnoea with such medications.

Many patients with epilepsy may have other comorbid conditions, particularly headache and neuropathic pain, which are known to adversely affect sleep. Therefore, patients with migraine might experience improved sleep by using agents that are also useful in this condition, most convincingly valproate[72,73] but also topiramate[74] and gabapentin.[75] Lamotrigine has been used for migraine but was ineffective in a placebo-controlled, randomised trial.[76] Zonisamide has also been used; however, no studies have been published to date.

Patients with chronic pain might have improvement in sleep with gabapentin, which has shown efficacy for various types of neuropathic pain.[77-79] Carbamazepine, topiramate and lamotrigine have also shown some usefulness in certain chronic pain syndromes,[80-82] although the evidence is less convincing.

4. Conclusions: Choosing and Using Sleep-Friendly AEDs

The choice of an AED for a patient with epilepsy always starts with an effective agent for the patient's seizure type. Multiple studies of both newer and older agents, however, suggest no overall differences in efficacy, especially among patients with partial seizures.[83-92] Now more than ever, with the large number of AEDs available, the 'drug of choice' is one individually selected for the patient. Keeping in mind that there is still much to be learned, especially about newer agents, in general there are relatively 'sleep-friendly' drugs: those that have few or no detrimental effects on sleep in most individuals. These include gabapentin, lamotrigine and (probably) levetiracetam and valproic acid. Benzodiazepines, barbiturates and phenytoin are known to have some potential for detrimental effects on sleep; however, all have the advantage of decreasing sleep latency. In patients who have chronic difficulties falling asleep, use of one of these agents (administered at bedtime) may avoid the need for an additional hypnotic medication. Some patients with epilepsy have comorbid conditions, including sleep disorders, but also migraine, chronic pain or depression. The choice of agents that are likely to improve these conditions will also improve nocturnal sleep.

The timing of the administration of AEDs is also important. Although the goal of AED treatment is

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always to achieve a steady concentration of the drug in the bloodstream, mild peak effects occur with all orally administered medications. Therefore, agents likely to cause sedation (phenobarbital, clonazepam, phenytoin) should be administered more towards bedtime when possible. Lamotrigine, felbamate and zonisamide can be alerting in some patients. Lamotrigine and zonisamide can be administered once daily in many cases, and this can be given in the morning. When once daily administration is not possible (as with felbamate or when lamotrigine is administered with an enzyme-inducing drug), doses can be given earlier in the day.

In all cases, simple awareness of the patient's functioning and the potential relationship of the AED to sleep is important. Whenever a patient reports daytime drowsiness, insomnia or (perhaps) dulling of memory, thought should be given to the potential role of the patient's AED and to the possible presence of a concurrent sleep disorder. Polysomnography should be strongly considered whenever a sleep disorder is suspected. Sleep habits should also be considered whenever instituting a new AED, either in a newly diagnosed patient or one whose seizures are incompletely controlled. Optimal sleep can make the difference between a highly functioning individual and one who may be seizure free but not operating at full potential.

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