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Sleep & Epilepsy: Clinical Applications

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Conflicts of Interest

☐ 1. I do not have any potential conflicts of interest to disclose, **OR**

x 2. I wish to disclose the following potential conflicts of interest:

- Reliant Physician Services LLC
- AASM PAC Advisory Panel
- Patent on a device for management of OSA

x 3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

☐ 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

Objectives

- Understand the relationship between Epilepsy and Sleep
- Impact of Sleep Deprivation on Epilepsy
- Polysomnographic findings in patients with Epilepsy (pwE)
- Learn about Epilepsies that are likely to occur in sleep
- Sleep disordered breathing in patient with Epilepsy.

History – Pre EEG Era

- The interface between Epilepsy and Sleep has been know since the times of Aristotle and Hippocrates.
- In 1885, Gowers WR reported that the relationship of seizures to the sleep-wake cycle.
- In 1929, Langdon-Down and Brain observed that nocturnal seizures peaked approximately 2 hours after bedtime and between 4 AM and 5 AM.

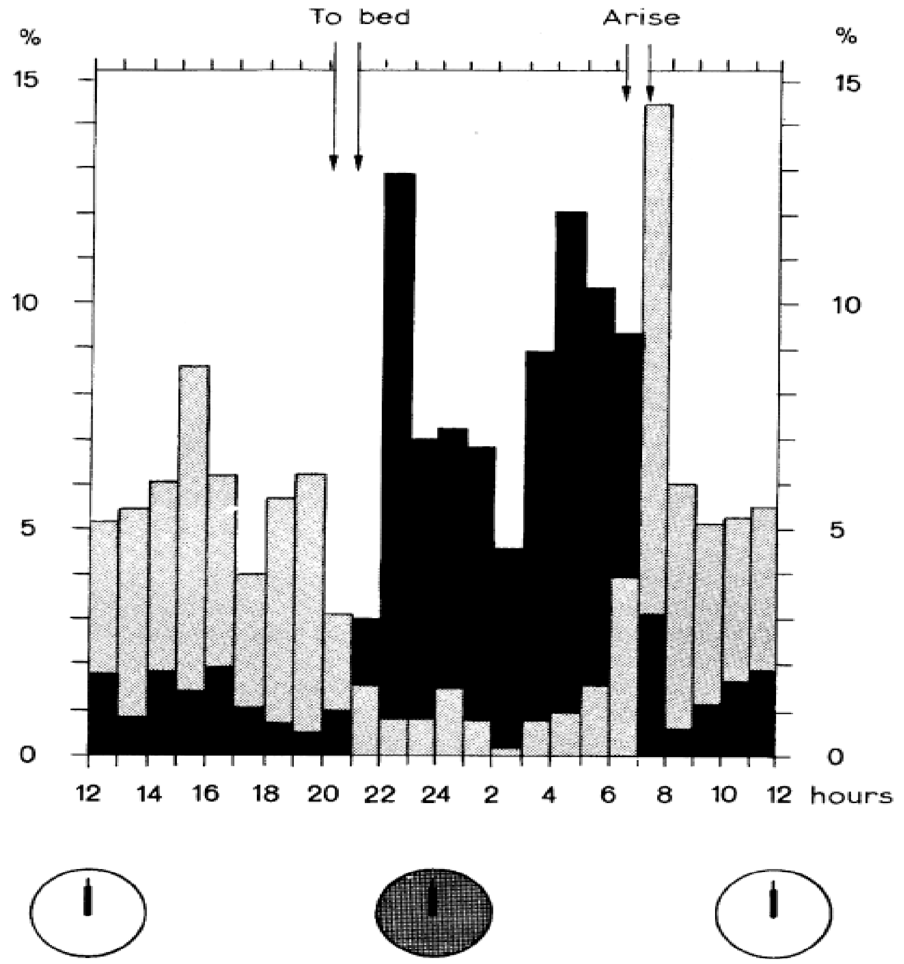


Fig. 1. Daily distribution of 2524 recorded major seizures registered from 66 institutionalized patients in the course of 6 months. The black entries represent the seizures of the 'night' group, the paler ones the 'day' group (Langdon-Down and Brain, 1929).

History- Pre EEG Era

Author	No. of patients	Diurnal Epilepsy (%)	Nocturnal Epilpesy (%)	Diffuse Epilepsy (%)
Gowers, 1865	84	42	21	37
Langdon-Down and Brain, 1929	66	43	24	33
Patry, 1931	750	45	19	36

Proportion of patients with Diurnal, Nocturnal and Diffuse Epilepsy in Early Clinical Observation Studies

History- Post EEG

- Han Berger, a psychiatrist, discovered EEG in 1920's which led to new avenue of research of Sleep and Epilepsy

- In 1947, Gibbs and Gibbs demonstrated that interictal epileptiform discharges were activated by sleep. This is even now the standard activating procedure both in inpatient and outpatient settings.

- In 1962, Janz, differentiated awakening, nocturnal and diurnal epilepsies and in 1966 Niedermeyer described the activating influence of arousal on epilepsy.

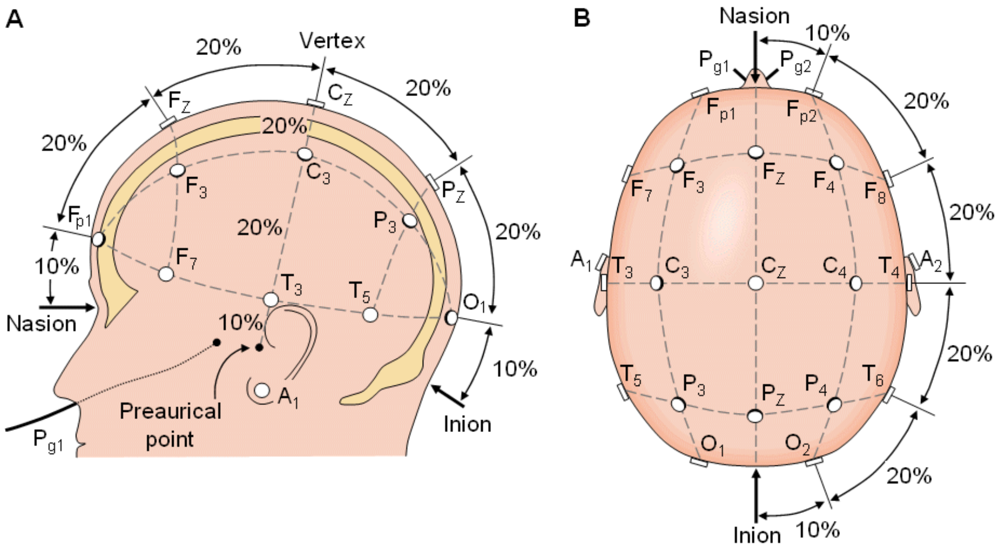
History- Post EEG

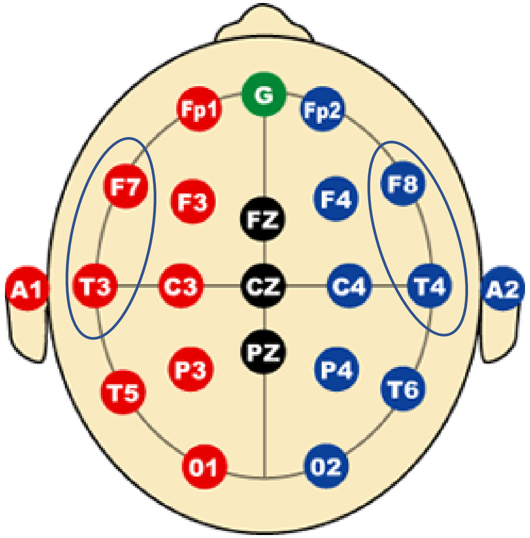
Author	No. of patients	Diurnal Epilepsy (%)	Nocturnal Epilpesy (%)	Diffuse Epilepsy (%)
Janz, 1962	2110	34	45	21
Janz, 1969	2925	33	44	23
Billiard, 1982	314	53	15	32

Association of Generalized Tonic-Clonic seizures in Regard to Sleep/Awake Schedule

EEG Placement: 10-20 system

- During PSG, we place the following electrodes:
- Occipital
- Central
- Frontal
- Maxillary
- Eye electrodes.



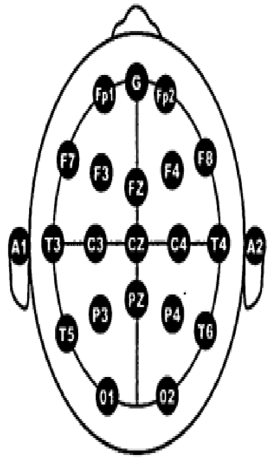


EPILEPTIFORM TRANSIENTS

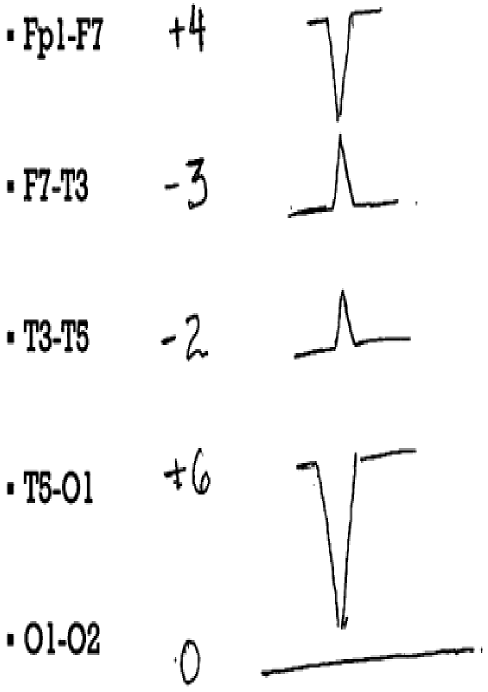
Transients	Duration	Variants
Spike	25-70 ms	Spike and wave complex; polyspike and wave complex
Sharp wave	70-200 ms	Sharp and wave complex; polysharp and wave complex
Sharply contoured slow wave (strictly not epileptiform)	>200 ms	

EEG Drawings

- Introducing concepts of
  - Phase Reversal
  - Electrical Field



Fp1=5, F7=1, T3=4, T5=6, O1=1, O2=1



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LET'S DEFINE SOMETHINGS

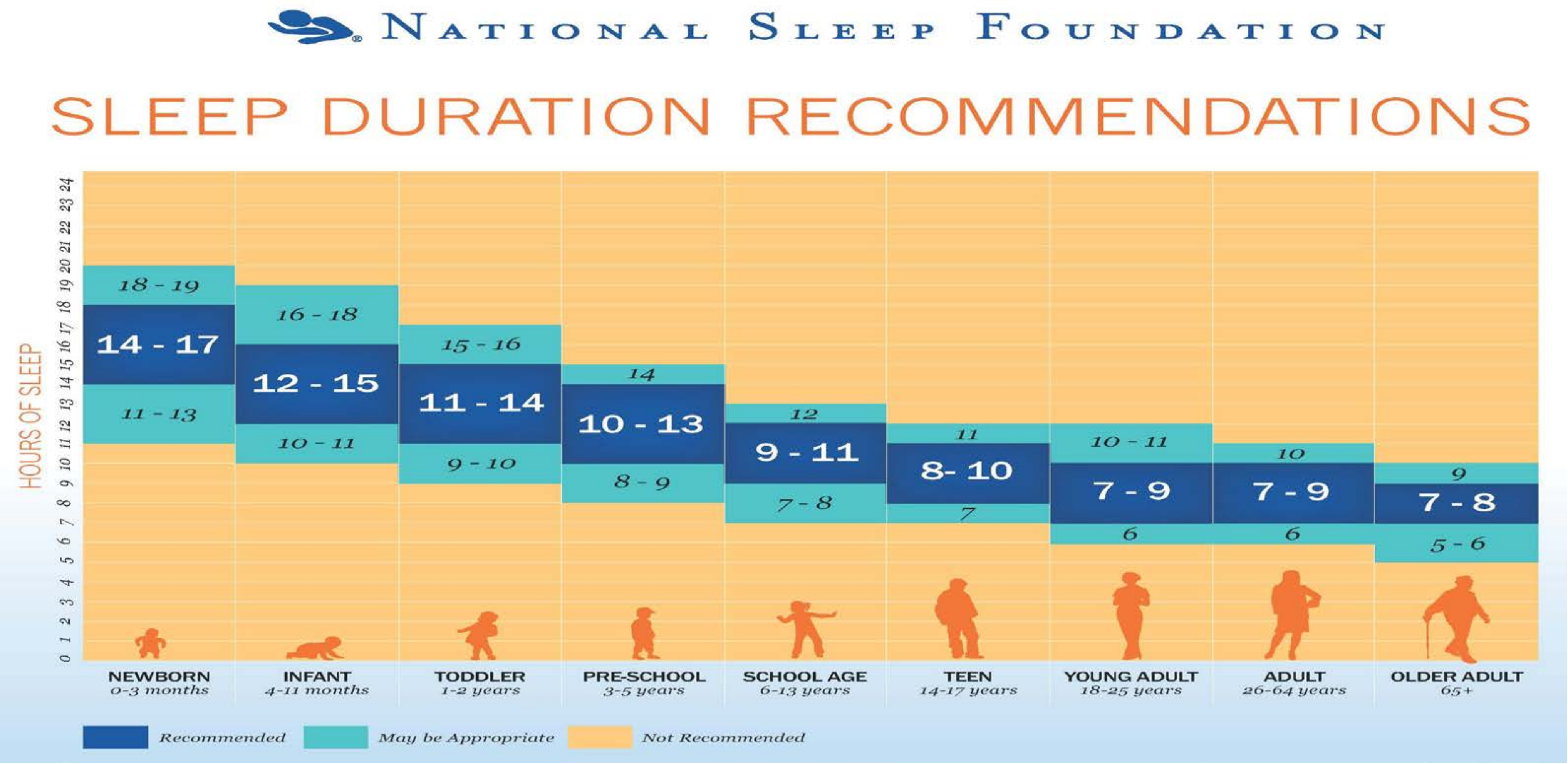
What's

- Ictal
- Interictal

What's

- Partial
- Generalized

Sleep Deprivation



Hirshkowitz, PhD et al, Sleep Health (2015), 233-243

Sleep Deprivation & Cortical Excitability

- In 1969 Janz described that “awakening epilepsies” frequently occurred after holidays or on Mondays. Also, students and bakers tended to have more seizures after sleep deprivation.

- Degen and Degen (1980) showed sleep deprivation to increase interictal discharges in patients (n= 127)with epilepsy. They found that only 19% of their cohort had interictal abnormalities on routine EEG but 64% had abnormalities with sleep deprivation.

- Rowan (1982) found in patients (n=43) with normal EEG and suspected seizures that only 14 % had new abnormalities when sleep was sedation whereas 44%had new abnormalities following sleep deprivation.

Sleep Deprivation & Cortical Excitability

- 29 patients who had REEG which recorded wake/sleep EEG that failed to showed ED
- Fifteen (52%) had activation on SD-EEG; exclusively during
  - Wakefulness in 1,
  - During sleep in 6 and
  - Wakefulness & sleep in 8

Fountain et al, J Clin Neurophysiology 1998

- In a retrospective study of 237 patients who had a follow up SD-EEG led to a diagnosis of epilepsy in 69 (almost 30%) of them.
- SD-EEG was more useful tool in patient with generalized epilepsy when compared with focal epilepsy.

Renzel et al, Clinical Neurophysiology 2016 (209-213)

Sleep Deprivation & Cortical Activity

- In pediatrics patients with suspected seizure disorder, initial EEG may be normal in half of them.
- 55 children were assessed who had initial negative EEG
  - Age 5–17 years (mean: 10 3.7)
  - 27 boys and 28 girls.
  - Sleep occurred in 51 (92.7%) after sleep deprivation and in only 1 (1.8%) during an awake record.

Shahar et al, E. J of Ped Neuro (2010, 308-312)

- Epileptic discharges were detected in 15 of 55 (27.2%) and more frequent during sleep.
- Eight abnormal records were detected in 18 (44%) children presenting with a focal seizure
- 7 of 35 (20%) associated with generalized seizures. Epileptic discharges were recorded mainly and more frequent during sleep

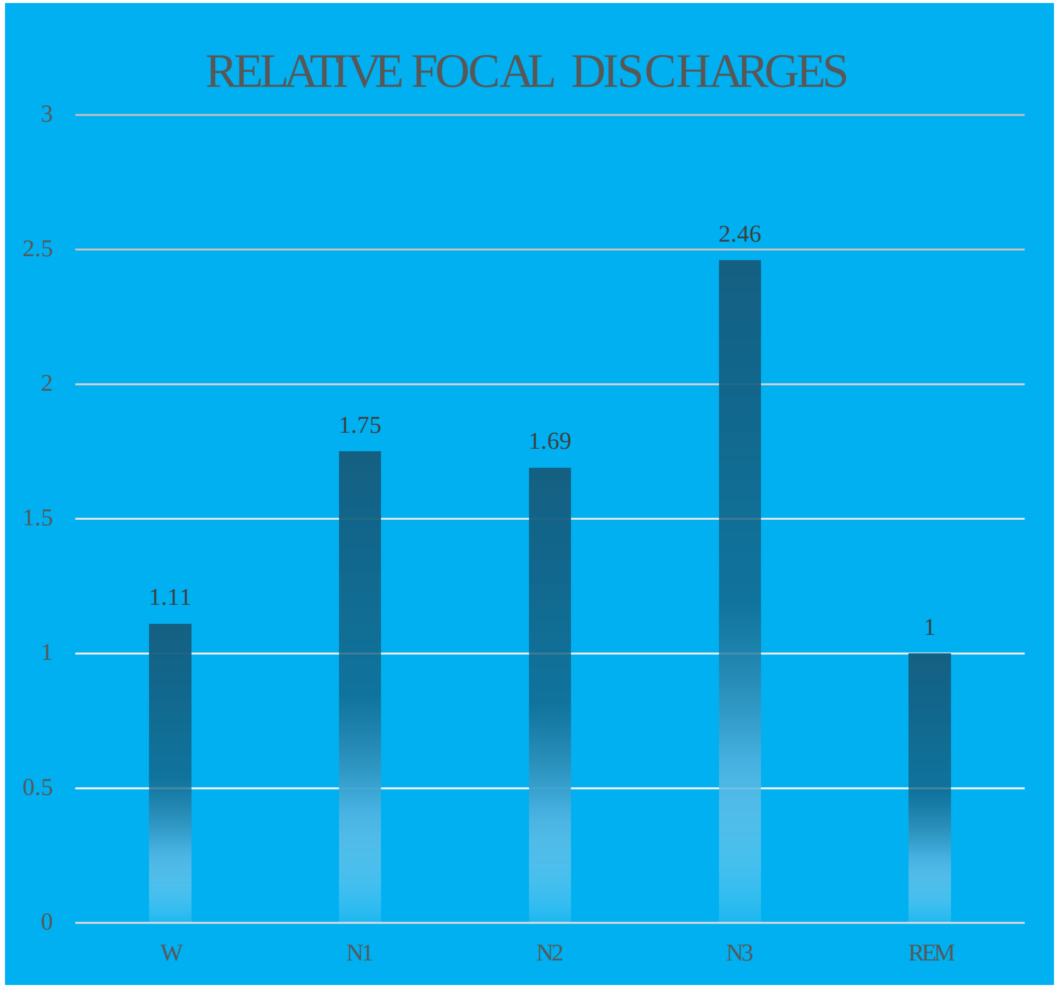
Sleep Deprivation- A strategy to Diagnose & Manage

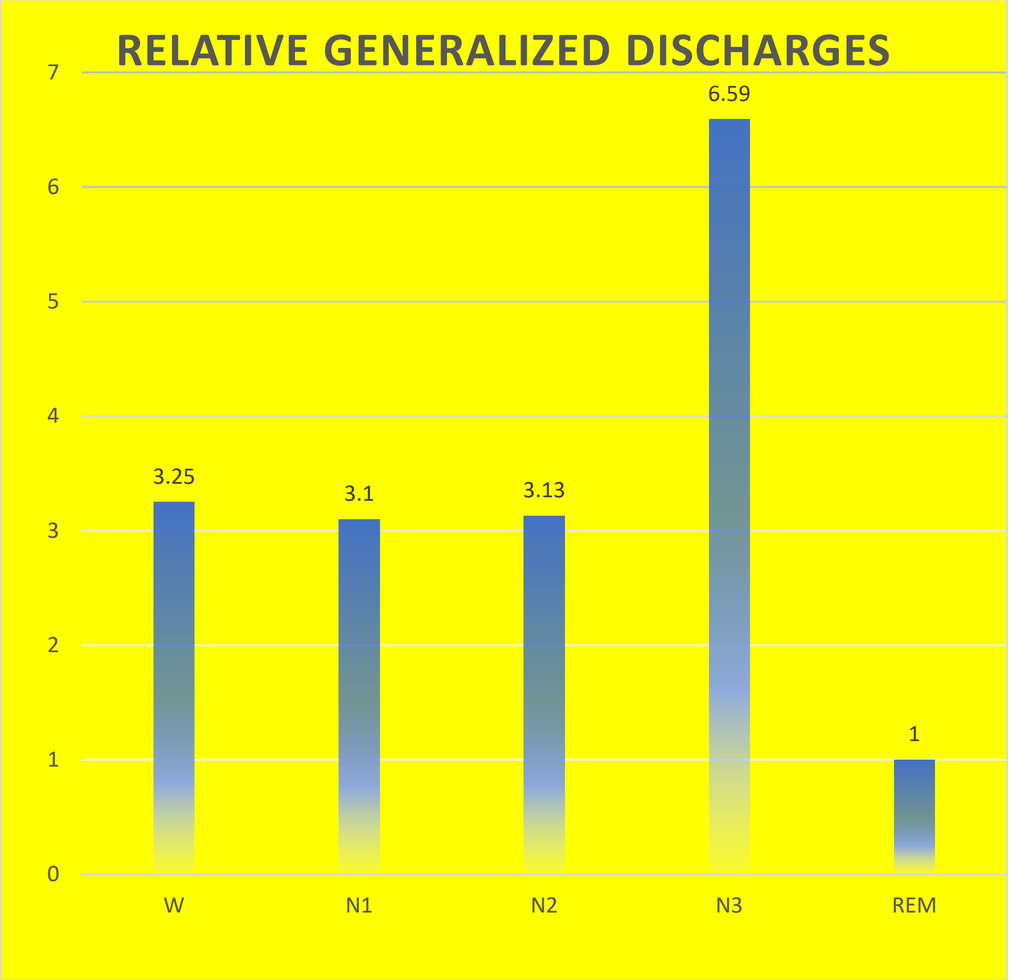
- SD is strategy often used at tertiary centers with epilepsy monitoring units
  - Restricting sleep in young children to less than 6 hours.
  - In adults, to less than 4 hours.
  - No napping in the daytime.
- SD prior to an ictal SPECT (single photon emission computed tomography).
- SD may help in pre-surgical evaluation in some epilepsy patients
- SD can be problematic: may affect the seizure characteristics
  - More prolonged
  - More intense

Interictal Discharges & Sleep Staging.

- NREM sleep is associated with an increased propagation of focal and generalized spikes, as an extension of electrical field.
- REM sleep is associated with focalization of interictal discharges or restriction of electrical field. REM foci is mostly unilateral and correlates with wake foci.
- REM sleep has the best localizing value for the primary area of epileptogenicity both in TLE and in extra temporal lobe epilepsy.

Interictal Discharges & Sleep Stage





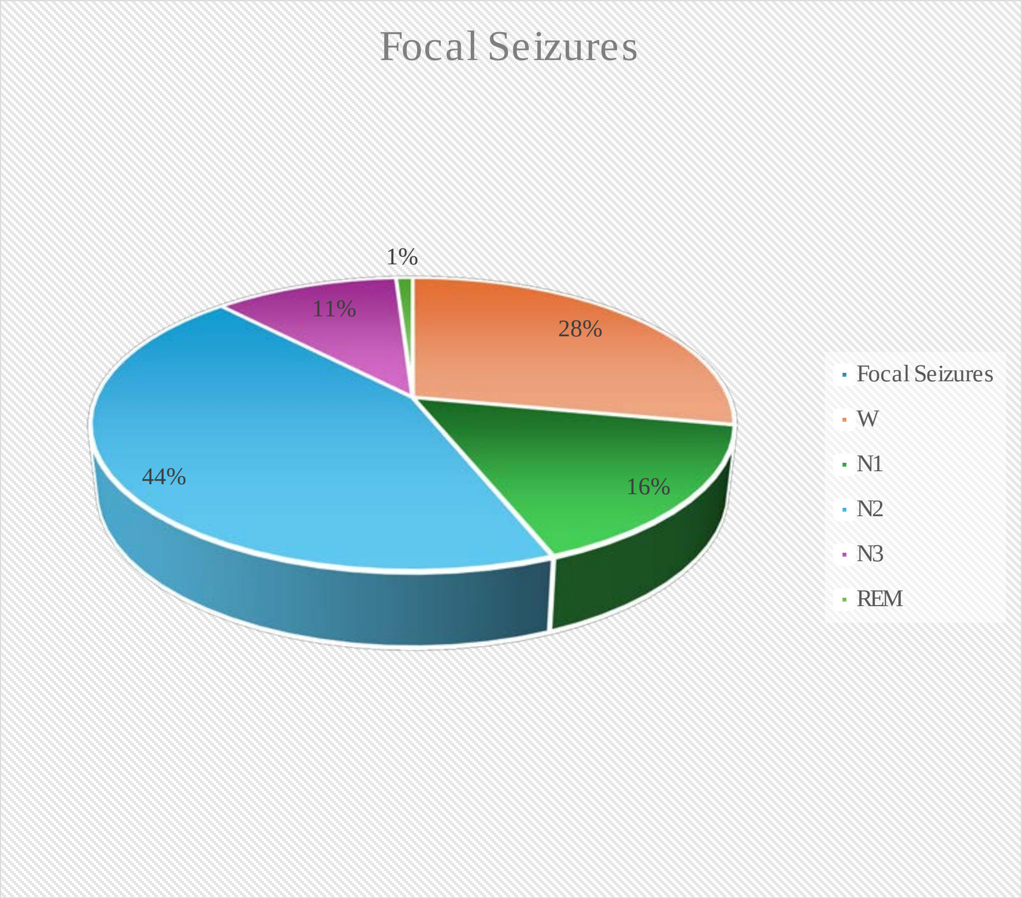
Ng et al, Epilepsy Res & Treatment, 2013

Sleep and Seizures

Herman and Minecan in separate papers showed that most sleep related seizures begin in NREM sleep with stage 2 having the highest seizure rate per hour and REM sleep having the lowest rate of seizures.

Authors		Stage 1	Stage 2	Stage ¾	REM
Herman	% of seizures not adjusted for time	23	68	9	0
Minecan	% of seizures not adjusted for time	20	61	14	5
Minecan	% of seizures adjusted for time	0.34	0.38	0.29	0.09

Focal Seizures & Sleep Stages



Ng et al, Epilepsy Res & Treatment, 2013

Circadian Rhythm in Seizures?

- Adults (using sophisticated recordings)

Seizure Onset	Clock
Occipital Lobe	4 PM- 7 PM
Mesial Temporal	4 PM- 7 PM
Parietal Lobe	4 AM- 7 AM
Frontal Lobe	4 AM- 7 AM

- In Children

Seizure Onset	Clock
Occipital Lobe	6 AM- 6 PM
Temporal Lobe	6 PM- 6 AM
Frontal Lobe	6 PM- 6 AM

Timing	Semiology
Datyime	Clonic , Atonic, Hypomotor or Myclonic
Nighttime	Automotor or Hypermotor

Sleep and Seizures

Herman and Janz separately found that frontal lobe seizures are more likely than other locations to occur during sleep. Some frontal and temporal lobe seizures occur near an arousal or awakening from sleep and this finding raises a question if the seizures cause the arousal or did the arousal promote the seizure.

Authors	Frontal	Temporal	Parietal	Parietal/Occipital
Janz	58%	25%	21%	NR
Herman	57%	43%	NR	13%

Manfredini found a circadian influence on simple partial febrile seizures with the peak incidence of seizures are over four fold greater between 5 pm and 11:59 PM then 6 to 11: 59 AM.

Sleep and seizure onset zones

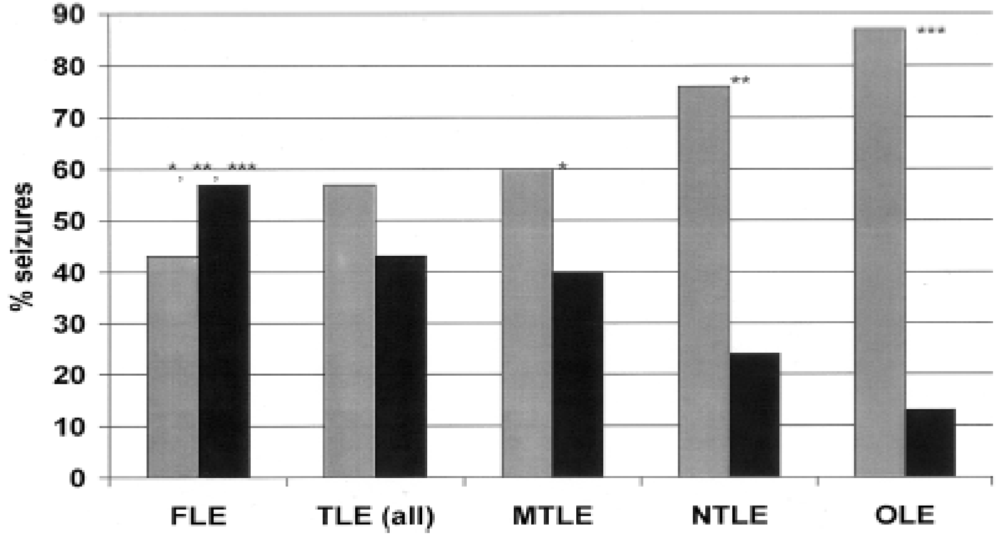


*Figure 2. Percentage of partial seizures arising during sleep from various seizure onset zones. Frontal lobe seizures were more likely to occur during sleep than seizures arising from other foci (p < 0.0001). FLE = frontal lobe epilepsy (n = 112), TLE = temporal lobe epilepsy (n = 382), MTLE = mesial temporal lobe epilepsy (n = 164), NTLE = neocortical temporal lobe epilepsy (n = 54), OLE = occipital or parietal lobe epilepsy (n = 45). Gray bars, awake; black bars, asleep. *p < 0.05; ***p < 0.001; ***p < 0.001.*

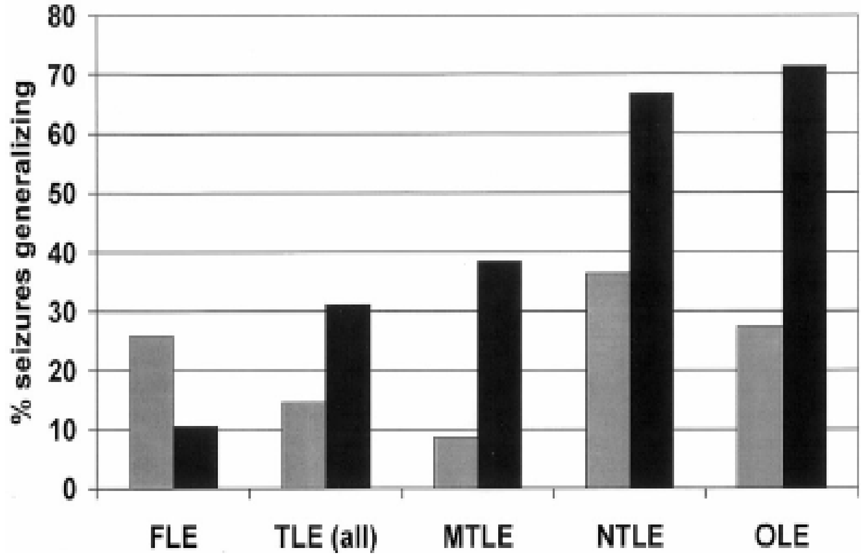


Figure 4. Percentage of partial seizures undergoing secondary generalization for various seizure onset zones. Sleep promoted secondary generalization of temporal lobe seizures (51 of 164, 31.1%), both MTLE (25 of 65, 38.5%) and NTLE (8 of 12, 66.7%), and occipitoparietal seizures (5 of 7, 71.4%), but not frontal (5 of 48, 10.4%) lobe seizures (p < 0.005). Gray bars, awake; black bars, asleep.

Distribution of partial seizures during the sleep wake cycle: Differences by seizure onset site

S.T. Herman, T.S. Walczak et al, Neurology 2001; 56; 1453-1459

Sleep Related Epilepsies

- Nocturnal Frontal Lobe Epilepsy.
- Benign Epilepsy of Childhood with CT spikes.
- Juvenile Myoclonic Epilepsy.
- GTC Seizures on awakening.
- Tonic seizures (as a component of LG syndrome).
- Benign Epilepsy with Occipital Paroxysms (BEOP).
- Certain forms of TLE.
- Continuous spike waves during NREM sleep (CSWS).

SRE or NREM Parasomnias

It all depends on YOU.

Semiology of the event- stereotyped motor events

# of attacks per night. (multiple per night)

Episode frequency per month

Episode duration (less than 2 minutes)

Daytime episodes

Dream Mentation

Sleep Stage/Time of the night

- Age of Onset
- Family History
- Triggers
- Eyes Open or Closed
- History of parasomnias.

NFLE: Frequency of Epileptiform Discharges

EEG	Scheffer et al.	Oldani et al.	Provini et al.	Derry et al.
IC –Awake	__	12%	33%	__
IC – Sleep	16%	50%	36%	__
Ictal	40%	55%	56%	38%

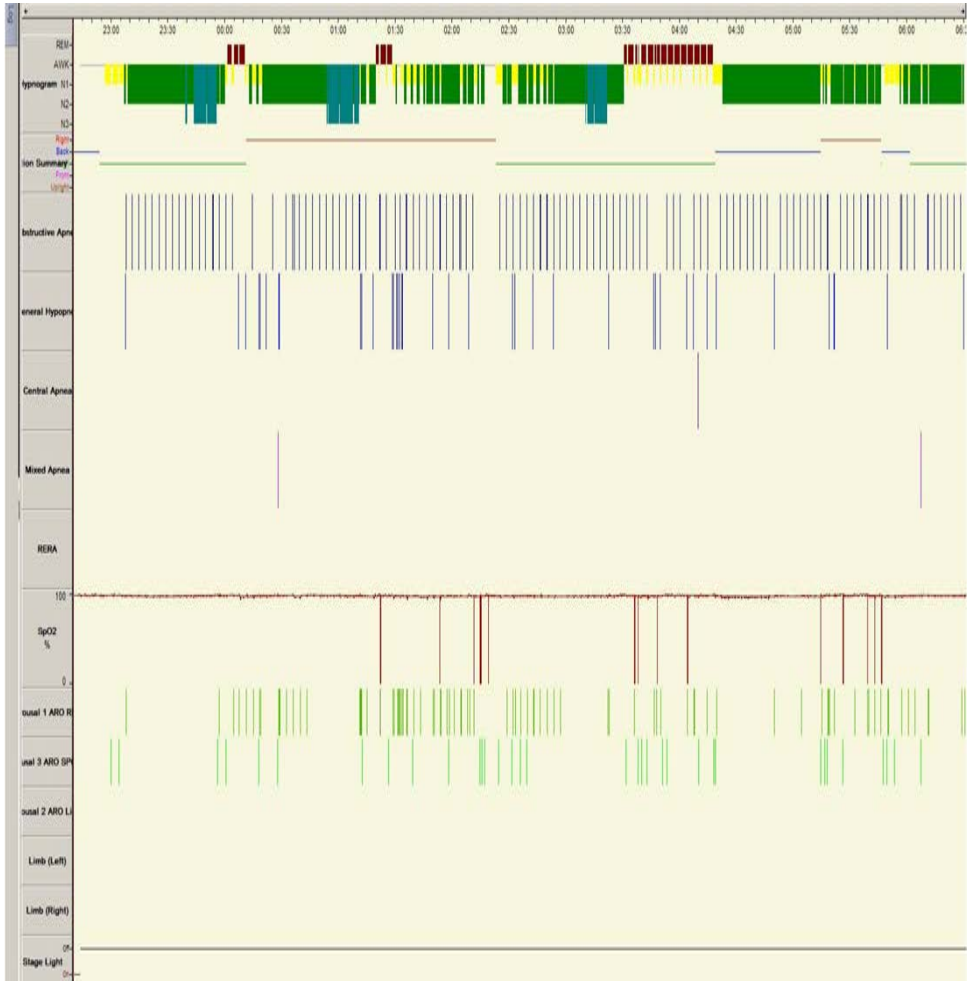
Epilepsy impacts Sleep- How ?

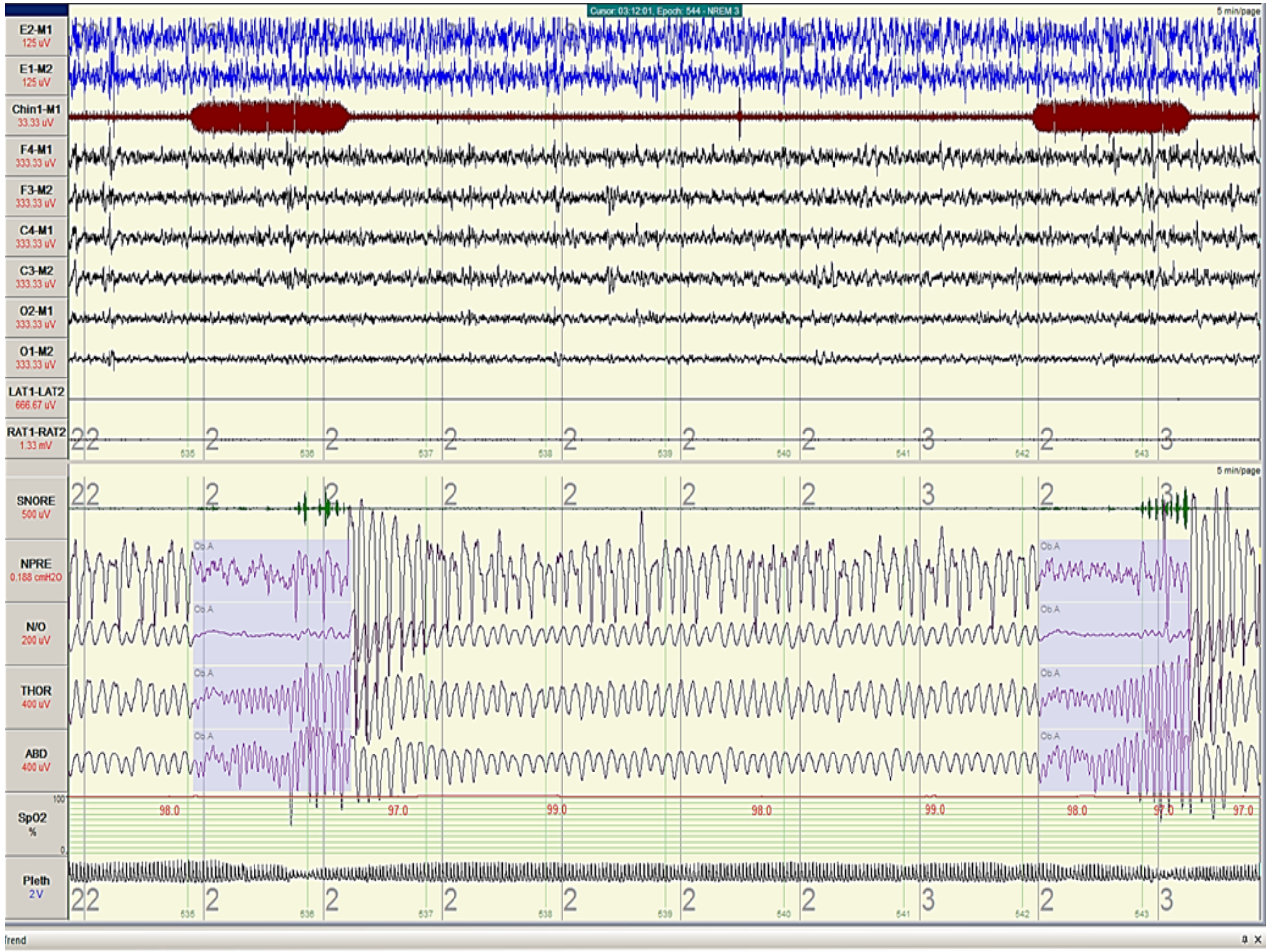
- pwE complaint of sleep disruption & daytime dysfunction (40-50% of them meeting the criteria for insomnia).
- Possible etiologies for sleep fragmentation:
    - Sleep Disordered Breathing (Obstructive sleep apnea or Hypoventilation)
    - Snoring or Upper airway resistance syndrome.
    - Nocturnal seizures which may go unnoticed or undetected
    - Periodic leg movements in sleep
- Sleep architecture changes
    - Reduced REM sleep (which tends to be protective).
    - High arousal index
    - Longer sleep onset latency

Effect of Rx for Epilepsy on Sleep.

- Treatment of Epilepsy with appropriate medications (AEDs), dose and at time often results in improves sleep
- While most AEDs result in hypersomnolence, some have been reported to lead to insomnia, particularly
  - Lamotrigine
  - Felbamate
- Some AEDs may result in mental health challenges such as anxiety or severe depression which may then lead to sleep disruption
  - Levetiracetam or Brivacetam
  - Oxcarbazepine
  - Tiagabine
  - Topiramate
  - Valporate

Effect of Rx for Epilepsy on Sleep.





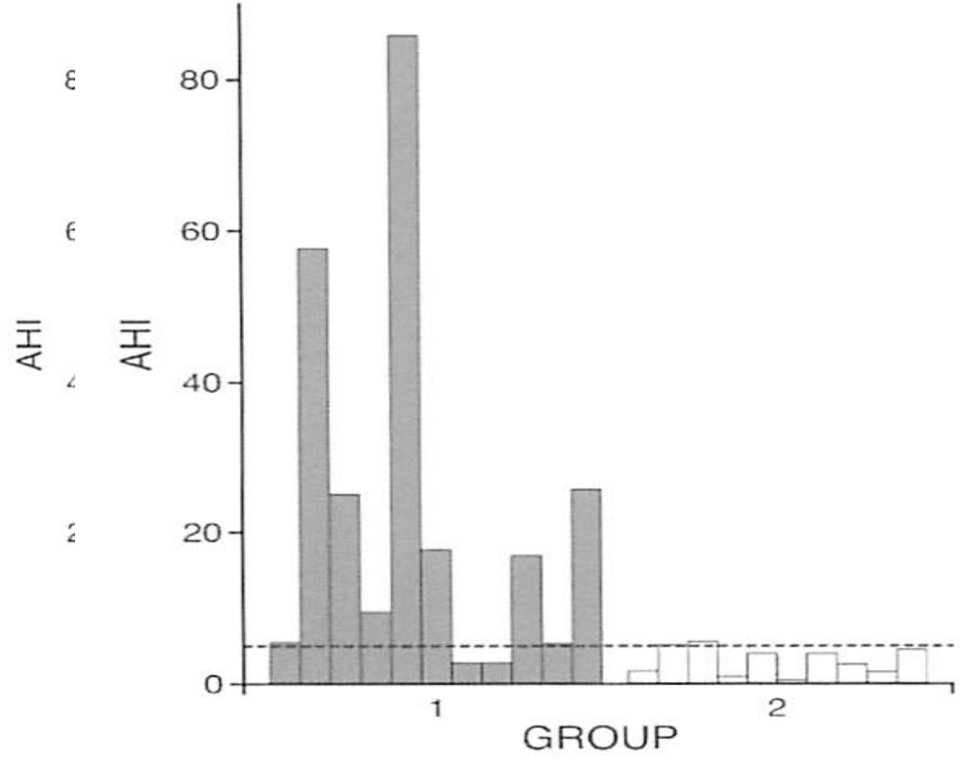
OSA in Epilepsy

- It is generally believed 1/3rd of patients with medication resistant epilepsy have OSA.
- In a recent study, OSA was present in 15.4% of epilepsy patients (n=197)
- Frequency of OSA was similar in refractory epilepsy patients (REP) vs. well controlled patients (WCE)

- Predictors of OSA in WEC
  - Male gender
  - Older age
  - Difficulty staying asleep
  - EDS
- Predictors of OSA in REP
  - Snoring
  - DM

Ping Li et al, Seizure, 2012

OSA in Elderly Patients with Epilepsy



	Group 1, n = 11	Group 2, n = 10	p Value
Apnea-hypopnea index	23.2 (26.2)	3.1 (1.8)	0.002
SA-SDQ score	16.3 (4.1)	12.6 (3.7)	0.04
Epworth Sleepiness Scale score	11.6 (3.6)	5.9 (5.3)	0.009
Age, y	58.0 (9.7)	57.1 (7.0)	0.81
Men	82%	20%	0.003
Body mass index	27.6 (5.3)	26.6 (6.0)	0.67
Neck circumference, in	16.1 (1.5)	14.8 (1.8)	0.09
No. of antiepileptic drugs	1.5 (0.5)	1.8 (0.6)	0.32
Monotherapy	45.4%	30%	0.49
Nocturnal seizures predominantly	2	4	0.36

Chihorek et al, Neurology, 2007

Impact of Rx for OSA on Seizures

- Retrospective analysis of pwE (n=41) on CPAP. Compliant (n=28) vs. non-compliant (n=13) showed
  - Seizures ↓ from 1.8 to 1 /month
  - No difference in non-compliant

  Seizure free= 57% vs. 23% (CPAP ☺)

  Vendrame et al, Epilepsia 2011

- Analysis of 61 pwE who were recommended CPAP. Adherent (n=24) vs. non-adherent or refused (n=37) showed
  - Seizure ↓ 4.40 to 2.52/month (p=0.013 ☺)
  - No difference in non-compliant

  Jo et al, JCSM 2022

Effect of T&A on seizure frequency

Studied retrospectively in 27 children with epilepsy (no change in AEDs)

37% (n=10)-seizure free.

11% (n=3)- 50% ↓

22% (n=6)- Frequency ↓

22% (n=6)- Frequency ↑

7% (n=2) - Frequency ↔

Segal et al, Pediatric Neurology, 2012

Take Home Points

- Sleep complaints are common in Epilepsy patients. Comprehensive assessment are often warranted.

- Understand EEG biomarkers when interpreting Polysomnogram and consider a full EEG evaluation where clinically applicable.

- Parasomnias can mimic nocturnal seizures. Avoid pitfalls and retrace your steps if expected clinical outcomes are lacking.

- Treating sleep disorders will improve sleep in pwE. Have patience with them as they may surprise you.

THANK YOU

&

GO BLUE