Sleep and Epilepsy

Beth Malow, MD, MS
Professor of Neurology and Pediatrics
Burry Chair in Cognitive Childhood Development
Director, Sleep Disorders Division
Vanderbilt University

Learning Objectives

- Sleep and epilepsy have reciprocal interactions.
- Sleep state modulates the expression of epileptic seizures and interictal epileptiform discharges
- In turn, epilepsy and its treatment influence sleep organization and may contribute to or ameliorate sleep disorders
- Therefore, paying attention to sleep may assist in the successful management of the epilepsy patient

Relationship of Epileptic Seizures to Sleep

- Seizures predominate during NREM sleep, and are more likely to occur in lighter stages of NREM sleep (stages 1 and 2).1,2
- NREM sleep activates frontal lobe seizures more than temporal lobe seizures.3-4
- Limbic seizures occur more during light than dark in animal models and humans.5
- Sleep, not clock time, is a robust stimulus for seizure onset, especially in frontal lobe seizures.6

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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

CSWS: REM vs non-REM Sleep
IEDs and Sleep (1998-2001)

- Depth of NREM sleep is important in activating interictal epileptiform discharges (IEDs) in the partial epilepsies.
  - 31/40 subjects with temporal lobe epilepsy had increased IEDs in NREM sleep stages 3 and 4 sleep compared to lighter NREM sleep and REM sleep.
  - In a separate study, IEDs were more prevalent at higher levels of log delta power. After adjusting for the level of log delta power, IEDs were more prevalent as sleep was deepening.
  - Sleep-modulated IEDs may have localizing and prognostic value.


IEDs/Sleep/Lateralization (2011)

REM sleep provoked the most lateralized IEDs compared to NREM and wakefulness.
Lateralization of REM IEDs corresponded with the hemisphere of ictal EEG and largest tuber.

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Epilepsy Affects Sleep Organization

On seizure free nights, sleep organization was affected in 80 epilepsy patients as compared to 17 normal controls:

- Decreased sleep efficiency (time asleep/time in bed)
- Increase in sleep stage shifts
- Increase in number and duration of awakenings

These parameters were most affected in untreated, newly diagnosed patients.

Treatment with carbamazepine for 1 month improved these parameters.

**Epilepsy Affects Sleep Organization**

- Temporal lobe epilepsy disrupts sleep organization more than frontal lobe epilepsy and idiopathic generalized epilepsy, even in the absence of seizures.
- Seizures themselves have profound effects on sleep architecture, even apart from the resulting arousals and awakenings.


**Seizures Suppress REM Sleep**

- 87 recordings in 21 patients comparing nights with seizures and seizure-free nights.
- Nighttime seizures reduced REM sleep and increased NREM stage 1 sleep, also decreased daytime alertness.
- Daytime seizures also reduced REM sleep the following night.


NTSZ: nocturnal seizure
BREM: seizure before first REM period

**Adverse Effects of Antiepileptic Drugs**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>51/144</td>
<td>35%</td>
</tr>
<tr>
<td>Gingival Hyperplasia</td>
<td>34/144</td>
<td>24%</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>23/144</td>
<td>16%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>16/144</td>
<td>11%</td>
</tr>
<tr>
<td>Irritability</td>
<td>10/144</td>
<td>7%</td>
</tr>
<tr>
<td>Vertigo</td>
<td>10/144</td>
<td>7%</td>
</tr>
</tbody>
</table>

AEs were patient-reported and AEDs included PHT, PB, CBZ, VPA. Beghi et al, Epilepsia 27(4):323-330, 1986.
Antiepileptic Drugs (AEDs) and Sleep

AEDs and Sleep– Unanswered Questions

- Are AEDs that reduce sleep stage shifts, arousals, and awakenings “better” than those that do not?
- Might these effects translate into improved daytime alertness, health-related quality of life, or even reduced seizure frequency?
- Does improving (or not suppressing) REM or slow wave sleep affect cognition?

| Table 3: Long-term Effects of AEDs on Nocturnal Sleep |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| TST SE SL 1 2 SW5 REM Arousal AW Stage shifts |
| PH  | - | T | T | T | 0 | 1 | 1 | T | - |
| PHVt| - | 0 | T | T | T | 0 | 0 | 0 | - |
| PRM  | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | - |
| CRC  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| VPA  | - | 0 | T | T | T | 0 | 0 | 0 | - |
| ESM  | - | 0 | 0 | 0 | 0 | T | - | 0 | - |
| LTG  | 0 | 0 | 0 | 0 | 0 | T | T | 0 | 0 |
| TPS  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

0 = no change; - = not reported; TST = total sleep time; SE = sleep efficiency; SL = sleep latency; 1 = NREM stage 1; 2 = NREM stage 2; SWS = slow wave sleep; AW = awakenings


AEDs

Consolidation of sleep

Improved alertness?

Improved memory?

Suppression of epileptic seizures
Vagus Nerve Stimulation

Differences in Mean Sleep Latency with VNS Stimulation

Case Example
This 61-year old man had his first seizure during sleep at age 33 in the setting of viral encephalitis. His seizures were well controlled with phenobarbital and phenytoin for 20 years, but then increased in frequency to several/week. He reported daytime sleepiness and a 20 lb weight gain. His wife noted that he snored heavily and occasionally stopped breathing during sleep.

Case Example
Polysomnography showed an apnea-hypopnea index (AHI) of 15.9 events/hr with a minimum oxygen saturation of 86%. A multiple sleep latency test revealed mild daytime sleepiness. He was prescribed continuous positive airway pressure (CPAP), with antiepileptic drug dosages held constant. He became seizure-free and reported improvement in daytime alertness.

Obstructive Sleep Apnea
One of the most common sleep disorders, with as many as 24% of men and 9% of women in the general population affected. 
93% of women and 82% of men with moderate to severe sleep apnea are undiagnosed.
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

Epilepsy and OSA– Older Studies

Sleep apnea may coexist with epilepsy; its treatment may improve seizure control, daytime sleepiness, or both.

- Tracheostomy diminished generalized seizures in 1 patient.
- CPAP or other therapy improved seizure control and daytime alertness in 6 of 7 patients with partial seizures.
- CPAP or positional therapy improved seizure control in 7 of 10 patients with seizures and OSA; 3 had antiepileptic medications optimized.
- CPAP improved seizure control or daytime sleepiness in 7 of 9 adults.

Prospective study showed 45% reduction in seizure frequency in 3 adults and 1 child treated with CPAP.


Epilepsy and OSA– NINDS Pilot Trial

NINDS Pilot Clinical Trial involving 45 participants at 4 sites (Vanderbilt, Michigan, Chapel Hill, Cleveland Clinic)

- 33 with OSA randomized to CPAP/placebo CPAP for 10 weeks.
- Differences in CPAP adherence in the therapeutic and sham CPAP groups were not statistically significant (66% of nights in the therapeutic group and 74% in the sham group).
- Therapeutic CPAP resulted in >50% seizure reduction in 28% of subjects as compared to 15% of subjects receiving placebo CPAP.

Epilepsy and OSA– Boston experience

41 patients with epilepsy and OSA, 28 CPAP-compliant and 13 not CPAP-compliant, identified from 10 year retrospective review (2000-2010)
- Seizure freedom: 16/28 (57%) vs. 3/13 (23%)
- Seizure reduction: 1.8 to 1/month in CPAP-compliant group (p = 0.01) vs 2.1 to 1.8/month in not CPAP-compliant group (p = 0.36)
- CPAP compliance may influence seizure control

Vendrame M et al, Epilepsia 2011

Epilepsy and OSA– Iowa Experience

33 patients with epilepsy and OSA, who had pre and post-treatment seizure data, identified from 10 year retrospective review
- Mean seizure reduction: 2.3 seizures/mo
  (95% CI = -4.5, -0.9, p = 0.04)
- Mean Pre/Post-nCPAP AED Load Reduction
  2.51 > 1.79 (0.72 Drug Load Reduction)
- Improved sleepiness in 15/33 (45.5%)
  using ESS>8, 42.9% improved
  T=2.036 (df=32) p=0.00009

St. Louis et al, Neurology 2011; 76 (Suppl. 4): A453

Iowa Study: Outcomes by Epilepsy Syndrome

<table>
<thead>
<tr>
<th>Epilepsy Type</th>
<th>Any Seizure Reduction</th>
<th>Responder (&gt;50% Reduction)</th>
<th>Seizure-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized n = 10</td>
<td>81.8%</td>
<td>63.6%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Partial n = 22</td>
<td>81.8%</td>
<td>63.6%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

St. Louis et al, Neurology 2011; 76 (Suppl. 4): A453.
How Might OSA Facilitate Seizures?

Proposed mechanisms include:
- Sleep deprivation resulting from frequent arousals from sleep, increasing neuronal excitability
- Frequent arousals or stage shifts into and out of sleep, facilitating sleep-related seizures
- Cytokines? (increased by sleep apnea, facilitators of seizures)
- Apneas and hypopneas causing seizures
- Episodes of hypoxemia
- Decreased cardiac output/arrhythmias

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Sleep Hygiene in People with Epilepsy (PWE)

- Prospective study of sleep hygiene in PWE, n=64 (43 partial onset, 21 generalized onset)
  - 22/62 (34%) had poor sleep hygiene (at least 3 poor sleep habits)
  - Poor sleep hygiene was associated with increased seizure frequency by regression model (p<0.05)


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Seventy-one subjects returned 15,179 complete diary days. Less sleep, and self-prediction had significant effects, whereas stress and anxiety did not. (Haut et al., Neurology, 2007).
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Is OSA More Common in Patients with Epilepsy?

- One third of 39 epilepsy surgery candidates had OSA (AHI >5) and 13% had AHIs >20
- 60% of intractable epilepsy patients (>4 seizures/month) had AHIs of 5 or greater, and 36% had AHIs of 10 or greater
- Age, body mass index, but not gender predict OSA.
- Possible reasons OSA may be more common:
  - Sedentary lifestyles?
  - Weight gain from antiepileptic drugs (AEDs)?
  - Effects of AEDs on the upper airway?

2. Vaughn BV, D'Cruz OF. Epilepsia. 2002;42(suppl 7):43.

What would a definitive trial of treating OSA in epilepsy accomplish?

- Heighten the awareness of identifying and treating OSA in epilepsy among practitioners, in that the vast majority of patients with OSA are still not diagnosed and treated, even by neurologists
- Epilepsy patients may be more at risk for OSA, and have more to gain from treatment
- Epilepsy patients tend to put seizures in the forefront, and may not be attuned to possibility that OSA may be contributing to daytime sleepiness, AED intolerance, and impaired quality of life
- Patients with epilepsy may be more likely to use their CPAP than the general population if they perceive a benefit in seizures or daytime sleepiness
What are important outcome measures for patients with epilepsy and OSA?

- Is seizure frequency the most important outcome?
- Other outcome measures to consider are:
  - Daytime sleepiness
  - Insomnia
  - Health-related quality of life
  - Ability to tolerate AEDs if OSA treated
  - Improvement in obesity
  - Minimizing cardiovascular/cerebrovascular consequences of OSA, especially in older adults with epilepsy

Conclusions

- Epilepsy and sleep are interrelated.
- Sleep influences the expression of interictal epileptiform discharges 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.