Sleep Disorders in Adults with Epilepsy

Madeleine Grigg-Damberger MD

Professor of Neurology, Albuquerque, NM, USA

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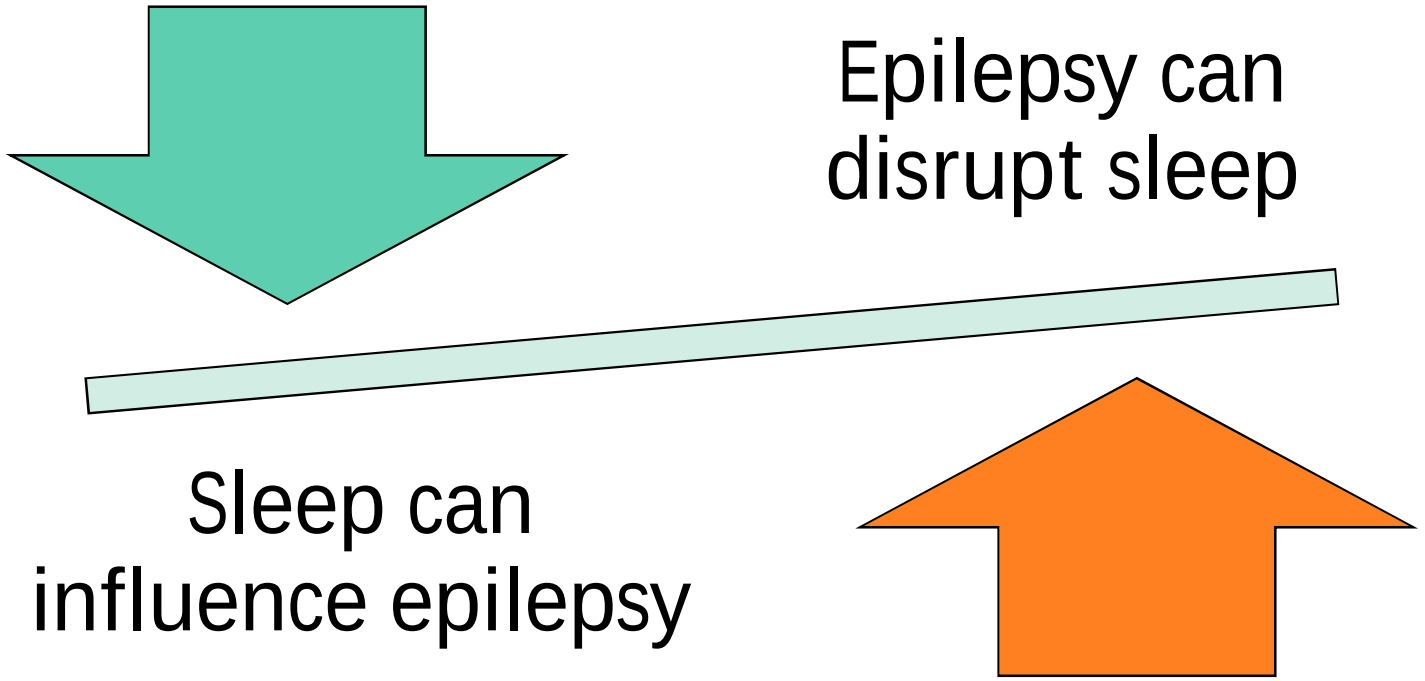
TC 47: Sleep Disorders: Neurosleep.

I have no conflicts of interest related to this talk

Objectives of Talk

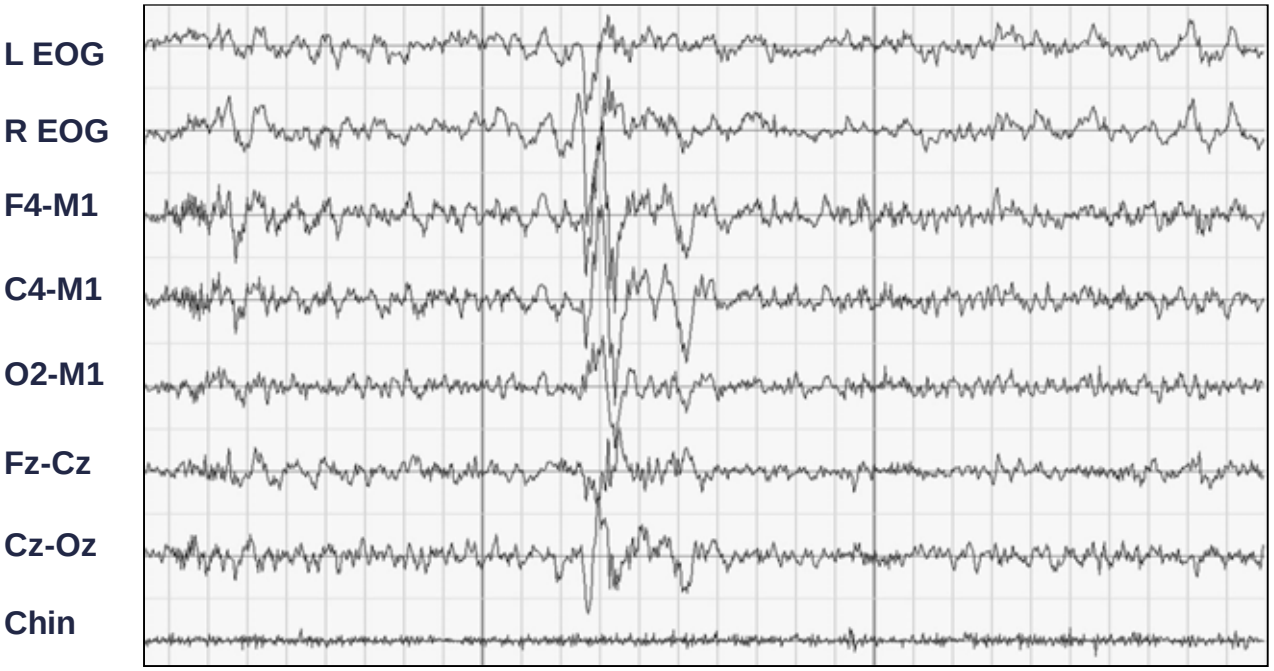
- Understand that insomnia, excessive daytime sleepiness (EDS), and obstructive sleep apnea (OSA) are 2-3 times more common in adults with epilepsy than the general population;
- Realize that sleep deprivation is more likely to trigger seizures in patients with idiopathic generalized epilepsies than focal epilepsies.
- Discuss objective alterations in sleep macro- and microarchitecture observed in epilepsy, and effects of a seizure during the sleep period or drug treatment on these.
- Review pathophysiological associations between Nocturnal Frontal Lobe Epilepsy (NFLE) and NREM arousal parasomnias;
- Learn how to evaluate for insomnia, sleepiness and OSA in patients with epilepsy.

Epilepsy and Sleep Have Complex Bidirectional Relationships



Overview Of Effects Of Sleep On Epilepsy
NREM Favors Expression of IEDs and SZs

Synchronous oscillations during NREM sleep (sleep spindles, K-complexes and NREM 3 slow waves) promote seizure (SZ) propagation, interictal epileptiform discharges (IEDs) and expression of seizure-related movements .

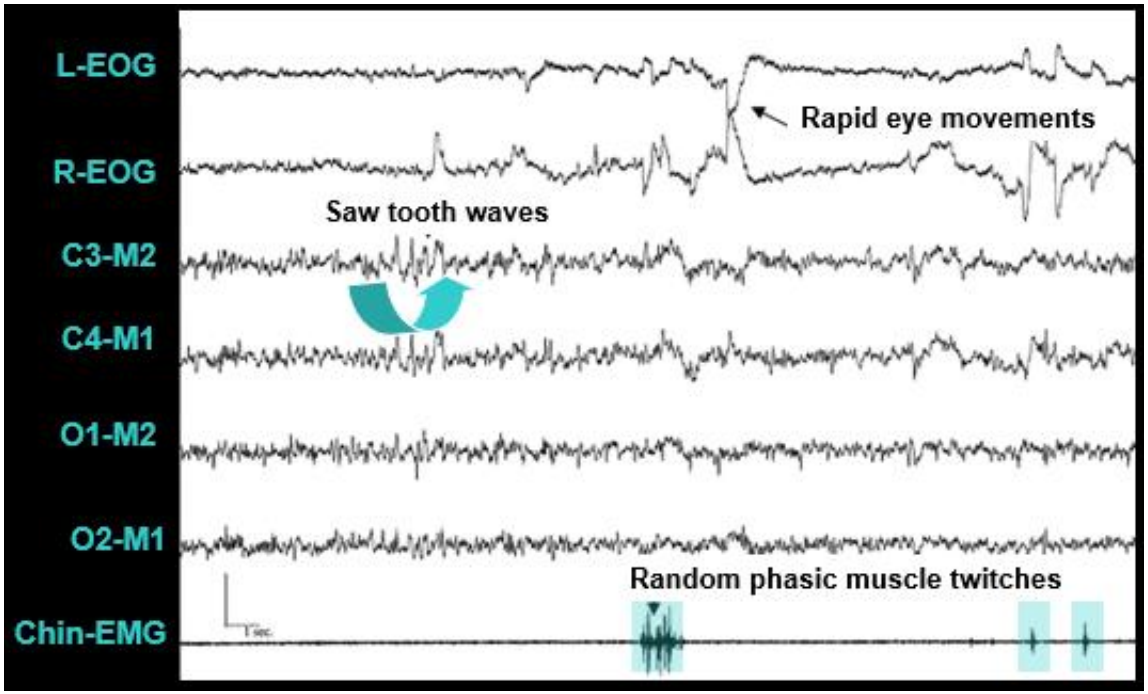


- NREM sleep = synchronized EEG and preserved antigravity muscle tone.

Overview Of Effects Of Sleep On Epilepsy

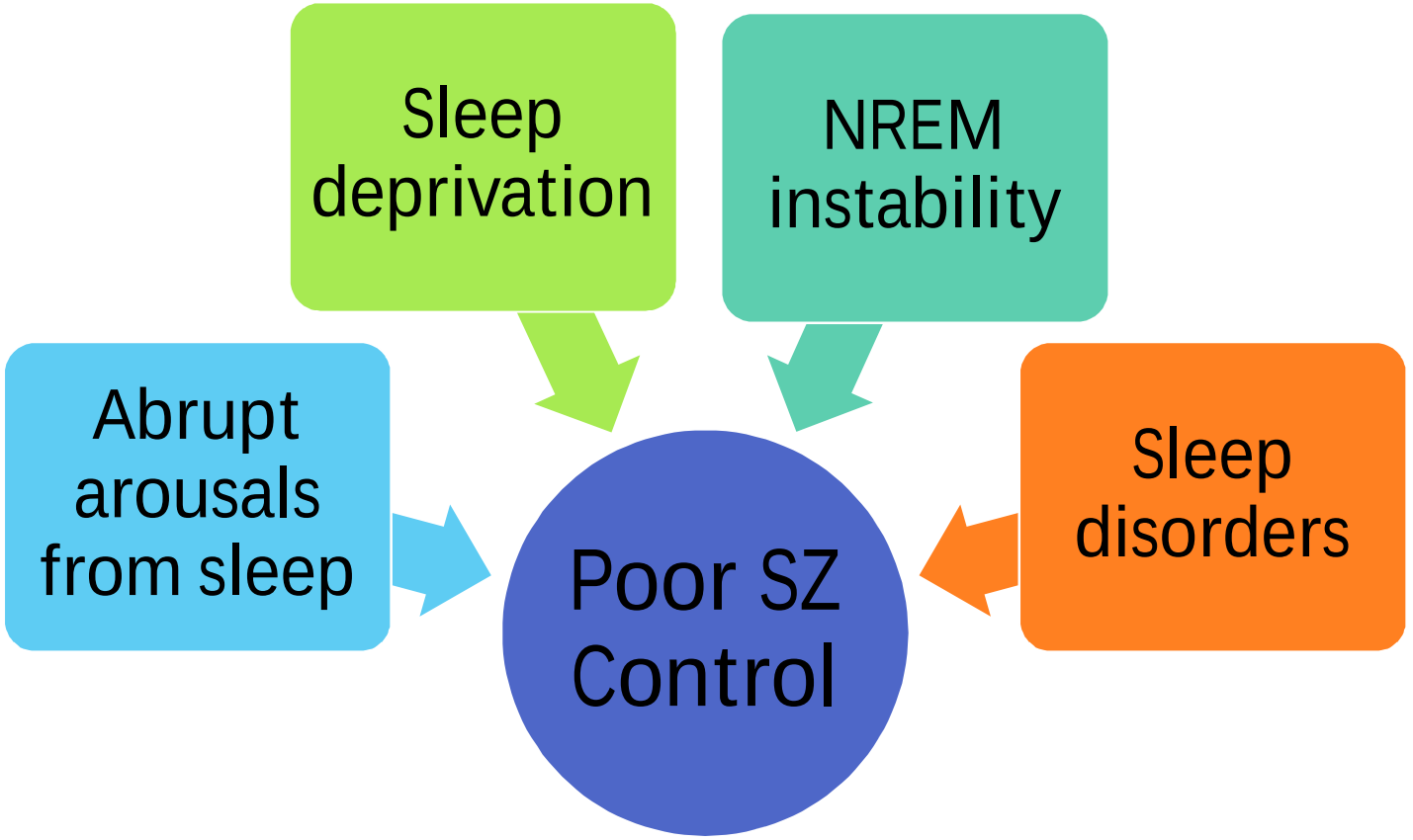
SZs and IEDs Inhibited During REM Sleep

- Desychronizing nature of EEG during REM sleep coupled with skeletal muscle atonia inhibits spread or generalization of IEDs or seizures.

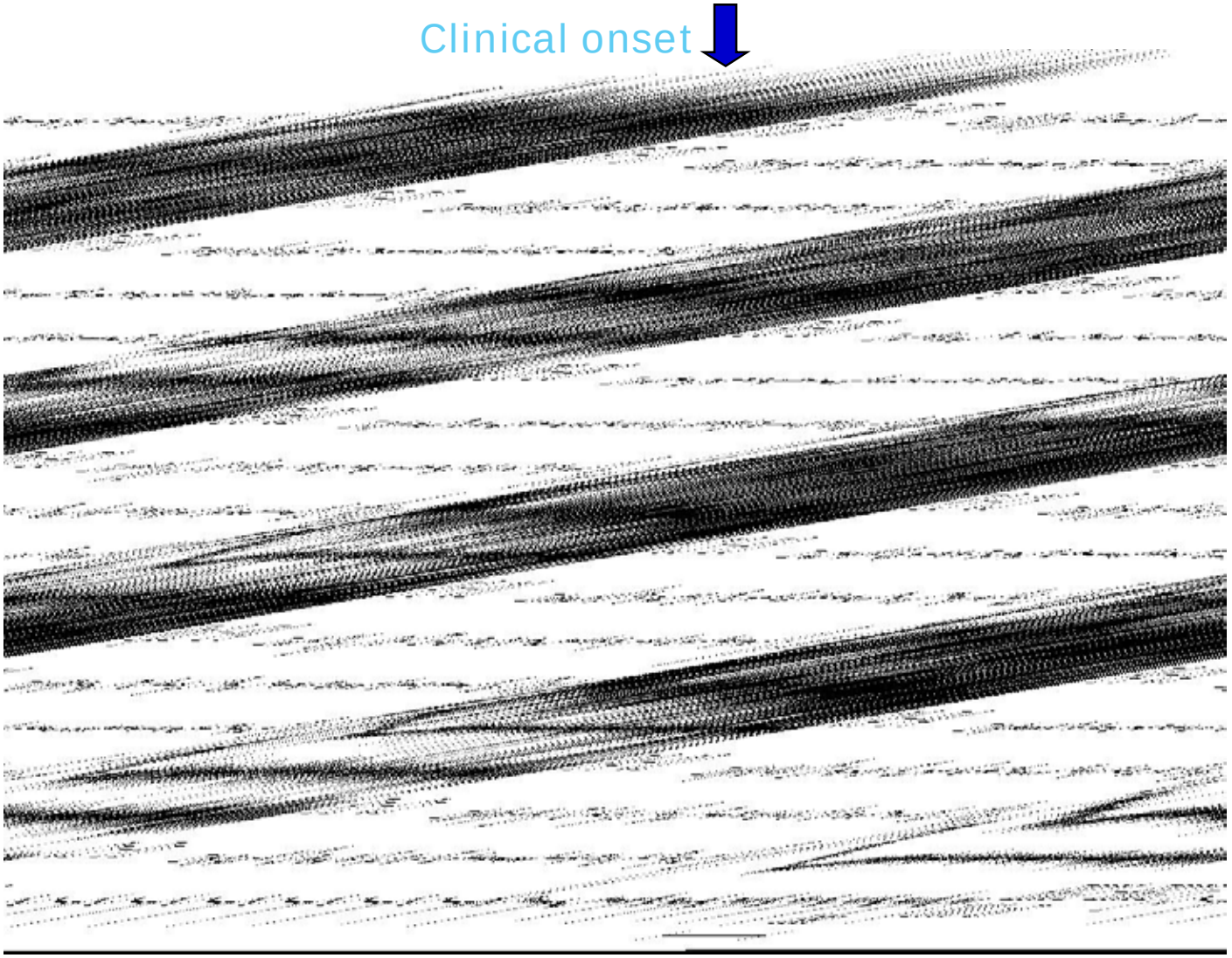


REM Sleep: desynchronized EEG and skeletal muscle atonia tends to inhibit expression of IEDs and SZs

Overview of Effects of Sleep Upon Epilepsy



Abrupt arousal from NREM sleep accompanies onset of a hypermotor nocturnal frontal lobe seizure.



Sleep/Wake State-dependent Epilepsies

- Awakening:
  - Generalized seizures upon awakening;
  - Juvenile myoclonic epilepsy (JME);
- NREM sleep:
  - Nocturnal Frontal Lobe Epilepsy (NFLE);
  - Benign focal epilepsy of childhood with centrotemporal spikes;
  - Panayiotopoulous syndrome (benign occipital autonomic epilepsy of childhood);
  - Lennox-Gastaut syndrome (tonic seizures)
  - Electrical status epilepticus during sleep and Landau-Kleffner syndrome.

Insomnia Most Common Primary Sleep Complaint in Adults with Epilepsy

Sleep and Epilepsy are Common but often Poor Bedfellows

- 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) and;
  - Obstructive sleep apnea (OSA).

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

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.

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).

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

Most Frequent Sleep Complaint in Adults with Epilepsy = Difficulty Staying Asleep (Sleep Maintenance Insomnia)

Prospective Case-control Study[1]

Sleep/wake complaint	Adults with epilepsy (n=100)	Healthy controls (n = 90)
Any complaint	30%*	10%*
Staying asleep	52%*	38%*
Falling asleep	34%	28%
Excessive sleepiness (EDS)	19%	14%
Restless legs (RLS)	18%	12%
Sleep apnea	9%	3%

Two Other Prospective Studies[2,3]

- 39% of 117 adults with focal epilepsy (n = 486) vs. 18% of controls complained of sleep complaints;[2]
- Insomnia reported by 25% of 124 consecutive adults visiting an epilepsy clinic and 17% complained of EDS.[3]

REFs: 1) Khatami et al. Seizure 2006;15(5):299-306; 2) de Weerd A Epilepsia 2004;45(11):1397-1; 3) Piperidou et al. 2008.

So, Does Insomnia (and Resultant) Sleep Deprivation Trigger Seizures?

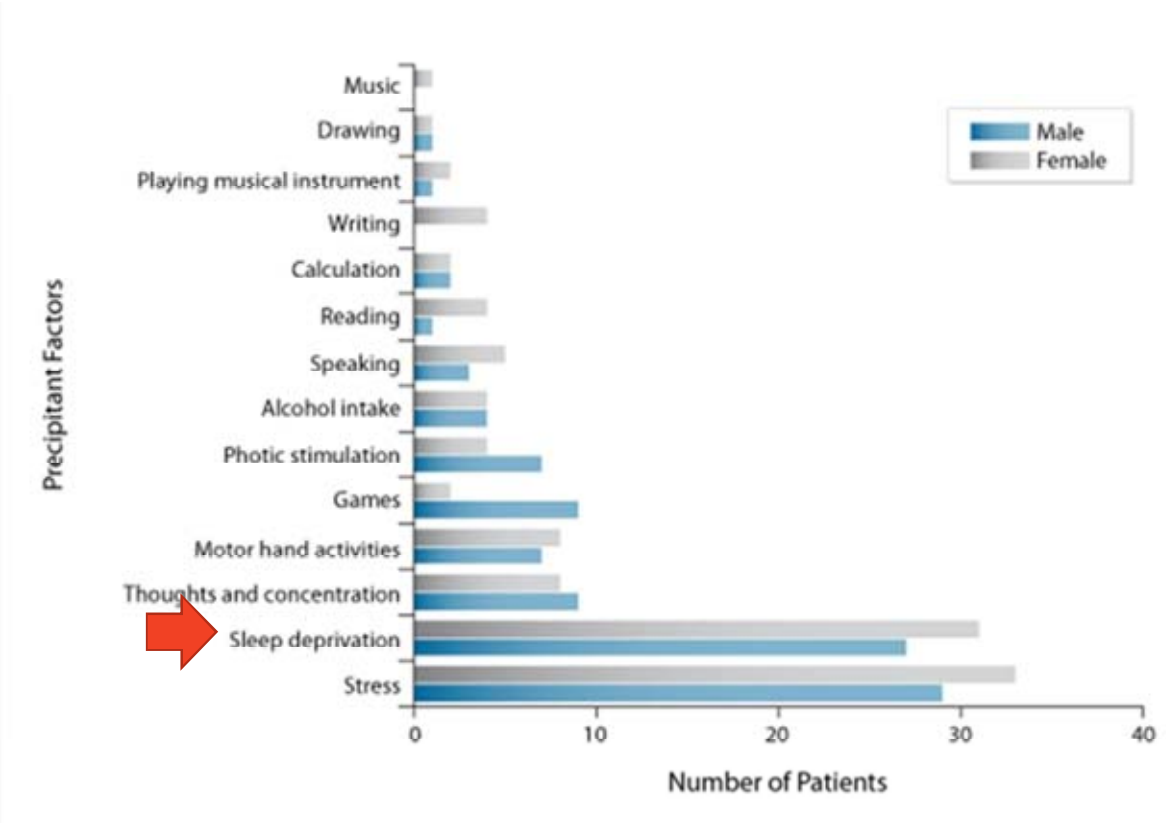
Sleep Deprivation Triggers Seizures in Only Some SZ Types & Epilepsy Syndromes

- Risk for sleep deprivation (SD) triggering SZs greatest for idiopathic generalized epilepsies, especially JME:[1]
  - Mean number and duration of IEDs during sleep and upon awakening increase in JME following SD;[2,3]
  - Seizures in JME are facilitated by SD and sudden arousal;[4]
  - SD ± acute drug withdrawal ± alcohol use cause for recurrence of seizures after a long period of remission in 105 patients with JME.[5]

REFs: 1) Serafini et al. 2013; 2) Marinig et al. 2000; 3) Sousa et al. 2005; 4) Genton et al. 2013; 5) Sokic et al. 2007.

Patients with Juvenile Myoclonic Epilepsy Most Likely to Report Sleep Deprivation Triggers Their Seizures

- 77% of 75 patients with JME reported sleep deprivation 2nd most likely trigger for their seizures (after stress);[1]
- Female JME patients more likely to report SD (and stress) as SZ triggers than males.



REFs: 1) de Sousa 2005; 2) Wandschneider 2012; 3) Crespel 2013; de Araujo 2013; 4) Genton 2013; 5) Zamarian 2013.

Why Don’t Patients with JME Listen?

- Subtle cognitive impairments in frontal lobe function and personality disorders in many with JME may in part explain their difficulties complying with advice:
  - Difficulty making advantageous decisions (poor gamblers):
  - More pronounced in those whose epilepsy is medically refractory.

- Advice to maintain regular sleep/wake schedules and sufficient nighttime sleep often go unheeded by patients with JME

Patients with JME More Likely to Be Night Owls than Those with TLE

- Recent prospective cross-sectional study compared sleep/wake complaints in 50 patients with well-controlled JME treated with valproate (VPA) with 50 healthy controls:[1]
  - 34% of JME patients reported EDS (Epworth $\geq$ 11) vs. 4% of controls;
  - 54% of JME patients reported insomnia vs. 24% of controls;
- Another study found 20 JME patients prefer late bed- and –wake times and feel awake later time of day compared with matched group of TLE patients.

REFs: 1) Krishnan P Epilepsy Beh 2012; 23(3):305-309; 2) Pung T Epilepsia 2006;47 Suppl 2:111-114.

- Epworth Sleepiness Scale (ESS) subjective rating of daytime sleepiness;
- Limited validity but often used to measure excessive daytime sleepiness (EDS) in patients.
- Abnormal ESS $\geq$ 11.

Epworth Sleepiness Scale (ESS)

Situation	Chance of dozing (0–3)			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place—for example, a theater or meeting	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch (when you've had no alcohol)	0	1	2	3
In a car, while stopped in traffic	0	1	2	3
Total Score				

0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing

Johns MW. *Sleep*. 1991;14:540.

Sleep Deprivation Probably Plays Far Weaker SZ Trigger Role Focal Epilepsies

Several SZ precipitants seem to involve relief from neurosteroidal modulation of $GABA_A$ receptors.[2]

- Sleep deprivation did NOT predict a SZ 12-24 h later:
  - Feeling emotional/tired/weary and/or difficulty with thoughts/concentrating é likelihood a SZ would occur within 12 h by odds ratios ranging from 2.0 to 3.4.
  - Improvements in mood reduced the risk for seizures 25%.

Seizure precipitants and seizure occurrence within 12 h.

Potential precipitant	Odds ratio (95% CI)	p-value
Hours of sleep 12 h prior to seizure	0.97 (0.86–1.11)	0.69
Hours of sleep 24 h prior to seizure	0.94 (0.84–1.04)	0.23
Menses	0.86 (0.4–1.7)	0.7

Premonitory features and seizure occurrence within 12 h.

Premonitory features (selected from 18)	Odds ratio (95% CI)	p-value
Blurred vision	**6.05 (3.18–11.49)**	**<0.001**
Light sensitivity	**3.38 (1.34–8.53)**	**0.01**
Dizziness	**3.66 (1.90–7.04)**	**<0.001**
Feeling emotional	**3.37 (1.99–5.70)**	**<0.001**
Concentration difficulty	**2.64 (1.59–4.39)**	**<0.001**
Hunger/food cravings	**2.56 (1.19–5.50)**	**0.02**
Noise sensitivity	**2.34 (1.10–4.97)**	**0.02**
Tired/weary	**2.01 (1.24–3.27)**	**0.005**
Thirst	**2.07 (1.08–3.95)**	**0.03**
Difficulty with thoughts	**2.18 (1.24–3.83)**	**0.007**
Hyperactive	1.50 (0.34–6.73)	**0.60**
Headache	2.10 (0.25–17.6)	**0.49**
Difficulty reading/writing	0.70 (0.09–5.49)	**0.73**
Number of significant premonitory features	**1.24 (1.13–1.35)**	**<0.001**

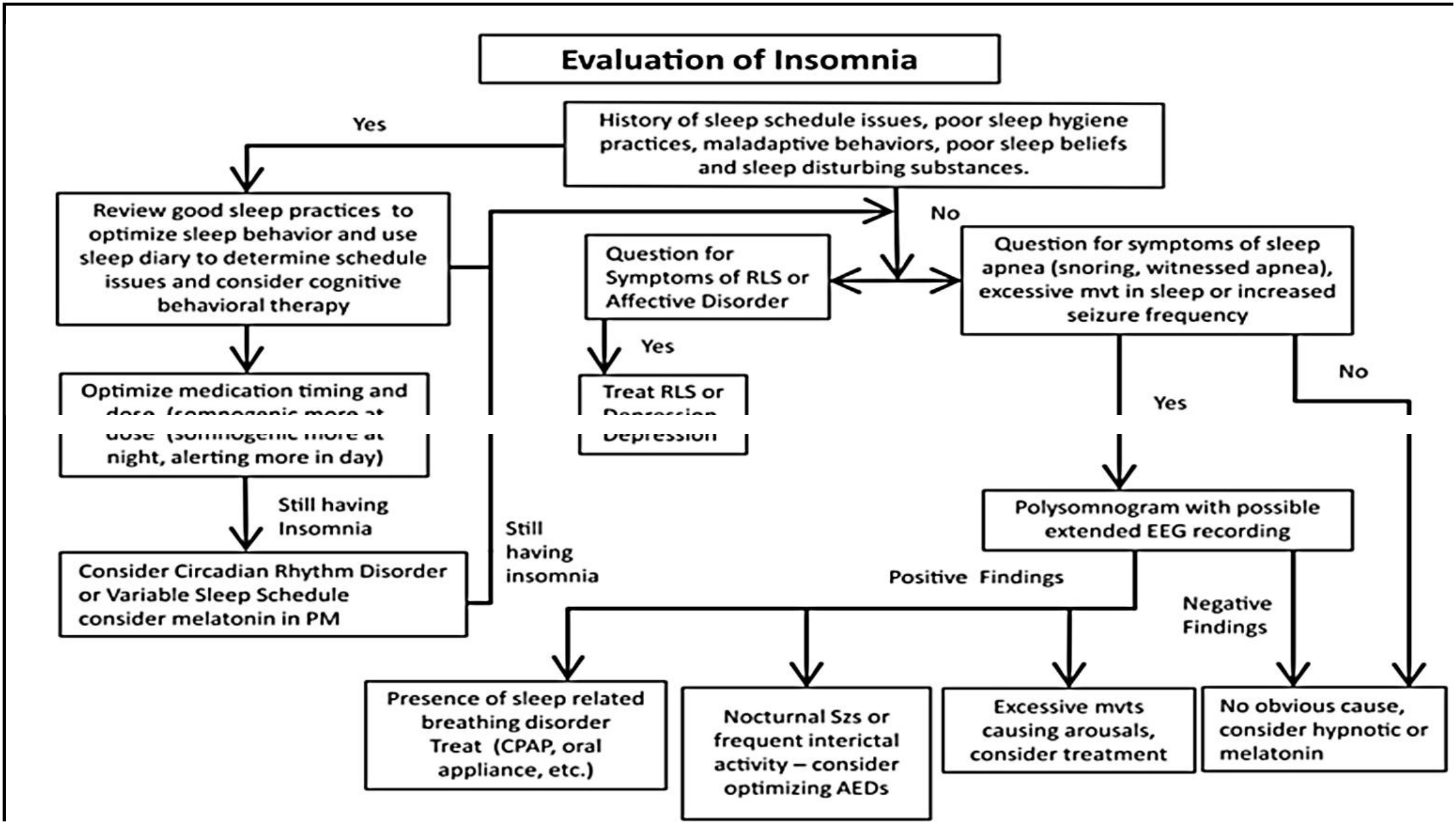
19 patients with focal epilepsy kept electronic diaries for 12-14 weeks tracking SZs and premonitory features:

REFs: 1) Haut SR et al. Epilepsy Behav 2012;23(4):415-421; 2) Huberfeld G C et al. Neuroscientist 2013 Jul 23.

Poor Sleep Hygiene Observed in Adults with Other Types of Epilepsy

- A large case-control study of 270 adults with epilepsy and controls compared sleep hygiene:
  - 23% of adults with epilepsy (AWE) smoked at bedtimes;
  - 29% AWE had irregular sleep/wake schedules or varying degrees of SD;
  - 17% AWE engaged in high concentration/upsetting activities at bedtime;
  - AWE much more likely to drink coffee before bedtime (50% vs. 30%) and nap after dinner (16% vs. 6%).
- Another study of 108 AWE found many did not practice healthy lifestyle behavior (including sleep hygiene) even if when compliant with their AED medication.

REFs: 1) Manni R Acta Neurol Scand 2000;101(5):301-4; 2) Kobau R Epilepsy Behav 2003;4(3):217-25.


Evaluation of Insomnia
History of sleep schedule issues, poor sleep hygiene practices, maladaptive behaviors, poor sleep beliefs and sleep disturbing substances.
Yes
No
Review good sleep practices to optimize sleep behavior and use sleep diary to determine schedule issues and consider cognitive behavioral therapy
Question for Symptoms of RLS or Affective Disorder
Question for symptoms of sleep apnea (snoring, witnessed apnea), excessive mvt in sleep or increased seizure frequency
Yes
Treat RLS or
Depression
Optimize medication timing and dose (somnogenic more at night, alerting more in day)
Yes
No
Still having Insomnia
Still having insomnia
Consider Circadian Rhythm Disorder or Variable Sleep Schedule consider melatonin in PM
Polysomnogram with possible extended EEG recording
Positive Findings
Negative Findings
Presence of sleep related breathing disorder Treat (CPAP, oral appliance, etc.)
Nocturnal Szs or frequent interictal activity – consider optimizing AEDs
Excessive mvts causing arousals, consider treatment
No obvious cause, consider hypnotic or melatonin

Excessive Sleepiness (EDS) is Second Most Common Sleep Complaint in Epilepsy

Excessive Daytime Sleepiness (EDS) = **Second Most Common Sleep Complaint**

- 48% of 99 unselected patients with epilepsy complained of EDS (Epworth Sleepiness Score of > 11):[1]
  - Anxiety (and to lesser extent neck circumference) correlated with EDS;
- 20% of 117 people with epilepsy complained of EDS vs. 7% of 30 healthy volunteers:[2]
  - Poor seizure control was the strongest independent risk factor for poor sleep quality (odds ratio [OR] = 2.4).

EDS in adults with epilepsy more likely to correlate with anxiety, depression, less often symptoms of OSA

REFs: 1) Chen NC Acta Neurol Taiwan 2011;20(4):249-56; 2) Giorelli AS Epilepsy Behav 2011;21(4):449-52.

Effect of AEDs on Sleep and Daytime Sleepiness Remains Uncertain

- Whether a particular AED causes insomnia and/or hypersomnia continues to be debated;
  - Studies abound but most are limited by small study sizes, lack of healthy controls, varying study designs and confounding factors (Derry and Duncan 2013).
  - Phenytoin may disrupt sleep causing increased arousals and reducing REM sleep time, although these effects may abate with chronic use.
  - CBZ appears to consolidate sleep, ê awakenings & arousals, é NREM 3 & REM sleep time.
  - Newer AEDs in general fewer long-term negative effects on sleep.

Derry and Duncan, 2013

Effects of AEDs on Sleep Often Transient

Drug	Sleep Complaint	Sleep Efficiency	Total Sleep Time	Sleep Latency	Arousals	Stage 1	Stage 2	Stages 3 and 4	REM Sleep
Phenobarbital	Sleepiness	↓	No change	↓	↓	↑	↑	No change	↓
Phenytoin	Sleepiness	↓	No Change	↓	↓	↑	↑	↓	No change
Carbamazepine	Sleepiness	↑	No change	↓	↓	No change	No change	↑	?
Valproate	Sleepiness	No change	No change	No change	↑	↓	No change	↑	No change
Ethosuximide	Insomnia	↓	?	?	↑	↑	No change	↓	↑
Felbamate	Insomnia	↓			↑				
Gabapentin	Sleepiness	↑	↑		↓	↓		↑	↑
Lamotrigine	Insomnia	No change	No change	No change	No change	No change	No change	↓	↑
Topriamate	Sleepiness	?	?	?	?	?	?	?	?
Vigabatrin	Sleepiness	?	No change	No change	?	?	?	?	?
Tiagabine	Varies	No change	No change	No change	–	↓	No change	↑	No change?
Levitiracetam	Sleepiness	↑	↑	No change	↓	No change	↑	↑	No change
Zonisamide	Insomnia	?	?	?	?	?	?	?	?
Pregabalin	Sleepiness	↑	↑	↓	↓	–	–	↑	–
Oxcarbazepine	Sleepiness	?	?	?	?	?	?	?	?
Lacosamide	Varies	?	?	?	?	?	?	?	?
Rufinimide	Sleepiness	?	?	?	?	?	?	?	?
Clobazam	Sleepiness	?	?	?	?	?	?	?	?
Retigabine	Varies	?	?	?	?	?	?	?	?

Table from Vaughn B et al. Neurol Clin 30 (2012) 1249–1274

Pregabalin and Gabapentin May Improve Sleep Quality

- Gabapentin and pregabalin are two AEDs which have been shown to improve quality of sleep in patients with pain (especially fibromyalgia, post-herpetic neuralagia, and diabetic neuropathy);
- Gabapentin before bed reduced nocturnal awakenings in late premenopausal women (Guttuso 2012) and improved sleep in children with refractory insomnia;[6]
- A recently published double-blind, placebo-controlled crossover study showed pregabalin increased NREM 3, decreased NREM 1 sleep, and improved attention in nine adults with well-controlled epilepsy and sleep maintenance insomnia.

REFs: 1) Manas, Ciria et al. 2011; 2) Misra, Kalita et al. 2011; 3) Biyik, Solak et al. 2012; 4) Roth, Lankford et al. 2012; 5) Holsboer-Trachsler and Prieto 2013; 6) Robinson and Malow 2012; 7) Bazil, Dave et al. 2012.

Impact of Nocturnal Awakenings on EDS Complaint in Patients with NFLE

- A case-control study compared 33 patients with NFLE (mean age 31 years, 51% M) with 27 healthy controls matched for age, sex and education;
- EDS a complaint in 56% of NFLE patients who reported spontaneous mid-sleep awakenings (vs. 18% who did not).

Epilepsia, 47(Suppl. 5):73–77, 2006
Blackwell Publishing, Inc.

Excessive Daytime Sleepiness and Subjective Sleep Quality in Patients with Nocturnal Frontal Lobe Epilepsy: A Case-Control Study

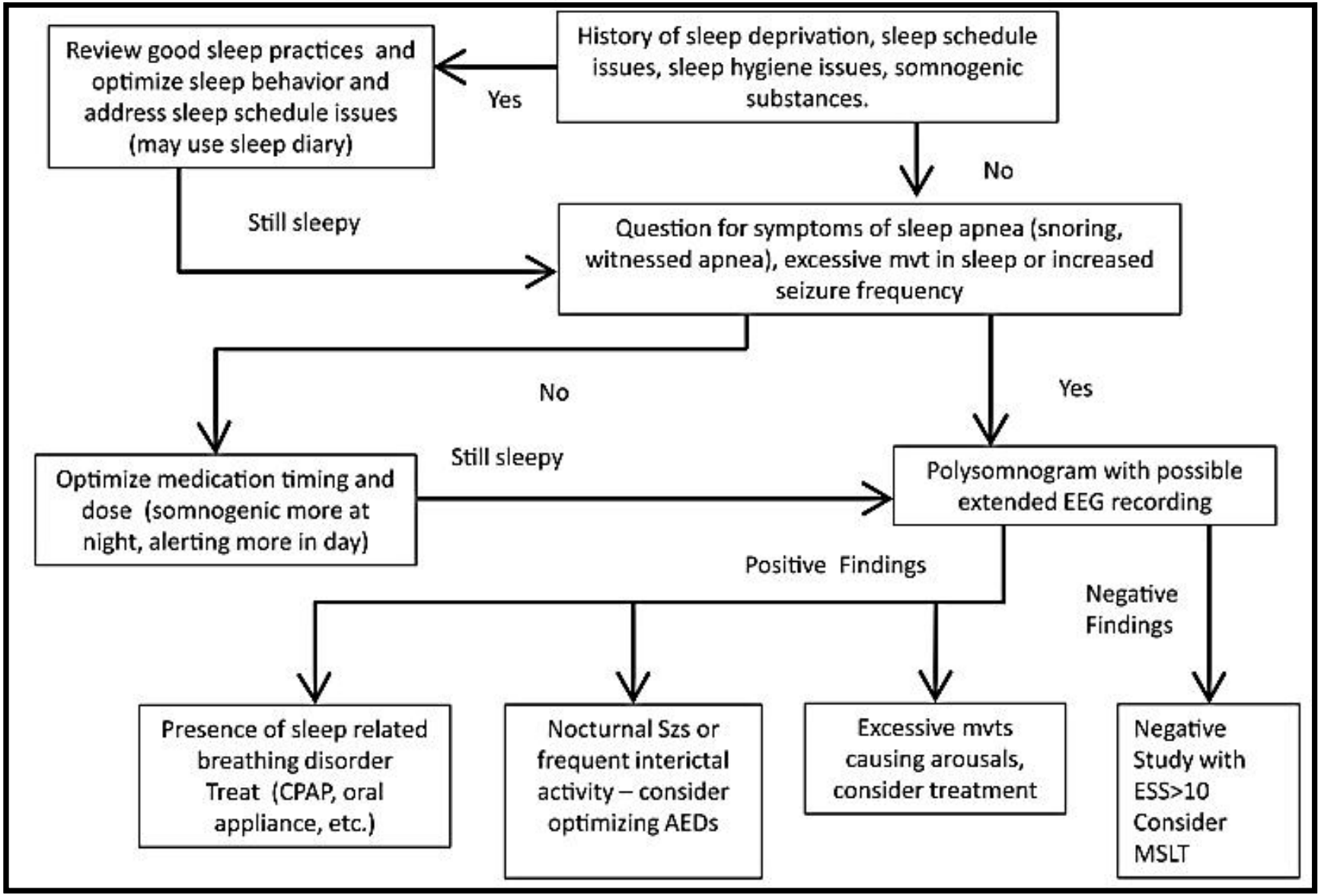
Luca Vignatelli, Francesca Bisulli, Ilaria Naldi, Simona Ferioli, Francesca Pittau, Federica Provini, Giuseppe Plazzi, Roberto Vetrugno, Pasquale Montagna, and Paolo Tinuper

Dipartimento di Scienze Neurologiche, Università di Bologna, Bologna, Italy

Sleep/wake complaint	NFLE patients (n = 33)	Healthy controls
Tiredness after awakening	36%	11%
Spontaneous mid-sleep awakenings	50%	22%
Epworth Sleepiness Score (ESS) (abnormal $\geq$ 10/24)	5.6 $\pm$ 3.2	5.7 $\pm$ 3.0

REF: Vignatelli L. Epilepsia 2006;47 Suppl 5:73-77.

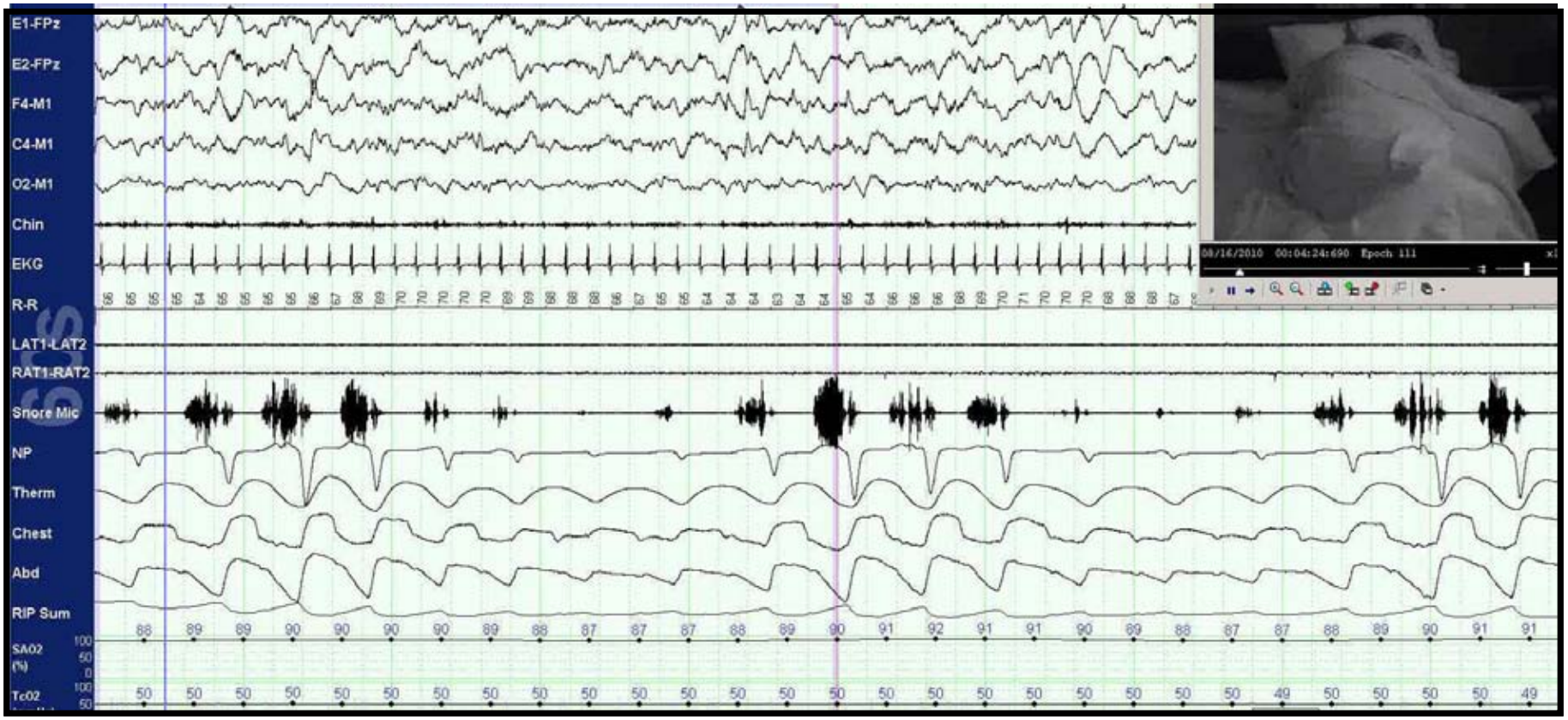
Evaluation of Excessive Daytime Sleepiness



Flow Chart from Vaughn B et al. Neurol Clin 30 (2012) 1249–74

Obstructive Sleep Apnea (OSA) is More Common in People with Epilepsy

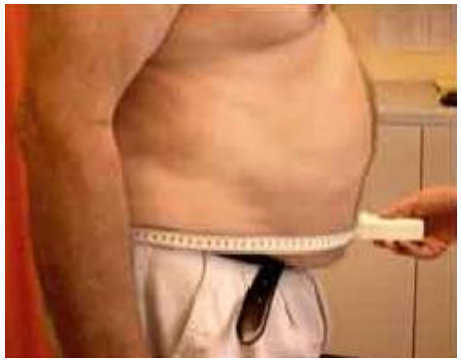
Obstructive Sleep Apnea (OSA) in Action

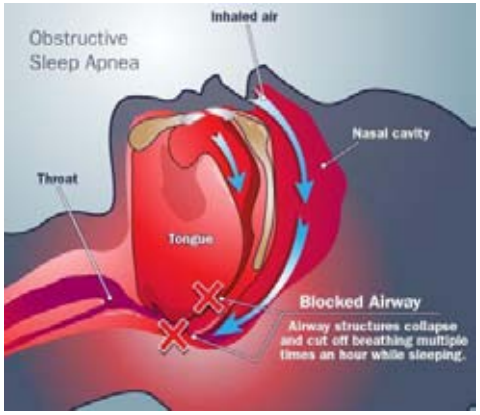


- Probably an AHI $\geq$ 15 lower cut-point for increasing risks of OSA and consistent with moderately severe OSA in adults, $\geq$30/h severe and increases risks for stroke and sudden death in sleep.

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 highlighted in orange found to be risk factors for OSA in adults with epilepsy

Prospective Study Identifying Predictors for OSA in Adults with Epilepsy

- Prospectively screened using structured interviews 283 adults with epilepsy (mean age 33; 48% men):
  - Recorded overnight home PSG in those in who OSA suspected;
  - Defined OSA as apnea-hypopnea index > 5/h;
  - 10% had OSA (15% male, 4% female);
  - OSA often mild (22% moderate, severe 11%).

Variable	OSA (AHI ≥ 5/h)	No OSA
Older (mean age)	46 years	33 years
Sleepier	23%	9%
Heavier (mean BMI)	29 kg/m^2	23 kg/m^2
First seizure when older (mean age)	32 years	19 years

Manni et al. *Epilepsia* 2003;44(6):836-840.

Other Small Case Series Identify Predictors for OSA in Adults with Epilepsy

- 11 patients with late-onset or worsening seizures had significantly higher AHI and EDS compared with 10 who were SZ-free or had improving seizure control;[1]
- 29 epilepsy patients (mean age 56 y, 25 men) with OSA[2]:
  - Onset of OSA symptoms in 72% (21/29) coincided with first episode of status epilepticus or a clear é seizure frequency;[2]
  - Median AHI 33; 52% had Epworth >10.

REFs: 1) Chihorek AM Neurology 2007;69(19)1823-7; 2) Hollinger 2006;

Predictors for OSA in Adults with Epilepsy

- Systematic evaluation of predictors for OSA in 130 consecutive adults referred to Cleveland Clinic;
  - OSA defined as a an apnea-hypopnea index ≥ 10/hour of sleep;
  - 30% AHI > 10/h; 16% AHI > 15/h).
- Predictors for OSA (using linear regression of log-transformed AHI against other variables):
  - Male gender;
  - Age >50 years;
  - Higher BMI;
  - History hypertension or dental problems.

- A history of epilepsy surgery appeared to be protective for OSA; only 1 of 17 operated patients had an AHI > 10.
- Self-reported EDS and Epworth Sleepiness Scores (ESS) were not helpful in predicting OSA, possibly related to the ceiling effect of general sleepiness among people with epilepsy from diverse causes.

REF: Foldvary-Schaefer N *Epilepsy Behav* 2012;25:363-7

Predictors of OSA in Adults with Epilepsy

- Li et al. (2012) compared likelihood of finding OSA in patients with medically refractory vs. well-controlled epilepsy, and impact of continuous positive airway pressure (CPAP) to treat it.
  - OSA 15% of their epilepsy population vs. 4.4% general population;
  - Predictors of OSA:
    - Among well-controlled: older (OR 1.0), male (OR 5), difficulty staying asleep (OR 5.7), daytime sleepiness (OR 7.5); lower SZ frequency, lower risk (OR 0.2)
    - Among medically refractory: diabetes (OR 9.4) and snoring (OR 12.6).

REF: Li P. et al. *Seizure* 2012;21(9):717-21.

Compliant CPAP Use Decreases SZ Frequency in Those with Medically Refractory Epilepsy + OSA

- 41 adults with epilepsy with OSA:
  - SZ frequency ê 1.8 to 1 SZ/month 68% CPAP-compliant;
  - No change SZ frequency non-compliant group (2.1 to 1.8/mont
  - 57% CPAP-compliant were SZ-free vs. 23% of non-CPAP complia 1.54]
- 35 adults with epilepsy + OSA [CPAP-Sham CPAP Pilot St
  - SZ frequency ê > 50% in 28% treated with CPAP compared wit CPAP;
- 30 adults with epilepsy + OSA:
  - SZ frequency ê from mean 1.3 to 0.4 / month in medically refractory who used it faithfully (only 50% did so), 3 became SZ-free.
  - No greater benefit for CPAP on SZ frequency in well-controlled before CPAP tx.

But only 3 small case-series!

REFs: 1) Vendrame M Epilepsia 2011; 2) Malow B 2008; 3) Li et al. 2012

Screen for OSA in Patients with Epilepsy (Stroke, TIA, HA, NMD, etc.)

- Ask about snoring, witnessed pauses, daytime sleepiness, awakening unrefreshed, and fatigue/tiredness;
- Consider OSA in every adult with epilepsy (and also stroke and TIA) especially those:
  - Medically refractory or late onset epilepsy, stroke and/or TIAs;
  - New or young onset or diastolic or medically refractory HTN;
  - Frequent office visits;
  - Depression + HTN + middle aged male (18-fold increase risk of untreated OSA)
  - Body habitus at risk for OSA;
- Confirm the history with bed partner and witnesses.
- If OSA possible, refer patient to sleep specialist.

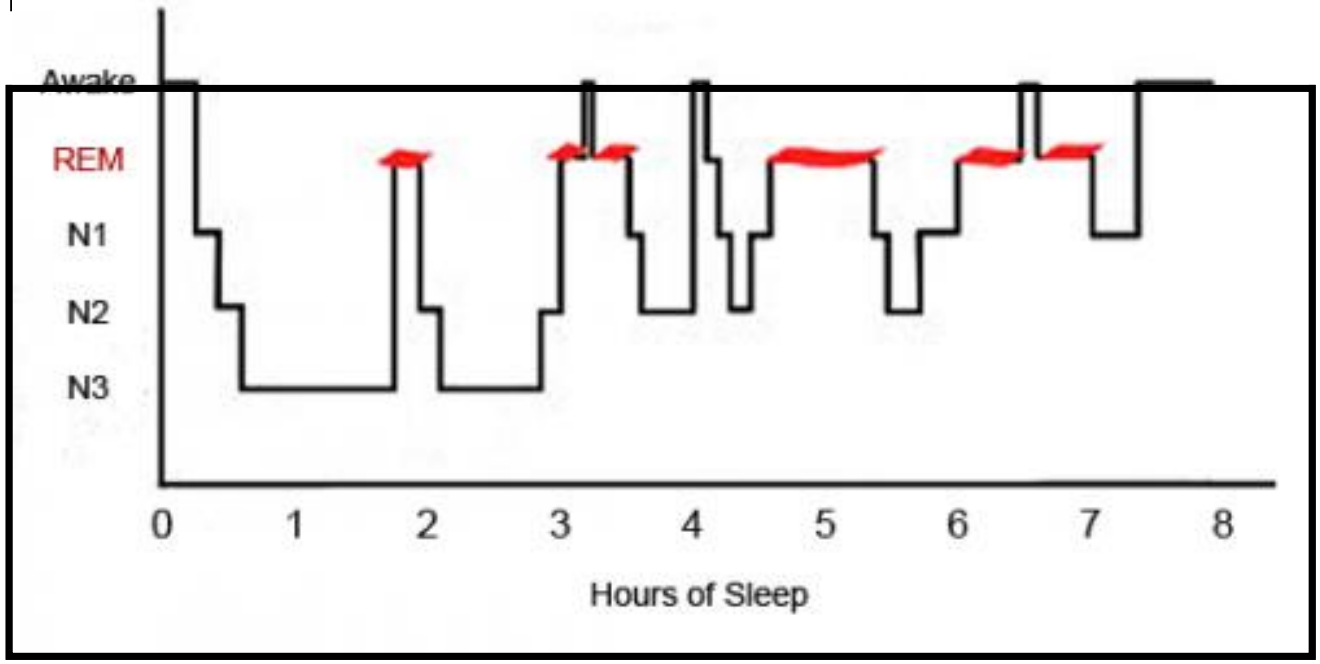
Is Sleep Architecture Disrupted in Epilepsy?

Abnormal Sleep Architecture in Patients with Epilepsy Depends on Seizure Type

- Alterations in sleep architecture on overnight polysomnogram (PSG) in adults with epilepsy compared with healthy controls have been long reported;
- Quantitative and qualitative disruption of sleep depends upon the origin of the seizure focus and seizure type;
- Abnormalities in sleep architecture more likely in patients with TLE on seizure-free nights than patients with idiopathic/genetic generalized epilepsy (IGE).

Sleep Architecture Abnormalities Reported in Patients with Some Epilepsies on Seizure-free Nights

- Reduced REM sleep time;
- Prolonged REM latency;
- Increased wake after sleep onset (WASO) è
  - Reduced total total sleep time and sleep efficiency, and/or
  - Increased number of arousals, awakenings and stage shifts.



- Sleep “macroarchitecture” in some patients is normal, or normalizes after treatment;
- Abnormalities in sleep architecture in more likely in TLE compared to idiopathic generalized epilepsies (IGE).

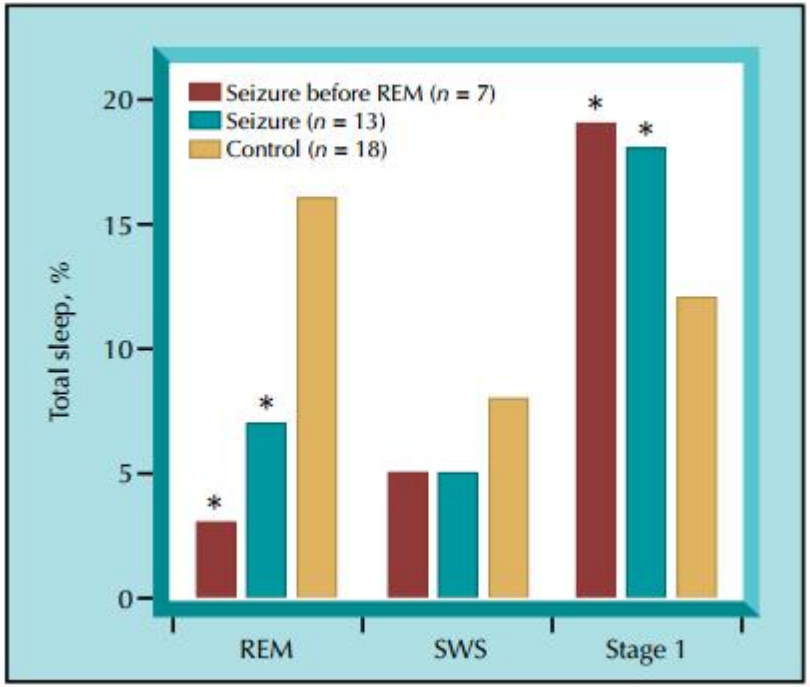
Temporal Lobe Complex Partial Seizure with or without Generalization in Sleep Disrupts Sleep Architecture Rest of Night

ORIGINAL CONTRIBUTION

Reduction of Rapid Eye Movement Sleep by Diurnal and Nocturnal Seizures in Temporal Lobe Epilepsy

Carl W. Bazil, MD, PhD; Luiz H. M. Castro, MD; Thaddeus S. Walczak, MD

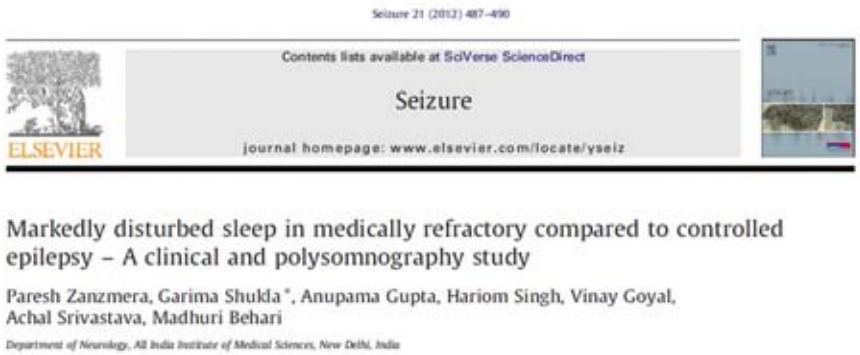
- If a CPS seizure with or without generalization occurred during a night of sleep:
  - é NREM 1 and ê REM sleep;
  - More pronounced when seizure occurred before the first REM period;
  - é drowsiness on MWT;
- Milder decrease in percent REM sleep time if seizure occur the previous day.



REF: Bazil C. Arch Neurol 2000;57:363-8

Sleep Architecture More Disturbed in Medically Refractory

- A recent prospective case-control study from Indian compared sleep architecture in 40 patients (median age 18) with epilepsy, 20 well-controlled; 20 medically refractory epilepsy.
- Self-reported sleep parameters medically refractory vs. well-controlled characterized their sleep at home:
  - Longer sleep duration (9 h vs. 8 hours);
  - Daytime napping (2 h vs. 0 h);
  - Total 24-h sleep time (10.5 vs. 9 h);
  - EDS (45% vs. 10%);
  - Epworth scores did not identify (ESS > 10, 30% vs. 10%)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Markedly disturbed sleep in medically refractory compared to controlled epilepsy – A clinical and polysomnography study

Paresh Zanzmera, Garima Shukla *, Anupama Gupta, Hariom Singh, Vinay Goyal, Achal Srivastava, Madhuri Behari

Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Sleep parameter on overnight PSG	Medically refractory (n = 20)	Well-controlled epilepsy (n = 20)
Total sleep time on PSG	ê 340 min	450 min
Sleep efficiency	ê 81%	96%
Wake after sleep onset (WASO)	é 20%	4%
Arousal Index	é 10/h	5/h
OSA (AHI ≥ 5)	20% (all mild)	0%

No seizures occurred during overnight PSG studies.

Zanzmera PG et al. Seizure 2012;21(7):487-90.

Sleep Macro- and Microarchitecture in NFLE

- Parrino (2012) analyzed baseline PSG recording in 40 randomly selected NFLE patients (mean age 31 ± 10 y, 50% M) and 24 age- and gender-matched healthy controls;
- Compared to controls, NFLE patients had:
  - é WASO, NREM 3 duration, REM latency;
  - ê REM sleep duration; and
- Compared to normal controls, patients with NFLE had é CAP rate (72% vs. 32%), indicative of é NREM instability.

REF: Parrino L et al. Epilepsia; 2012:53(7):1178-84.

Epilepsia, 53(7):1178–1184, 2012
doi: 10.1111/j.1528-1167.2012.03502.x

FULL-LENGTH ORIGINAL RESEARCH

Distinctive polysomnographic traits in nocturnal frontal lobe epilepsy

*Liborio Parrino, *Fernando De Paolis, *Giulia Milioli, †Gioia Gioi, *Andrea Grassi, *Silvia Riccardi, *Elena Colizzi, and *Mario Giovanni Terzano

*Sleep Disorder Center, Department of Neuroscienze, Azienda Ospedaliero-Universitaria, Parma, Italy; and †Sleep Disorder Center, Policlinico Universitario Monserrato, Cagliari, Italy

Purpose: To describe the polysomnographic features and distribution of epileptic motor events, in relation to conventional sleep measures and cyclic alternating pattern (CAP) parameters, in 40 untreated patients with nocturnal frontal lobe epilepsy (NFLE).

Methods: We analyzed the basal polysomnographic recordings of 40 patients (20 male and 20 female; mean age: 31 ± 10 years) with a diagnosis of nocturnal frontal lobe epilepsy. Conventional sleep measures and CAP parameters were assessed. Polysomnographic recordings were subdivided in sleep cycles. The distribution of the epileptic motor events (including minor motor events, paroxysmal arousals, tonic-dystonic, or hyperkinetic seizures and epileptic nocturnal wandering) was analyzed throughout: total sleep time, non–rapid eye movement (NREM) and REM sleep, light sleep (S1 + S2), slow wave sleep (SWS), each sleep cycle, CAP or non-CAP sleep, phase A and phase B of CAP. Only clear epileptic motor events supported by video–polysomnographic evidence were taken into consideration. Polysomnographic findings of patients with NFLE were compared with those of 24 age- and gender-balanced healthy subjects without sleep complaints.

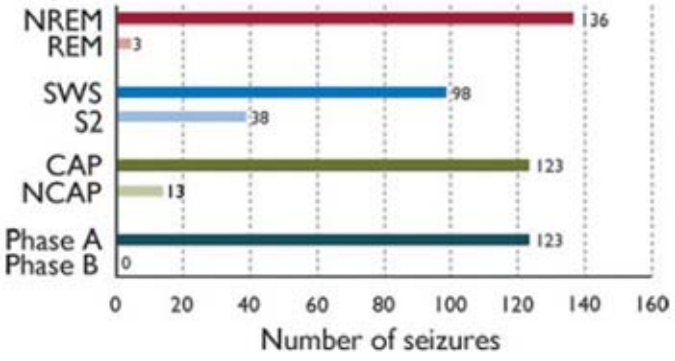
Key Findings: Compared to controls, patients with NFLE showed a significant increase in wake after sleep onset, SWS duration, and REM latency, whereas REM sleep duration was significantly lower in NFLE patients. The patients with NFLE showed a significant increase of CAP time, CAP rate (72% vs. 32% in control group), CAP cycles, and mean duration of a CAP sequence. These findings were associated with a significant enhancement of all subtypes of the A phases of CAP (mainly subtype A1). A total of 139 epileptic motor events supported by video-polysomnographic evidence were counted: 98% of all seizures occurred in NREM sleep and 72% of NREM seizures emerged from SWS, the latter being particularly collected in the first sleep cycles and decreasing in frequency together with the progressive decline of deep sleep. Ninety percent of total NREM seizures occurred during a CAP sequence, and CAP-related seizures occurred in association with a phase A.

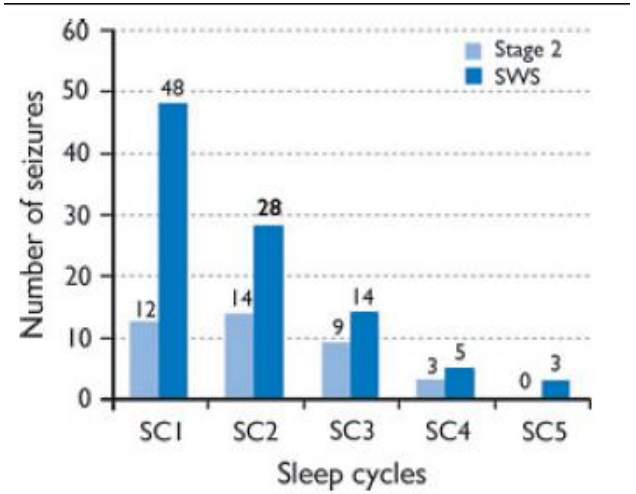
Significance: Significant polysomnographic alterations seem to emerge in patients with NFLE (increased REM latency, epileptic fragmentation of SWS, and increase of CAP rate). The analysis of seizure distribution showed that most epileptic events occurred in SWS, with predominance in the first sleep cycle and decreasing in frequency together with the homeostatic decline of SWS across the night. Within the NREM sleep, CAP is a manifestation of unstable sleep and represents a powerful predisposing condition for the occurrence of nocturnal motor seizures, which arise in concomitance with a phase A.

KEY WORDS: Polysomnography, Nocturnal frontal lobe epilepsy (NFLE), Cyclic alternating pattern (CAP), Seizures.

Sleep Microarchitecture in NFLE

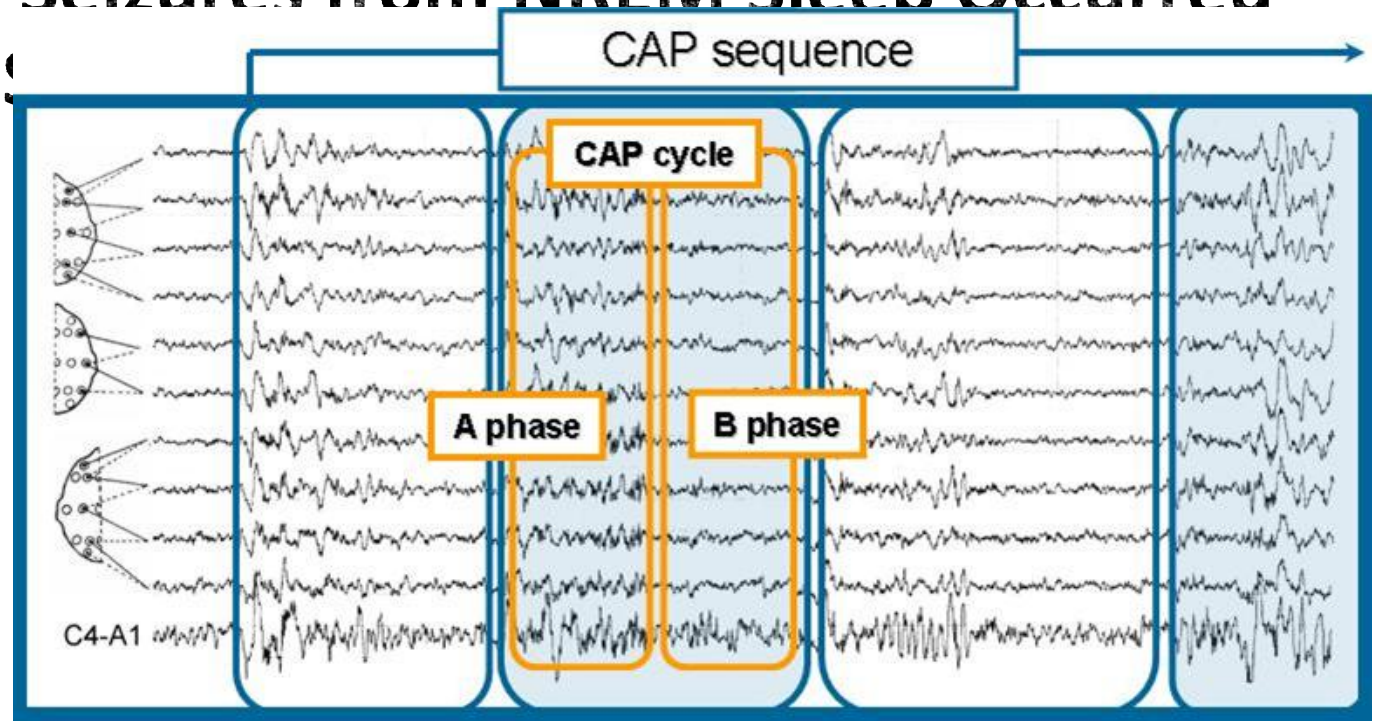
- Most had nightly seizures:
- 98% of seizures occurred during NREM sleep; 72% from NREM 3 [other studies show NREM 2];
- Most NFLE seizures occurred in first two sleep cycles when EEG synchronization greatest.





90% of NFLE Seizures from NREM Sleep Occurred During a CAP S

- Cyclic alternating pattern (CAP) is considered a marker of sleep instability and correlates with subjective sleep quality;
- Normal CAP rates:
  - 43% teenagers;
  - 32% young adults;
  - 55% older adults;
- Elevated CAP rates are seen in patients with a variety of different sleep disorders:
  - Epilepsy, OSA, PLMS, sleep bruxism, NREM arousal disorders.



Can identify 3 neurophysiological states in NREM sleep: phase A, phase B, and non-CAP. During CAP, sleep process swings from periods of activation (phase A) to periods of deactivation (phase B), later characterized by a paucity of phasic events. Non-CAP =

90% of seizures occur during

Does Sleep Architecture Improve if Seizures are Treated and Controlled?

- Zanzmera (2013) found improvements occurred in total sleep and REM sleep time among 11 patients with TLE who became seizure-free following epilepsy surgery.[1]
- De Paolis (2013) repeated PSGs in 12 patients with NFLE after treatment (CBZ most, 2 TPM, 1 LEV)[2]
  - é sleep efficiency (+10%), é NREM 3 duration (+20 min);
  - ê REM sleep latency (-56 min); ê WASO (-35 min);
  - No significant increase in REM sleep duration and percentage;
  - Compared to controls, REM sleep latency (-23 min) and percentage (-4%) remained significantly lower while NREM 3 duration (+30 min) and percentage (+8%) were higher but CAP rate remained elevated (+26%).

REFs: 1) Zanzmera PG et al. Seizure 2012;21(7):487-90; 2) De Paolis et al. Sleep Medicine 2013;14:597-604

Why are Arousal Parasomnias and Sleep Bruxism More Common in Patients with NFLE?

Increased Lifetime Risk for Parasomnias in NFLE Patients and Relatives

- Parasomnias are not more common in adults with a wide variety of different epilepsies and seizure types compared to healthy age-matched controls;[1]
- Bisulli et al. (2010) reported 5- to 6-fold higher lifetime risk for NREM arousal parasomnias (sleepwalking, sleep terrors, confusional arousals) and sleep bruxism in patients and families with NFLE:[2]
- Initially attributed to misdiagnosed NFLE seizures, but other pathophysiological mechanisms may better explain these associations.

REFs: 1) Khatami et al. Seizure 2006;15(5)299-306; 2) Bisulli et al. Epilepsia 2010,

Hypotheses for Similarity of NFLE and Arousal Parasomnia Behaviors

State dissociations and local sleep

- When transition between 2 sleep states more gradual or rapidly oscillates, dissociated states can be seen with state markers from one state intruding into another.
- Only parts of our brain asleep during NREM 3 sleep (local sleep).

Central pattern generators (CPGs)

- CPGs = genetically determined neural circuits give rise to species-specific stereotyped patterns of primitive motor activity essential for survival (suck/swallow/lip-smacking, locomotion, violent gestures, defensive postures);
- Complex automatic behaviors of DoA and NFLE resemble each because arousal triggers same neuronal networks (CPGs).

Arousal instability and pathologic cholinergic arousal systems

- Arousal instability has been linked to variety of sleep-related motor phenomena.

Probably All Three Hypotheses (and More) Contribute to NFLE and DoA Events

- Intracranial EEG (ic-EEG) recordings in patients with MR epilepsy have demonstrated that only parts of the brain sleep (so-called local sleep);
  - Intracerebral recording during a confusional arousal demonstrated arousal in primary motor and cingulate cortices with increased delta in frontoparietal association cortices preceded the onset and persisted during the event;
- An arousal (spontaneous or triggered by an epileptic burst, noise, apnea, or leg movement) triggers these CPGs:
  - Sudden noise coupled with 25-hour sleep deprivation has been used to trigger sleepwalking events in the sleep laboratory.
  - Autonomic arousal (with increased cardiac SNS activity) precedes behavioral arousal in NFLE and DoA;
- Hypothesis:
  - Epileptic discharges trigger micro-aroual fluctuations à increased NREM sleep instability à incorporated into oscillatory framework and reinforced à stronger autonomic activation à motor manifestations appear.

Future Directions:
Chronobiology and Chronopharmacology Used to Treat Epilepsy

JME More Affected by Circadian Timing

- Myoclonic jerks and photosensitivity are more likely to occur in the early morning, and enhanced by sleep deprivation;[1-2]
- IED discharge rates were highest between one hour prior to the final awakening and the first 30 minutes after awakening;[3]
- Cortical excitability measured using Transcranial Magnetic Stimulation (TMS) higher in the morning in IGE, especially those with JME.[4-7]

REFs: 1) 1) Kasteleijn-Nolst Trenite DG, *Epilepsy Behav 2013;*28 Suppl 1, S25-29; 2) Lodderkemper T *J Clin Neurophysiol* 28(2), 146-153 (2011). 140; 3) Danuka AK *Seizure* 10(5), 374-378 (2001); 4) Manganotti P *J Neurol Neurosurg Psychiatry* 77(1), 56-60 (2006); 5) Badawy RA, *Neurology* 73(3), 218-222 (2009); 6) Del Felice A. *Epilepsy Res*, (2011) 144; 7) Puri V. *Seizure*, (2013).

Knowing Timing of the Seizures Helps with Diagnosis and Timing of Antiepileptic Medications

Seizure type	Midnight	3 am	6 am	9 am	Noon	3 pm	6 pm	9 pm	Midnight
Generalized			Generalized seizures: 6 am to Noon						
Temporal	Temporal seizures: 9 pm to 9 am							Temporal seizures: 9 pm to 9 am	
Frontal	Frontal seizures Midnight to 6 am								
Parietal			Parietal 6-9 am						
Occipital				Occipital 9 am-noon		Occipital 3-6 pm			

Specific circadian patterns of seizures (n = 225 children and 1,008 seizures). Study by *REF: Loddenkemper T. et al. Neurology 2011;76(2):145-53.*

Certain SZ Types and Epilepsy Syndromes Exhibit Preferential Timing of Seizure in Relation to Sleep/Wake or Circadian Clock Time

Awake	Day	Asleep	Night
Hypomotor	Atonic	Tonic	Automotor
Atonic	Hypomotor	Automotor	
Epileptic spasms		Parietal	
Generalized			

§ Based upon evaluation of 1,008 seizures in 225 children (mean age 8.5 ± 5.7 years). *Loddenkemper et al. Neurology 2011;76(2):145-53.*

What is Chronopharmacology?

- Evaluates how circadian rhythms (and sleep/wake states) affect pharmacodynamics and pharmacokinetics of a particular drug or treatment including a drug's absorption, metabolism, elimination, and distribution;
- Identify how AED levels, adverse effects, and toxicity change in relation to circadian rhythms (chronopharmacology known for >100 drugs, but only few AEDs).

Chronotherapy Applied to Epilepsy Just Beginning

- Chronotherapy applied to treat epilepsy focuses on dosing AED(s) at times of greatest seizure susceptibility (wake/sleep, time of day, menstrual cycle, sleep deprivation).
- Chronopharmacological behavior for most AEDs is not yet known.
- Dosing an AED cognizant of its chronopharmacology (if relevant) is just beginning to be studied.

Use Chronopharmacology and Chronotherapeutics to Tailor Epilepsy Tx

- Adjust timing and doses of anti-seizure medications in synchrony with circadian rhythms;
- Dose AED(s) at times of greatest seizure susceptibility (wake/sleep, time of day, menstrual cycle, sleep deprivation);
- Reduce adverse effects and toxicity;
- Couple with optimal sleep/wake practices.

Efficacy of Evening Dose of AED

- A randomized case-control study compared bid or QHS dosing of PHT or CBZ in 102 patients with poorly controlled GTC SZs and subtherapeutic AED levels;
  - Single evening dose which was 66-75% their usual total daily dose.
- 85% of patients who took PHT or CBZ QHS became SZ-free (vs. 38% dosed bid);
  - QHS dosing = AED levels more often therapeutic and toxic side effects were less.

Yegnanarayan R, Mahesh SD, Sangle S: Chronotherapeutic dose schedule of phenytoin and carbamazepine in epileptic patients. *Chronobiol Int* 23(5), 1035-1046 (2006).

Nocturnal Epilepsy = Adjust Daily Dose to 2/3 at Night

- 17 children with predominantly nocturnal epilepsies:
  - Adjusted daily dose of AED to 2/3 at night, 1/3 in am;
  - 75-90% reductions in SZ frequencies;
  - 65% became SZ-free.

Guilhoto LM, Loddenkemper T, Vendrame M, Bergin A, Bourgeois BF, Kothare SV: Higher evening antiepileptic drug dose for nocturnal and early-morning seizures. *Epilepsy & behavior : E&B* 20(2), 334-337 (2011).

Circadian Timing of AEDs: Human Studies

Anti-seizure drug	Effects
Midazolam continuous IV infusion	Mild day/night fluctuations in midazolam levels (Klotz U 1984)
Diazepam	More rapid Cmax and shorter Tmax following morning compared with evening dose in 28 healthy volunteers due to changes in absorption and distribution (Nakano S 1984)
Carbamazepine	Higher plasma levels of CBZ and 10,11 Epoxide during night compared to day 24-hours post-dose of CBZ-ER may be due to changes in plasma distribution and protein binding (Olano I, 1998),

Circadian Timing of AEDs: Human Studies

Anti-seizure drug	Effects
Valproate	Binding to plasma proteins important role in VPA distribution: higher binding of VPA proteins in afternoon. Maximal free VPA levels 2 to 6 am. Patients taking VPA twice daily (morning and evening) had higher serum VPA levels and decreased Tmax following the morning dose compared to the evening dose (Yoshiyama et al. 1989) Excretion of VPA metabolites (3-oxo VPA and VPA glucuronides) lowest between 2-8 am may be related to differences in circadian oscillations in renal function particularly creatinine excretion (Reith DM 2001)

Summary

- Insomnia, excessive daytime sleepiness (EDS), and obstructive sleep apnea are more 2-3 times more common in adults with epilepsy than the general population, and should be evaluated to provide optimal seizure control and improved quality of life;
- Sleep deprivation is more likely to trigger seizures in patients with idiopathic generalized epilepsies, especially juvenile myoclonic epilepsy.

Summary

- Increased wake after sleep onset and reduced REM sleep are seen in many patients with epilepsy even on nights free from seizures. NREM instability remains elevated after epilepsy is controlled.
- Sleep and its complex interactions with epilepsy are rewarding areas for translational research.
- Chronopharmacology and chronobiology are promising fields for research.