



SLEEP DISORDERS IN ADULTS WITH EPILEPSY

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EPILEPSY AND SLEEP

Effects of sleep on epilepsy

- Non-rapid eye movement (NREM): state of EEG synchronization, relative preservation of muscle tone
 - Intra-epileptiform (IED) discharges are activated (most occur during N1 and N2 stage)
 - Spike frequency increases with increasing depth of sleep
 - Perpetuated by hypersynchrony of neuronal networks
 - More diffuse discharges
- Rapid eye movement (REM): desynchronization of EEG, skeletal muscle atonia
 - Spike frequency decreases
 - Restricted field of discharges (used to identify focus of seizures)
- Adenosine
 - Decreases in sleep



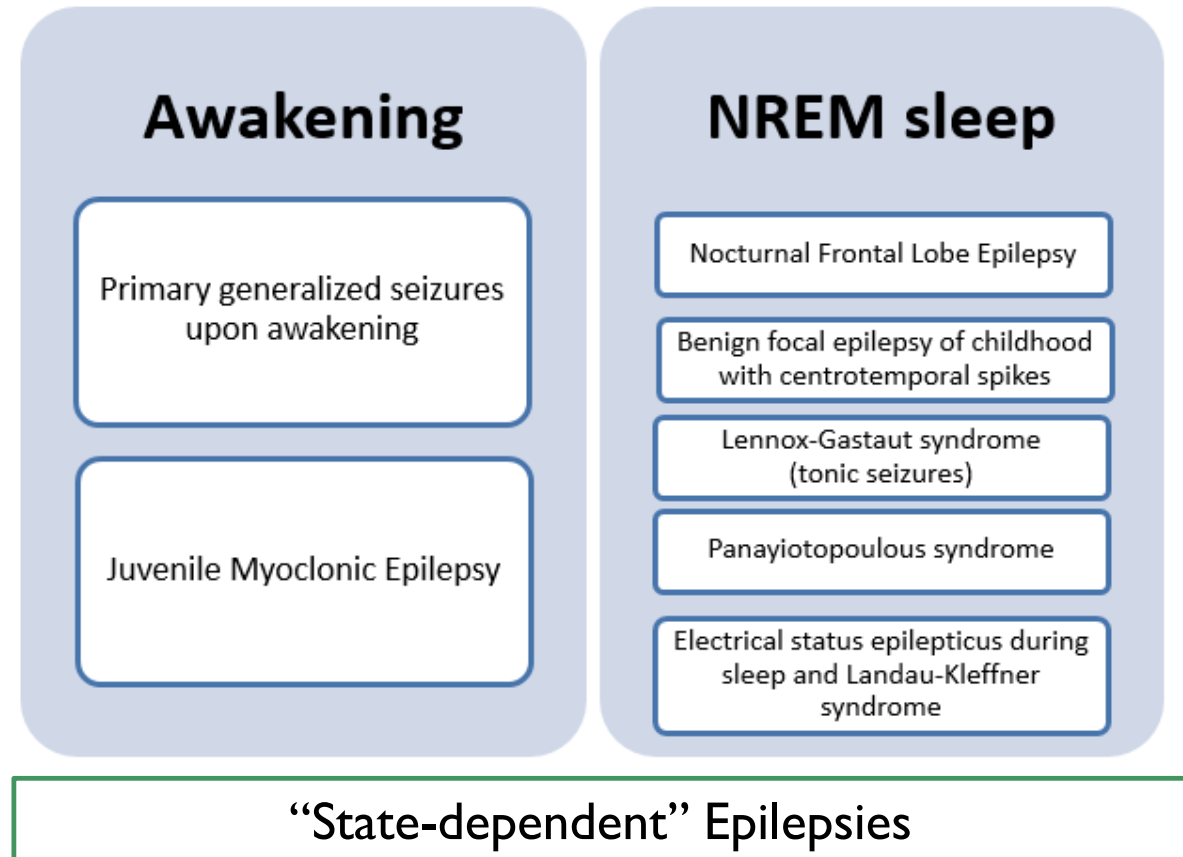
EPILEPSY AND SLEEP

Sleep architecture in Epilepsy

- Reduced REM sleep time
- Prolonged REM latency
- Increased wake after sleep onset (WASO)
 - Reduced total total sleep time and sleep efficiency
 - Increased number of arousals, awakenings, and stage shifts
- Sleep macroarchitecture in some patients is normal, or normalizes after treatment
- Abnormalities in sleep architecture is more likely in temporal lobe epilepsy (TLE) compared to idiopathic generalized epilepsies (IGE)

EPILEPSY AND SLEEP

- Some epilepsy syndromes occur primarily in sleep or upon awakening
- A large prospective study found 7.5% of 1,200 patients had seizures restricted to sleep:
 - If a patient has SZs only during sleep > 2 years, unlikely to have a SZ awake (and could drive a motor vehicle even if not SZ-free;
 - Only 11% of people with sleep-related SZs developed seizures when awake, typically within 2 years of the first nocturnal SZ:
 - Diurnal SZs in them were often triggered by sudden withdrawal of antiepileptic medication (AED);



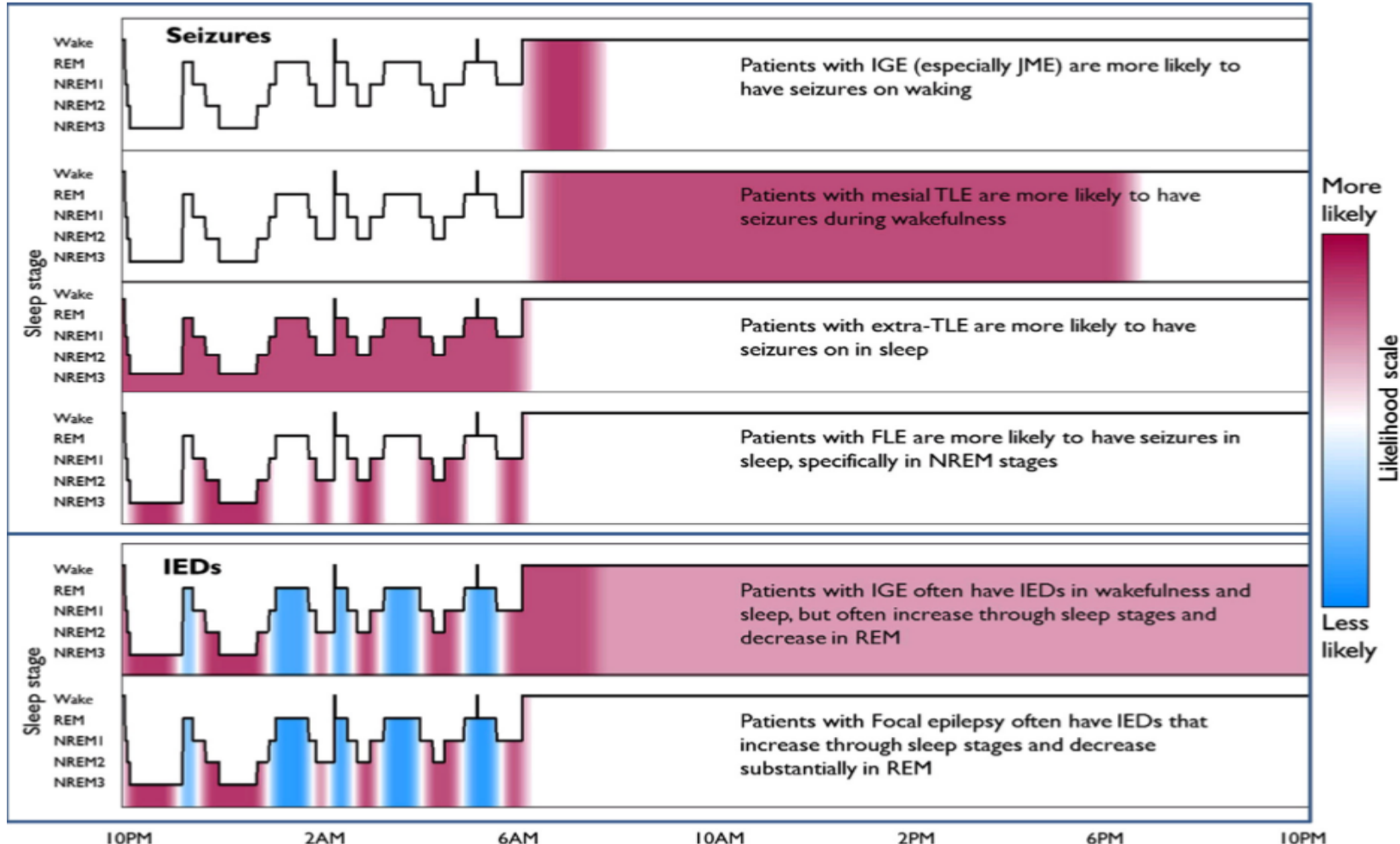
EPILEPSY AND SLEEP

Timing seizure types and epilepsy syndromes

- Sleep: Tonic-clonic seizures, tonic, automotor, frontal and parietal seizures
- Wakefulness: Absence, atonic, myoclonic seizures, myoclonic, epileptic spasms
- Peak frequency of epilepsies vary with circadian rhythm
- Seizure occurrence correlates with dim light melatonin secretion



EPILEPSY AND SLEEP



SLEEP DEPRIVATION AND EPILEPSY

- Seizure precipitant (especially in awakening epilepsies)
- Triggering factor for seizures in 71% of cases in recent study of 104 patients
- Can induce IEDs
- Sleep deprivation EEG protocol
- Juvenile Myoclonic Epilepsy

Table 1**Contribution of AED on sleep disorders and sleep architecture**

AED	Sleep Disorders		Sleep Architecture	
	Positive Effects	Negative Effects	Positive Effects	Negative Effects
Phenobarbital	Insomnia	Obstructive sleep apnea	↓SL	↓REM
Benzodiazepines	Insomnia, Willis Ekbom disease, REM sleep disorder	Obstructive sleep apnea	↓SL, ↓arousals, ↓CAP rate	↓REM ↓N3
Carbamazepine	Willis Ekbom disease	None	None	↓REM, ↑Sleep stage shifts
Valproate	Willis Ekbom disease	Obstructive sleep apnea	Sometimes no effect	↑1N Reduction in REM
Gabapentin	Willis Ekbom disease, insomnia	Obstructive sleep apnea	↑N3, ↓arousals ↑sleep efficiency	None
Lamotrigine	Consolidating sleep reducing arousals stage shifts	Insomnia; REM sleep behavior disorder	↓Sleep stage shifts, ↓arousals, ↑REM	↓N3(possible)
Levetiracetam	Willis Ekbom disease (case reports)	Insomnia	↑N3 Stage shifts and wake after sleep onset were significantly decreased	None
Pregabalin	Willis Ekbom disease, insomnia, daytime attention	Obstructive sleep apnea	↑N3, ↑REM, ↓arousals	None
Topiramate	Weight loss, Obstructive sleep apnea	Willis Ekbom disease	No changes	No changes
Zonisamide	Obstructive sleep apnea	Willis Ekbom disease	No changes	No changes

SEIZURE DISORDERS DURING SLEEP

- Nocturnal Temporal Lobe Epilepsy
- Benign Epilepsy of Childhood with Centro-temporal Spikes
- Nocturnal Paroxysmal Dystonia
- Nocturnal Frontal Lobe Epilepsy
- Autosomal Dominant Frontal Lobe Epilepsy

CHARACTERISTICS OF NOCTURNAL EVENTS

Feature	Disorders of Arousal	REM Sleep Behavior Disorder	Nocturnal Seizures	Psychiatric Disorders
Time of night	First third to half of night	Latter half of sleep period during REM	Sporadic	Sporadic
Eye opening	Yes	No	No	Yes
Stereotypic movements	No	No	Yes	No
Memory	Partial or no memory	Vivid dream recall	Variable	Variable
Duration	Minutes	Seconds to minute	Minutes	Minutes to hours
Frequency	Typically 1 or less per night	Nightly events during REM	Sporadic to multiple per night	Sporadic
PSG findings	Arousal from slow-wave sleep	Excessive electromyography tone in REM	Epileptiform activity	Wake state before the event

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EPILEPSY AND SLEEP

- Prevalence of primary sleep disorders in epilepsy

PRIMARY SLEEP DISORDERS IN EPILEPSY

- **Primary sleep disorders are 2-3 times more common in adults with epilepsy compared to age-matched controls in the general population:**
 - Especially when seizures are poorly controlled and/or
 - Complicated by comorbid neurological conditions.
- **Most common sleep disorders in people with epilepsy:**
 - Sleep maintenance insomnia
 - Excessive daytime sleepiness (EDS)
 - Obstructive sleep apnea (OSA)

REFs: 1) DeWeerd A *Epilepsia* 2004;45(11):1397-1404; 2) Khatami R *Seizure* 2006;15(5):299-306; 3) Piperidou C *Seizure* 2008;17(7):588-94; 4) Jenssen S *Epilepsy Behav* 2006;9(4):632-5.



Adults with epilepsy who complain of sleep problems have lower quality of life (QOL) compared to those with epilepsy but no sleep complaints.

SLEEP MAINTENANCE INSOMNIA

Most common sleep complaint in adults with epilepsy

- **51%** of 152 patients with epilepsy (mean age 46 years) reported moderate to severe insomnia
- **72%** rated themselves as “poor sleepers”
- Poorer sleep quality and more severe insomnia correlated with:
 - Higher numbers of antiepileptic medications (AEDs); and
 - Were significant predictors of lower quality of life (QOL).



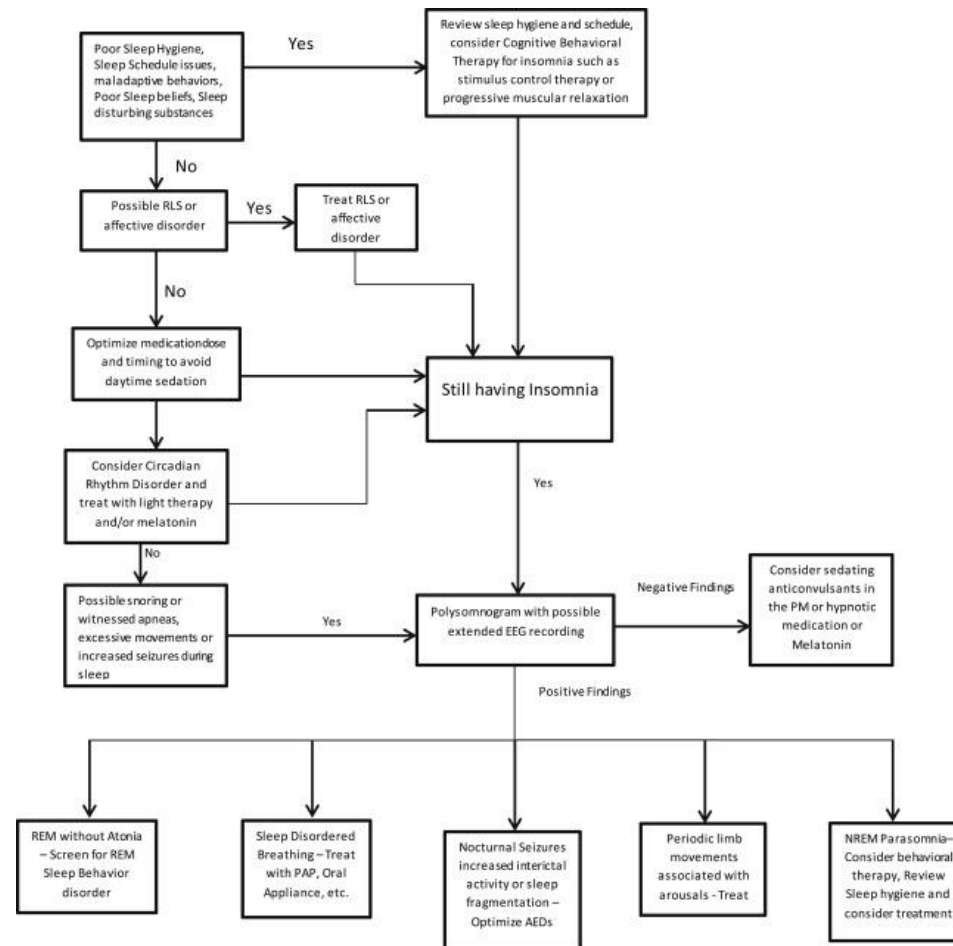
Vendrame M et al. *J Clin Sleep Med.* 2013;9(2):141-6.

INSOMNIA IN ADULTS WITH EPILEPSY

Etiology of sleep disruption in epilepsy:

- Inadequate sleep hygiene
- Coexisting sleep disorders
- Nocturnal seizures
- Effect of antiepileptic drugs

ALGORITHM FOR EVALUATION OF INSOMNIA IN EPILEPSY



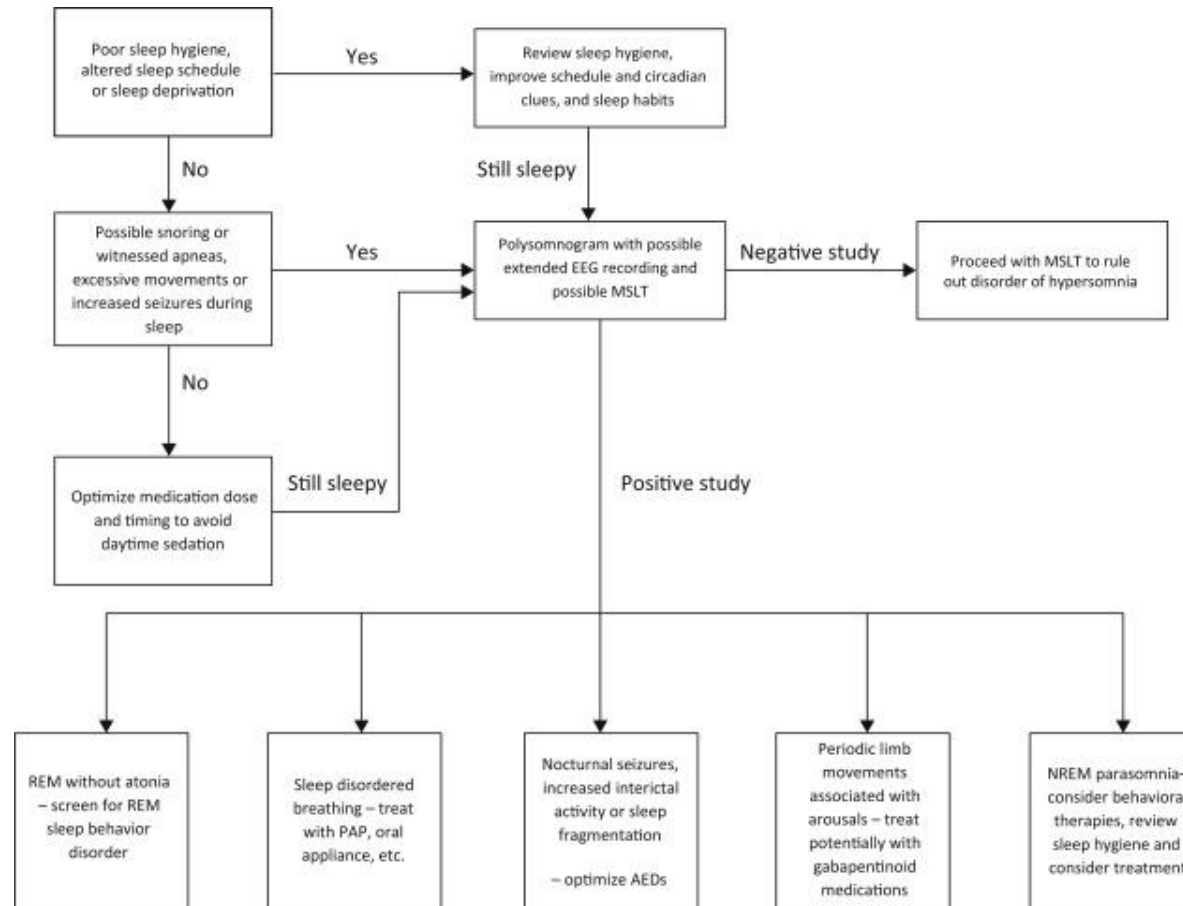
EXCESSIVE DAYTIME SLEEPINESS

Second most common sleep complaint in adults with epilepsy

- **48%** of 99 unselected patients with epilepsy complained of EDS (Epworth Sleepiness Score of > 11)
 - Anxiety (and to lesser extent neck circumference) correlated with EDS
- **20%** of 117 people with epilepsy complained of EDS vs. **7%** of 30 healthy volunteer
 - Poor seizure control was the strongest independent risk factor for poor sleep quality (odds ratio [OR] = 2.4)



EVALUATION OF HYPERSOMNIA IN EPILEPSY



OBSTRUCTIVE SLEEP APNEA IN ADULTS WITH EPILEPSY

Prevalence of OSA in patients with epilepsy

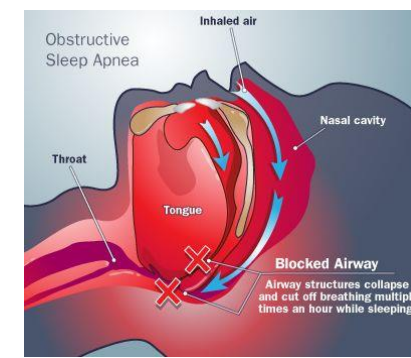
Meta-analysis by Zhang Lin et al in 2016:

- Prevalence of mild-to-severe OSA (AHI or RDI >5) in people with epilepsy was 33.4% (95%CI20.8–46.1%) compared to 21.2 % of general population in USA
 - Mild-to-severe OSA in males with epilepsy is 44.8% compared to 27.5 % in general population
 - Mild-to-severe OSA in females with epilepsy is 25.5% compared to 12.4% in general population
- Prevalence of moderate-to-severe OSA (AHI or RDI >15) in people with epilepsy was 9.7 % (95 % CI 5.1–14.4 %)
- Patients with refractory epilepsy are not more susceptible to OSA compared to those with controlled epilepsy (OR 1.66; CII.22-2.27 P=0.43.)

OBSTRUCTIVE SLEEP APNEA IN ADULTS WITH EPILEPSY

OSA Risk factors and comorbidities

- **Males**
- **Overweight or obese**
- African-Americans
- Post-menopausal women
- Family history
- **Large neck size**
- Alcohol or tobacco use
- **Middle age**
- Stroke
- Medically refractory **hypertension**
- Atrial fibrillation



Risk factors that are highlighted are found to be risk factors for OSA in adults with epilepsy

OBSTRUCTIVE SLEEP APNEA IN ADULTS WITH EPILEPSY

Proposed mechanisms for seizure facilitation in OSA

- Sleep deprivation from frequent arousals increases neuronal excitability
- Frequent arousals or stage shifts
- Intermittent hypoxia → oxidative stress → activation of inflammatory pathways → IL6 and TNF alpha
- Decreased cerebral blood flow

OBSTRUCTIVE SLEEP APNEA IN ADULTS WITH EPILEPSY

- CPAP treatment in people with epilepsy and OSA:
- Higher seizure-free rate (OR 4.03; 95 % CI 1.15 –14.1; P = 0.01).
- Increase in successful outcomes as compared to the untreated patients (OR 5.26; 95 % CI 2.04–13.5; P < 0.001).



OBSTRUCTIVE SLEEP APNEA IN ADULTS WITH EPILEPSY

Vagal nerve stimulation effect on respiration

- Used for medically refractory focal epilepsy
- Prevalence of OSA is 43.1% compared to 33.4% in all patients with epilepsy
- Decreases REM sleep
- Increases awakenings, wake after sleep onset, NREM I sleep stage

PARASOMNIAS AND EPILEPSY

- NREM disorders of arousal
- Sleep related bruxism
- Nocturnal Frontal Lobe Epilepsy

SUMMARY

- Sleep and epilepsy are common but are bad Bed Fellows
- Sleep and epilepsy have complex bidirectional relationship
- Sleep maintenance insomnia is most common complaint in adults with epilepsy
- Excessive daytime sleepiness is second most common complaint
- Adults with epilepsy are at increased risk for OSA

QUESTIONS



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