Bidirectional Relationship Between Epilepsy, Sleep Quality, and OSA

A Comprehensive Review of Adult and Pediatric Literature for Clinical Epileptologists

Sleep Medicine as an Emerging Field

- Sleep was an emerging field in 1980
- American Sleep Society & Board was established in 1990
- Fastest Growing field in medicine
- Encompass from basic science to clinical neurology, psychiatry, pulmonology, ENT & dentist that related to sleep & its disrders
- Age range : newborn to eldery

Sleep & Epilepsy

- These conditions have “Bidirectional effects”:
  - Epilepsy -> Sleep
    - Changes in Sleep Architecture -> Epilepsy & Seizure
    - Increased incidence of obstructive sleep apnea / OSA -> Sleep deprivation -> Increased Seizure
    - Seizures -> precipitating parasomnia / DDx
    - Hypersomnia / EDS
  - Sleep -> Epilepsy DDx
    - Parasomnia
    - PLMS
    - Rhythmic Movement Disorder
    - REM Behaviour Disorder

Sleep Starts

- A normal (although not understood) physiologic event, and they should not be confused with seizures or other neurologic conditions.
- The most common is the motor sleep start(hypnic jerks) :
  - a sudden jerk of all or part of the body, occasionally awakening the victim or bed partner.

Sleep starts

- Variations : sleep starts, which occur without the body jerk.
  - visual sleep starts
    - flashes of light, fragmentary visual hallucinations
  - auditory sleep starts
    - loud bangs, snapping noises
  - somesthetic sleep starts
    - pain, floating, something flowing through the body

- "exploding head syndrome" : a sensation of a loud sound like an explosion or a sensation of"bursting" of the head
  - Sleep -> Epilepsy
  - Could be a variant of a sensory sleep start.
  - Epilpesy -> sleep
  - DDX : may represent the sole manifestation of a seizure.

Pierce Headache 2001 ; 41: 602-603 & Walsleben et al , Sleep Res. 1993;22;248

Parasomnia

- Epilepsy -> Sleep
- REM : recurrent dreams, nightmares
- NREM disorders of arousal : sleepwalking and sleep terrors.
- May Miss Dx of seizure related dreams and nightmares -> misinterpreted as a primary sleep phenomenon.
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFL) may also manifest as recurrent nightmares.

Epsteins AW: 1964,1966, Boller F. :1975, Synder CH** Pediatrics 1958, Scheffer Brain 1995

Hypersomnia & EDS vs Epilepsy

- EDS in a patient on AED must not summarily be attributed to antiepileptic medication !
  - Some epileptic patients remains hypersomnolent after D/C of AED.
  - Seizure-free preadolescent children with epilepsy are sleepier than healthy controls.
  - No difference in MSLT in children with epilepsy ON/OFF AEDs
  - In adult, patients with epilepsy had poor sleep quality but normal sleepiness.
    - a higher PSQI, close to the pathologicalcut-off, compared to controls, but a similar and unremarkable ESS, Meta-analysis 25 studies, 8196 Pts.

Epilepsia, 33(4):687491, 1992
Sleep Medicine Reviews, (57), June 2021, 101466

Prevalence of Sleep Disorders in the Epilepsy Population

- Prevalence of sleep complaints:
- Epileptic Pts-> Inc sleep disturbance vs normal

controls .: Stores et al.,

  - using parental questionnaires,
  - 79 school children with epilepsy vs 73 healthy control children.
  - children with epilepsy-> higher rates of sleep disorders, particularly poor quality sleep and anxieties about sleep
  - A significant association between seizure frequency and anxieties about sleeping

Sleep disturbance in childhood epilepsy: clinical implications, assessment and treatment

Gregory Stores

Stores G. *Arch Dis Child* 2013;**98**:548–551. doi:10.1136/archdischild-2013-303825

Prevalence of sleep disorders in the epilepsy population

- Cortesi et al.
  - sleep problems and their association with behavioral and adjustment problems in children with idiopathic epilepsy
  - More sleep problems vs siblings and healthy controls.
  - Within the epileptic group, children with current seizures -> more of sleep problems than did seizure-free children

Sleep problems and daytime behavior in childhood idiopathic epilepsy
F Cortesi[1], F Giannotti, S Ottaviano
Epilepsia. 1999 Nov;40(11):1557-65.

Observational pilot study of obstructive Sleep Apnea, reported symptoms in Thai Children with epilepsy, experience at King Chulalongkorn Memorial Hospital

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Background

The complex interplay between sleep, sleep disorders, and epilepsy is important for the care of epilepsy patients.[1] Sleep disruption of any kind, including from sleep disorders, can worsen epileptic seizures and contribute to intractability.[1] One of the sleep disorders is obstructive sleep apnea (OSA) which impacts epilepsy control.

Objectives

The primary objective is to estimate symptoms of obstructive sleep apnea and excessive daytime sleepiness (EDS) in children with epilepsy (CWE) compare with non-epileptic patients. The secondary objective is to compare effectiveness between Thai PSQ-SRBD (Pediatric Sleep Questionnaire – Obstructive sleep-related breathing disorder) and Thai ESS (Epworth Sleepiness Scale).

Observational pilot study of obstructive Sleep Apnea, reported symptoms in Thai Children with epilepsy, experience at King Chulalongkorn Memorial Hospital

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Methods

The prospective pilot study was conducted on January to March 2021. Epilepsy arm's subjects were recruited from Pediatric Neurology clinic. Controlled arm's subjects were children attending Chula health promotion group. Thai PSQ-SRBD and Thai ESS were applied to both groups.

Parametric data was analysed with independent T-test and Non parametric data was analysed with Chi square test via SPSS programe.

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orial Hospital

Table 2	Control (n=66)	Epilepsy (n=53)	P Value
PSQ SRBD			
mean ± SD	0.21 ± 0.17	0.3 ± 0.19	0.009*
<, =0.33	54 (81.8%)	30 (57.7%)	0.004*
> 0.33	12 (18.2%)	22 (42.3%)	
Epworth			
mean ± SD	4.47 ± 3.05	5.75 ± 4.11	0.061
< 10	62 (93.9%)	42 (79.2%)	0.016*
>, =10	4 (6.1%)	11 (20.8%)	

- 53 CWE completed ESS and 52 CWE completed Thai PSQ-SRBD. Compare to the control group, CWE significantly has more OSA symptoms (22/53 (42.3%) vs 12/66 (18.2%) and sleepiness (11/53 (20.8%) vs 4/66 (6.1%)) based on abnormal Thai PSQ-SRBD and ESS (P 0.04* and 0.016* respectively).

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Table 3	Monotherapy	Polytherapy	P Value
PSQ SRBD	(PSQ n=34, ESS n=35)	(n=18)	
mean ± SD	0.25 ± 0.19	0.38 ± 0.19	0.023*
<, =0.33	23 (67.6%)	7 (38.9%)	0.046*
> 0.33	11 (32.4%)	11 (61.1%)	
Epworth			
mean ± SD	5.89 ± 3.57	5.5 ± 5.11	0.777
< 10	29 (82.9%)	13 (72.2%)	0.366
>, =10	6 (17.1%)	5 (27.8%)	

- CWE with polytherapy (11/53) showed significantly more OSA symptoms compare to CWE with monotherapy (35/53, P 0.046*)
- ESS in CWE sub-group analysis did not reveal any significant difference regarding excessive day time sleepiness

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Conclusion

In conclusion, OSA symptoms and EDS are significantly more common in CWE than in control. CWE with polytherapy is more likely to report OSA symptoms. High seizure frequency may be a confounding factor, but do not alone reach statistically significant association.

In our experiences, Thai PSQ-SRBD can differentiate OSA symptoms in subgroup of CWE while ESS has more limited use. Further study with larger number of patients and polysomnography for OSA confirmation are warranted.

Sleep disturbances in people with epilepsy; prevalence, impact and treatment

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- Sleep Med Rev. 2011 Dec;15(6):357-68. Epub 2011 Mar 24. Review

Sleep problems in Ped & adults with epilepsy, questionnaire-based / PSG-baserd studies

Sleep problems in adults with epilepsy, questionnaire-based studies

N=9

Sleep disorders in people with epilepsy, measured with PSG-studies.

N=13

Sleep problems in children with epilepsy; questionnaire-based studies

N=9

Polysomnographic findings in children with epilepsy

N=7

	Population sample	Results	Conclusions
Kotagal et al. [102]	Nine patients with spastic quadriparesis and epilepsy with a mean age of 36.7 months	– ↑ respiratory disturbances per h/sleep, with 5 of 9 being diagnosed with OSA – ↓ changes in body position during sleep – IED averaged 23% of the total arousals in this group	OSA, ↓ changes in body position during sleep and IED are prevalent in the sleep of patients with CP contributing to sleep fragmentation
Maganti et al. [100]	Eleven children with primary generalized epilepsy who were seizure free and ages 5–18 years old	– ↑ stage 1 sleep and REM latency – Worse attention and exhibited ↑ CBCL and internalizing behavior problem scales	Further studies are needed to determine whether abnormalities in sleep architecture contribute to poor daytime behavior and attention
Malow et al. [103]	Sixteen subjects with mean age 33.6 ± 11.1 with medical refractory seizures who underwent a PSG and MSLT before and after 3 months of VNS	– MSL ↑, indicating ↓ daytime sleepiness – The amount of REM sleep or other sleep stages recorded on PSG did not change with VNS treatment	Treatment with VNS at low stimulation settings ↑ daytime sleepiness, even in subjects without ↓ in seizure frequency
Nunes et al. [96]	Seventeen children with partial refractory epilepsy	– [illegible] time and total sleep [illegible] – ↓ # > of stage shifts per hour – [illegible] and the REM latency [illegible] ↑	Patients with partial refractory epilepsies have only mild sleep structure abnormalities, and this can be considered as an effect of the epilepsy syndrome per se or as a result of the chronic AED
Becker et al. [11]	Fourteen children with epilepsy compared with patients with diagnosed OSA	– No difference in snoring, excessive daytime sleepiness and restless sleep were seen – 50% of children with epilepsy had behavioral problems	Neurobehavioral problems in children with epilepsy may in part be attributed to an underlying sleep disturbance
Nagarajan et al. [104]	Seven children with epilepsy on VNS	– ↓ effort and tidal volume occurred in seven children, concordant with VNS activation	RPCS occur in most children with VNS
Kothare et al. [101]	Forty children with epilepsy Eleven children with OSAS without epilepsy	Primary snoring 42%, OSA 20%,obstructive hypoventilation 12.5%, UARS8%, PLMS 10% Children with poor seizures controls had ↓ sleep efficiency arousal index, and ↑ REM Patients with epilepsy with OSA had ↑ BMI, ↑sleep latency, ↑arousal index, ↓ AHI but significantly more severe desaturation in comparison to the patients with uncomplicated obstructive sleep	A significant proportion of children with epilepsy referred for PSG with diverse sleep problems have SDB including OSA. Patients with epilepsy and OSA had significantly more severe desaturation than patients with OSA without epilepsy

OSA-obstructive sleep apnea; IED-inter-ictal discharges; CP-cerebral palsy; REM-rapid eye movement; CBCL-child behavior checklist; RPCS-respiratory pattern changes in

Practice points

1. Sleep disturbances are about 2–3 times more prevalent in both children and adults with epilepsy than in healthy controls.
2. Especially excessive daytime sleepiness and sleep maintenance insomnia are reported which can only be partially explained by the use of AEDs and seizure occurrence.
3. Sleep problems in people with neurodevelopmental disorders seem to be due at least partly to epilepsy and not only to the underlying encephalopathy.
4. Sleep disorders which coexist in people with epilepsy have detrimental effects on seizure control and QoL.
5. OSAS is the most frequently found co-morbid sleep disorder in both children and adults with epilepsy, but data for other disorders are scarce.
6. Treatment of a co-existing primary sleep disorder may improve seizure control, QoL and daytime behavior in people with epilepsy.

E.G.A. van Golde et al. / Sleep Medicine Reviews 15 (2011) 357–368

Effect of Epilepsy on Sleep

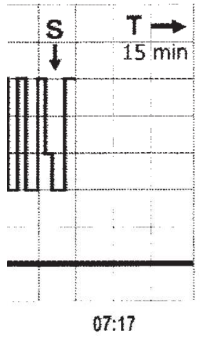
- Epilepsy /Seizures promote sleep disruption and significantly affect both the quality, quantity, and the architecture of sleep.
- Patients with epilepsy : macro-structure sleep abnormalities
  - increased number and duration of awakenings during sleep,
  - reduced sleep efficiency,
  - reduced or abnormal K complexes and sleep spindles,
  - reduced and fragmented REM sleep, and increased stage shifts

Nunes ML, Ferri R, Arzimanoglou A, Curzi L, Appel CC, Costa da Costa J. Sleep organization in children with partial refractory epilepsy. J Child Neurol 2003;18(11):763-6.

Table 2. Comparison of Sleep Parameters in Children With Epilepsy (With and Without Seizures During Polysomnography) and Controls

Sleep Parameters	*Patients With Seizure*	*Patients Without Seizure*	*Controls*	*ANOVA*
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	P
TIB (min)	355.33[a] (± 90.5)	437.13[b] (± 84.3)	559.90[c] (± 46)	< .001
TST (min)	333.22[a] (± 66.9)	407.63[b] (± 63.0)	521.00[c] (± 39.5)	< .001
AW/h*	0.53 (± 0.4)	0.59 (± 0.4)	0.45 (± 0.3)	.893
SS/h	3.96 (± 1.6)[a]	4.14 (± 1.1)[a]	6.32 (± 1.8)[b]	.005
S1%*	7.31 (± 11.4)	7.05 (± 10)	5.90 (± 3.2)	.552
S2%	42.11 (± 10.4)[a]	51.30 (± 6)[b]	52.24 (± 3.2)[b]	.008
S3–4%	36.72 (± 13.8)[a]	24.68 (± 7.4)[b]	16.55 (± 5.6)[b]	.001
REM%*	16.23 (± 9.5)	16.93 (± 4.4)	22.15 (± 1.7)	.154
FRL*	175.78 (± 161.3)	155.13 (± 47.2)	111.18 (± 36.2)	.232

*Analysis of variance (ANOVA) performed on ranks. Index letters noncoincident represent differences with statistical significance after the Duncan post hoc test. AW/h = number of awakenings per hour; FRL = first rapid eye movement latency; REM = rapid eye movement; S1% = percentage of stage 1 shifts; S2% = percentage of stage 2 shifts; S3–4% = percentage of stage 3–4 shifts; SS/h = number of stage shifts per hour; TIB = total time in bed; TST = total sleep time.



Figur
ing, f

night and early in the morn-

Effect of epilepsy on sleep: Seizure

- On Seizure Night:
  - disrupt the sleep-wake state,
  - nocturnal insomnia and EDS
- On Seizure Free Night :

  (vs non-epileptic controls)
  - IEDs may cause sleep disruption, preventing normal progression though sleep stages

Becker DA, Fennell EB, Carney PR. Sleep disturbance in children with epilepsy. Epilepsy Behav 2003;4(6):651–8.

Effect of epilepsy on sleep
Children with Epilepsy :

- Becker et al reports Changes in
  - TST, sleep latency, and spontaneous arousals
  - more common in children w/generalized seizures > simple or CPS.
  - REM sleep may be decreased by 50% in children with primary generalized tonic-clonic seizures

Becker DA, Fennell EB, Carney PR. Sleep disturbance in children with epilepsy. Epilepsy Behav 2003;4(6):651–8.

Effect of epilepsy on sleep: Patients with seizures

- Reduction in total sleep time (TST)
- Reduction in REM sleep
  - Reduced REM sleep is seen with seizures occurring during the day
  - more so when seizures happen at night during sleep.
- Increased REM sleep, on the other hand, is seen with good seizure control

Vaughn BV, D' Cruz OF. Sleep and epilepsy. Semin Neurol 2004;24(3):301–13
Bazil CW. Sleep and Epilepsy. Semin Neurol 2002;22(3):321–7.

Touchon J, Badly-Moulinier M, Billiard M, Besset A, Cadilhac J. Sleep organization and epilepsy. Epilepsy Res 1991;2(Suppl):73–81.

Effect of epilepsy on sleep
Reasons for Dec. REM Sleep

- Sleep was more disrupted, /frequent awakenings ->less TST, Less REM sleep time.
- Circadian Pattern Changes -> delaying its onset.
- Seizures may also have a direct REM suppressant effect without disruption of circadian rhythms.
- AEDs may alter REM sleep

Bazil CW, Castro LH, Walczak TS. Reduction of rapid eye movement sleep by diurnal and nocturnal seizures in temporal lobe epilepsy. Arch Neurol 2000;57(3):363–8.

Temporal Lobe EMU Data

- 37 EMU Pts at baseline (Sz Free) vs after CPS/GTC
- Daytime seizures-> significant decrease in REM sleep the following night (18 vs. 12% for baseline) w/o significant changes in other sleep stages or in sleep efficiency.
- Night time seizures -> MORE decrease in REM was more pronounced (16 vs. 7%) + increases in stage 1 and decreases in sleep efficiency.

Reduction of rapid eye movement sleep by diurnal and nocturnal seizures in temporal lobe epilepsy.

Bazil CW, Castro LH, Walczak TS. Arch Neurol. 2000 Mar;57(3):363-8.

Sleep before and after temporal lobe epilepsy surgery

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[b] Neurology Unit, University-Hospital S. Maria della Misericordia, Udine, Italy
[c] Neurology department, Laquintinie Hospital, Douala, Yaoundé, Cameroon
[d] Research Unit "Movement Disorders" (URMA), Department of Neurobiology, Institute of Functional Genomics, CNRS UMR5203 – INSERM U661 – UM1, Montpellier, France
[e] Service Neurochirurgie, Hôpital Gui de Chauliac, Montpellier, France

- 11Pts refractory MSTE-> S/P op + seizure free
- Treatment with AEDs was not significantly modified before the second year of follow-up.
- Evaluated before surgery, at 1& 2Y FU
- w/ videoEEG monitoring (24 h/24).
  - interictal epileptiform abnormalities
  - sleep macrostructure

Hypnogram Preop/1y/2y

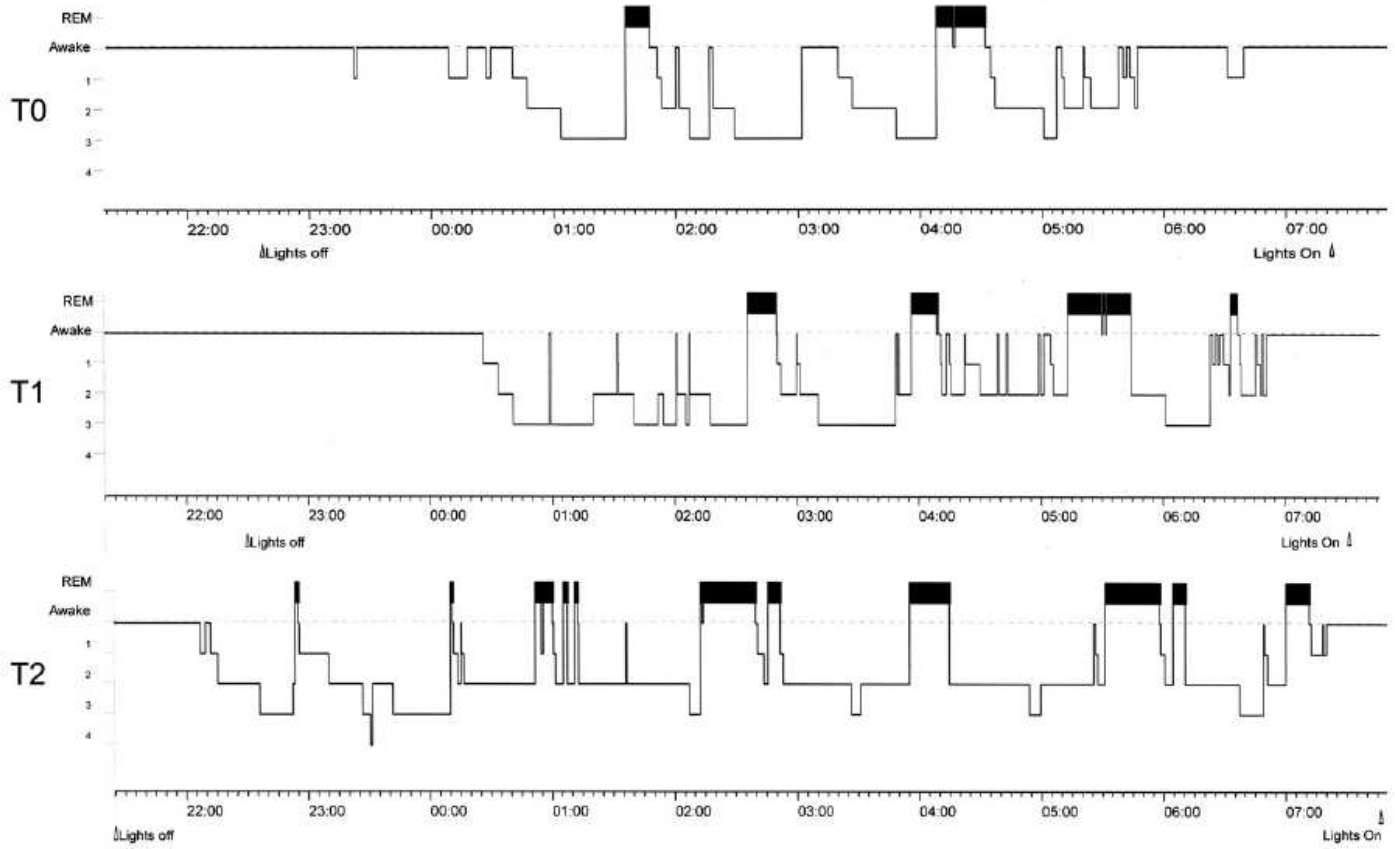


Fig. 1. Three hypnograms from the same patient can be observed. T0: hypnogram of the presurgical night. It is characterized by frequent awakenings, a short total sleep time and a low percentage of REM sleep. T1: hypnogram of the night obtained 1 year after surgery. When compared to the figure on top a longer duration of sleep and of REM sleep can be observed. T2: hypnogram from the night obtained at the second year of follow up. Sleep appears more organized with a longer duration, fewer awakenings and more REM sleep.

Variation of Sleep Stages Preop/1y/2y

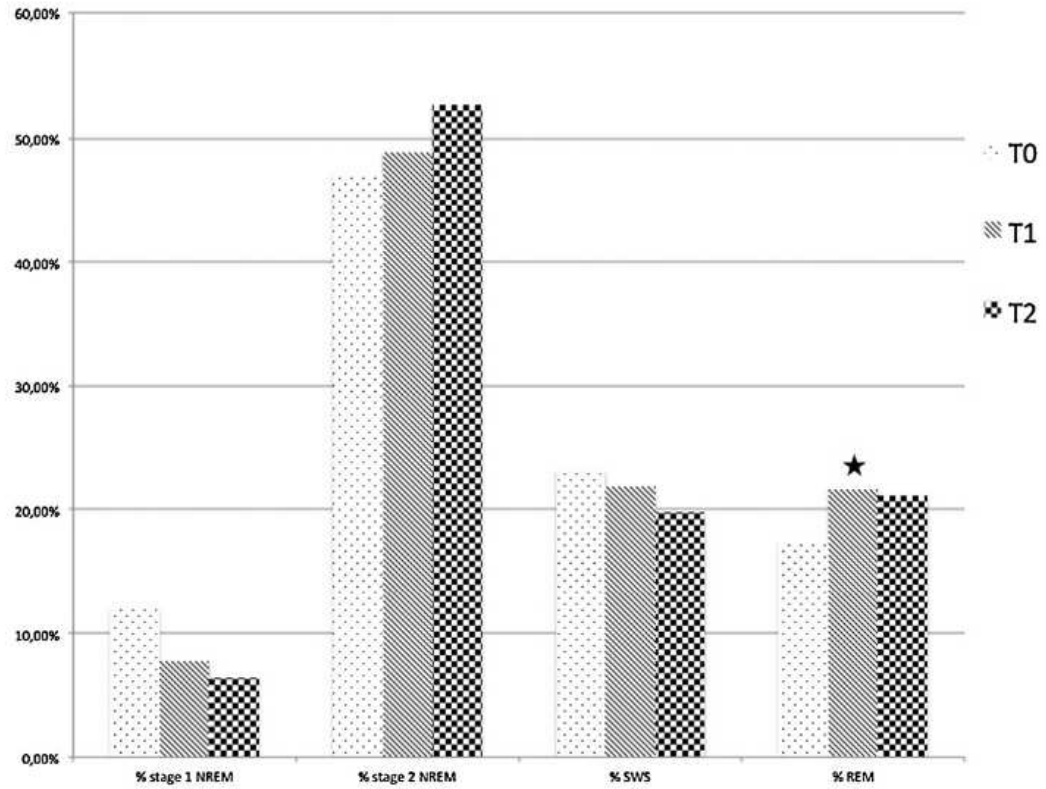


Fig. 2. Variations of percentages of sleep stages at T0 (pre-surgical), T1 (1 year after surgery) and T2 (2 years after surgery). ★Indicates statistically significant difference ($p < 0.05$).

Results & Conclusions

- Reduction of their IEAs.
- At 1-year follow-up,
  - TST & REM sleep increased (p = 0.032 and p = 0.006, respectively).
  - Most significant variations were noted 1 year after surgery.
- At 2-year follow-up,
  - Increase of REM sleep (p = 0.028).
  - No significant variations were observed between the first and the second year after surgery.
- Conclusions: Temporal lobectomy ->
  - Improve sleep macrostructure by reducing the number of seizures and of IEAs.
  - Indirectly confirm the role of epilepsy in disrupting sleep organization chronically.

Effect of Sleep on Epilepsy

1) Relationship of the sleep-wake state to epilepsy and inter-ictal epileptiform discharges (IEDs)
2) Effect of sleep deprivation on epilepsy and IEDs
3) Mechanisms influencing sleep and epilepsy

Mechanisms influencing sleep and epilepsy

- NREM sleep -> "synchronization of the brainstem RAS, thalamus,and cortex."
- "Deepening of NREM sleep"
  - ->Less Ach effect ->progressive hyperpolarization of thalamo-cortical neurons.
  - **Changing hyperpolarization level may facilitate IEDs and seizures.**
  - -> Inc. Sz & IEDs
- Maximally facilitatory depends on
  - age, epilepsy syndromes, and specific seizure subtypes and IEDs.

Steriade M, Conteras D, Amzica F. Synchronized sleep oscillations and their paroxysmal developments. Trends Neurosci 1994;17(5):199–208.

Mechanisms influencing sleep and epilepsy

- **"Brain-activated behavioral stages"**
  - REM sleep and wakefulness
  - EEG-desynchronization
- REM
  - inhibition of thalamocortical synchronizing mechanisms
    - ->desynchronized EEG pattern
    - ->inhibition of spread of epileptiform discharges,
  - skeletal muscle paralysis.

Shouse MN, Siegel JM, Wu MF Szymusiak R, Morrison AR. Mechanisms of seizure suppression during rapid-eye movement sleep in cats. Brain Res 1989;505(2):271–82.

Steriades M, Conteras D, Amzica F. Synchronized sleep oscillations and their paroxysmal developments. Trends Neurosci 1994;17(5):199–208.

Mechanisms influencing sleep and epilepsy

- Epileptic Pts-> Sz/IED susceptible to sleep stage transitions.
  - OSA ->fragment sleep ->worsening seizure frequency
  - Rx->improve seizure control.
  - AEDs may have indirect effects via stabilization of sleep and reduction of sleep transitions .

Wirrell EC. Benign epilepsy of childhood with centrotemporal spikes. Epilepsia 1998;39(Suppl 4):S32–4.

Bazil CW. Nocturnal seizures. Semin Neurol 2004;24(3):293–300.

Malow BA, Fromes GA, Aldrich MS. Usefulness of polysomnography in epilepsy patients. Neurology 1997;48(5):1389–94.

Ferrillo F, Beelke M, Nobili L. Sleep EEG synchronization mechanisms and activation of interictal epileptic spikes. Clin Neurophysiol 2000;111(Suppl 2):S65–73.

Devinsky O, Ehrenberg B, Barthlen GM, Abramson HS, Luciano D. Epilepsy and sleep apnea syndrome. Neurology 1994;44(11):2060–4.

Mechanisms influencing sleep and epilepsy

- **Arousals** =Tx "**Deep-Lighter-Deep sleep**"
  - "On the descent back to the deeper levels of sleep, seizures are more likely to occur"
  - **Changing hyperpolarization level may facilitate IEDs and seizures.**

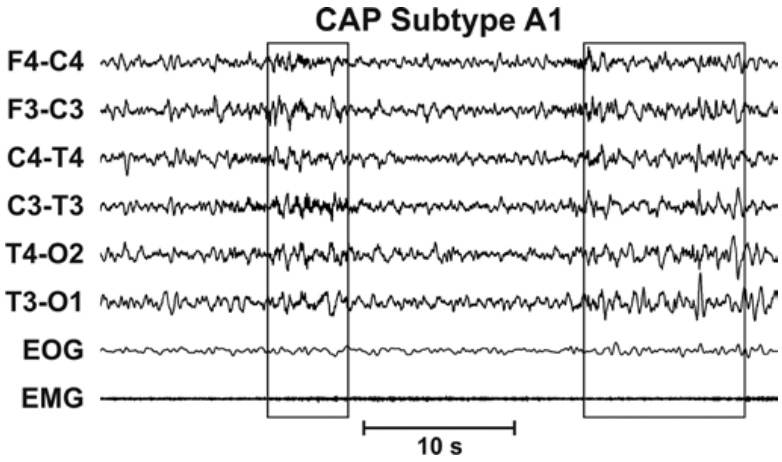
Touchon J, Badly-Moulinier M, Billiard M, Besset A, Cadilhac J. Sleep organization and epilepsy. In: Degen R, Rodin E, editors. Epilepsy, sleep and sleep deprivation. New York: Elsevier; 1991. p. 73–81.

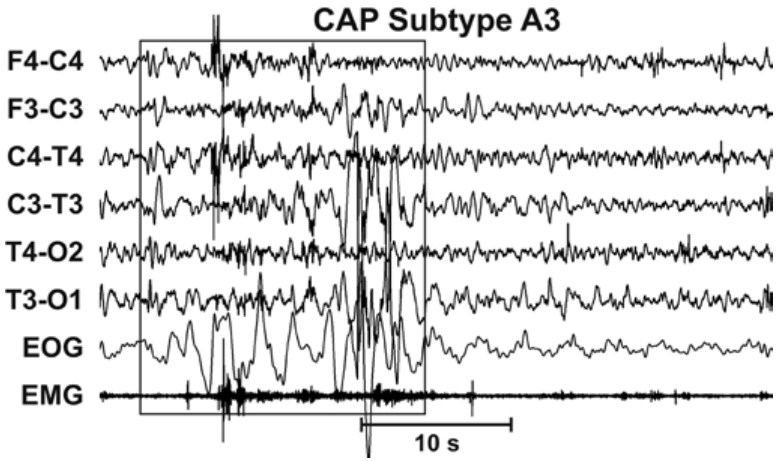
Mechanisms influencing sleep and epilepsy

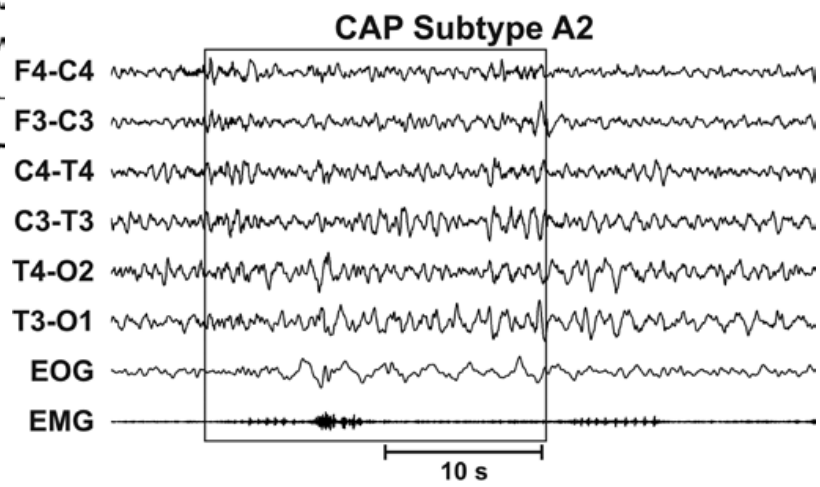
- Touchon et al :
  - "patients with epilepsy->**less sleep continuity + more sleep fragmentation" even W/O seizures!"**
- Miano et al :
  - "seizures tend to occur more in sleep during cyclical alternating patterns (CAP), a pattern commonly seen with sleep fragmentation".

Touchon J, Badly-Moulinier M, Billiard M, Besset A, Cadilhac J. Sleep organization and epilepsy. In: Degen R, Rodin E, editors. Epilepsy, sleep and sleep deprivation. New York: Elsevier; 1991. p. 73–81.

Miano S, PiaVilla M, Blanco D, Zamora E, Rodriguez R, Ferri R, et al. Development of NREM sleep instability-continuity (cyclic alternating pattern) in healthy term infants aged 1 to 4 months. Sleep 2009;32(1):83–90.





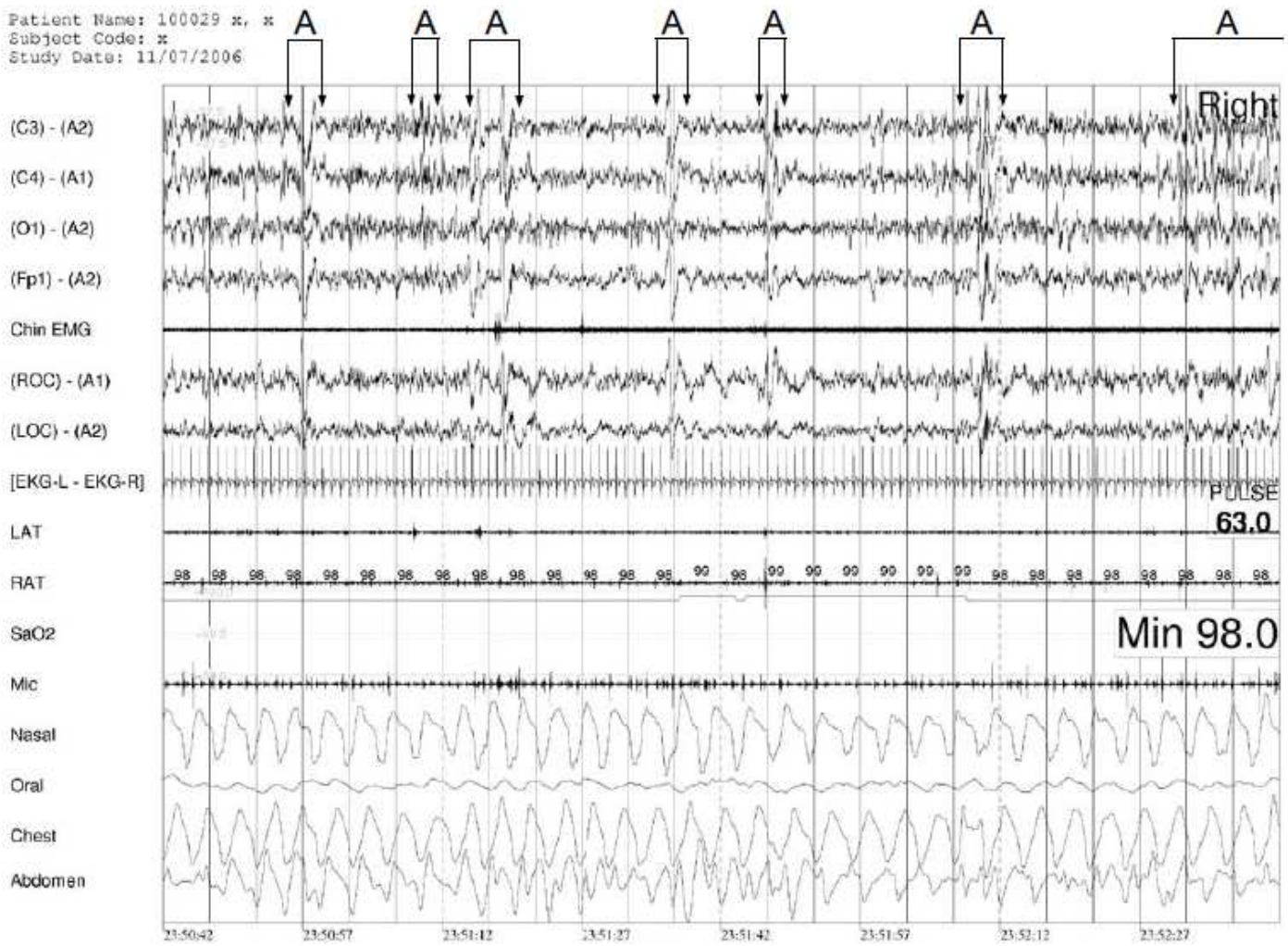


DEVELOPMENT OF CAP IN INFANTS

Development of NREM Sleep Instability-Continuity (Cyclic Alternating Pattern) in Healthy Term Infants Aged 1 to 4 months

Silvia Miano, MD[1]; Maria PiaVilla, MD[1]; Dora Blanco, MD[2]; Elena Zamora, MD[2]; Rosa Rodriguez, MD[3]; Raffaele Ferri, MD[3]; Oliviero Bruni, MD[4]; Rosa Peraita-Adrados, MD[4]

A1—Slow electroencephalographic (EEG) synchrony is the predominant activity, mostly composed by high-voltage delta bursts. Middle panel: CAP Subtype A2—Mixture of slow and fast EEG activities, including bursts of theta rhythms, and other faster rhythms superimposed, associated or not with EMG activation.
Bottom panel: CAP Subtype A3—EEG activity with predominant fast low-voltage rhythms; more than 50% of phase A is occupied by fast EEG activities, including EEG arousals, polyphasic bursts, and high-voltage delta waves with an amplitude one-third higher, or more, than the background activity, followed by theta and other faster rhythms.



The Cyclic Alternating Pattern Demonstrates Increased Sleep Instability and Correlates With Fatigue and Sleepiness in Adults with Upper Airway Resistance Syndrome

Christian Guilleminault, MD, BioID; M. Cecilia Lopes, MD, PhD; Chad C. Hagen, MD; Agostinho da Rosa, PhD

Mechanisms influencing sleep and epilepsy

- GABA
- Adenosine
- Melatonin in High/Low dose
- Dec. CSF hypocretin-1

Mechanisms influencing sleep and epilepsy

- How sleep/sleep deprivation activate seizures is unclear
  - GABA modulation
  - Offset of adenosine with sleep onset

Jones BE. Glia, adenosine, and sleep. Neuron 2009;61(2):156–7.

Offset of adenosine with sleep onset

- Adenosine (AD) =/= caffeine,(AD receptor antagonist).
- AD antagonists increase waking and decrease sleep EEG slow wave activity in humans and rodents
- AD/AD analogs increase sleep and enhance slow wave activity -> an endogenous sleep promoting substance & "Antiepileptic"
- Adenosine is regulated by astrocyte with adenosine kinase (ADK), hence it is "pro-epileptogenic agent"
- **Adenosine acts as an anti-epileptogenic agent, while ADK acts as a pro-epileptogenic agent.**

Offset of adenosine with sleep onset

- Adenosine levels rise in the brain after prolonged wakefulness
- @ transition wake->sleep, Inc. ADK levels, with lowered seizure threshold.
- **ADK hypothesis of epileptogenesis**; astorgliosis in the hippocampus -> up-regulation of ADK activity→associated with epilepsy
- ? therapeutic Sz Rx w/ adenosine agonists or ADK antagonists.

Boison D, Stewart KA. Therapeutic epilepsy research: From pharmacological rationale to focal adenosine augmentation. Biochem Pharmacol 2009;78(12):1428–37.

Mechanisms influencing sleep and epilepsy

- Stewarts et al: Melatonin enhances hippocampal excitability ->pro-convulsant at high doses
- Munos->anti-epileptic properties in lower doses .
- Conflicting reports on seizure control when prescribing melatonin for people with epilepsy.
-

Sheldon SH. Pro-convulsant effects of melatonin in neurologically disabled children. Lancet 1998;351(9111):1254.

Jan JE, Hamilton D, Seward N, et al. Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. J Pineal Res 2000;29:34–9.

Peled N, Shorer Z, Peled E, Pillar G. Melatonin effect on seizures in children with severe neurologic deficit disorders. Epilepsia 2001;42(9):1208–12.

Rejdak K, Papuć E, Grieb P, Stelmasiak Z. Decreased cerebrospinal fluid hypocretin-1 (orexin A) in patients after repetitive generalized tonic-clonic seizures. Epilepsia 2009;50(6):1641–4.

Muñoz-Hoyos A, Sánchez-Forte M, Molina-Carballo A, Escames G, Martin-Medina E, Reiter RJ, et al. Melatonin's role as an anticonvulsant and neuronal protector: experimental and clinical evidence. J Child Neurol 1998;13(10):501–9.

Yildirim M, Marangoz C. Anticonvulsant effects of melatonin on penicillin-induced epileptiform activity in rats. Brain Res 2006;1099(1):183–8.

Stewart LS, Leung LS. Hippocampal melatonin receptors modulate seizure threshold. Epilepsia 2005;46(4):473–80.

Mechanisms influencing sleep and epilepsy

- Rejdak et al:
- Ramelteon, a selective **melatonin receptor agonist,**
- evaluated in two animal models of epilepsy,
- it possesses **anticonvulsant properties in a chronic epilepsy model**

Rejdak K, Papuć E, Grieb P, Stelmasiak Z. Decreased cerebrospinal fluid hypocretin-1 (orexin A) in patients after repetitive generalized tonic-clonic seizures. Epilepsia 2009;50(6):1641–4.

Mechanisms influencing sleep and epilepsy

- **Dec. CSF hypocretin-1** in pts w/repetitive GTC seizures or status epilepticus
  - hypocretin-1 deficiency may contribute to the typical somnolence after generalized tonic/clonic seizures.
  - The exact mechanism of is unclear

Rejdak K, Papuć E, Grieb P, Stelmasiak Z. Decreased cerebrospinal fluid hypocretin-1 (orexin A) in patients after repetitive generalized tonic-clonic seizures. Epilepsia 2009;50(6):1641–4.

Etiology/Result of sleep disruption in epilepsy

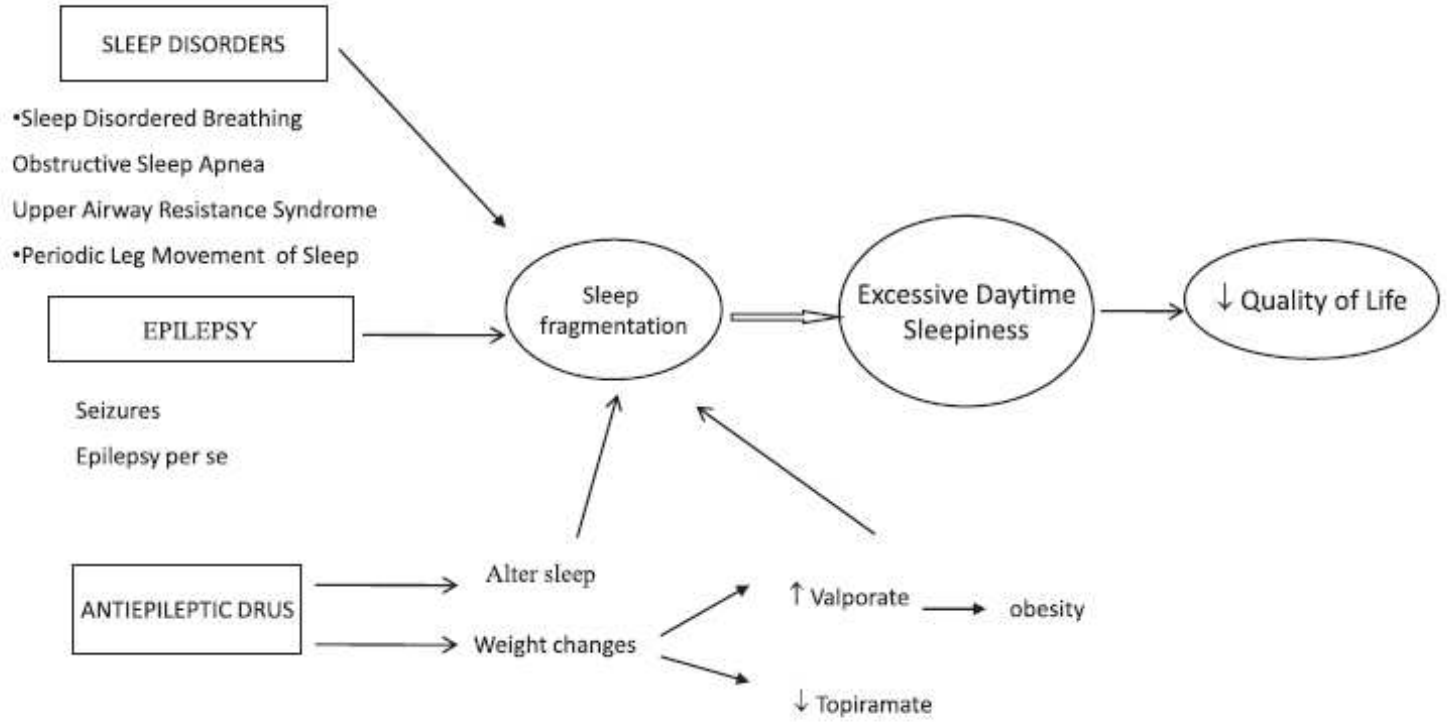


Fig. 2. Etiology of sleep disruption in children with epilepsy.

Effects of anti-epileptic drugs on sleep complaints and sleep architecture

Drug	Sleep complaint	Sleep efficiency	TST	SL	Arousals	% Stage 1	% Stage 2	% SWS	% REM
Carbamazepine	S	↑	0	↓	↓	0	0	↑	↓/0
Ethosuximide	I	↓	?	?	↑	↑	0	↓	↑
Gabapentin	S	↑	↑	?	↓	↓	0	↑	↑
Lamotrigine	I	0	0	0	0	0	0	?	↑
Levetiracetam	S	0	0	0	0	0	↑	↓	0
Phenobarbital	S	↓	0	↓	↓	↑	↑	0	↓
Phenytoin	S	↓	0	↓	↓	↑	↑	↓	0
Tiagabin	I	?	?	?	?	?	?	?	?
Topiramate	S	?	?	?	?	?	?	?	?
Valproate	S	0	0	0	↑	↓	0	↑	↓
Vigabatrin	S	?	?	0	?	?	?	?	?
Zonisamide	I	?	?	?	?	?	?	?	?

TST = total sleep time; SL = sleep latency; SWS = slow wave sleep; REM = rapid eye movement; S = sleepiness; I = insomnia; ↑ = increase; ↓ = decrease; 0 = no change ? = unknown.

Sleep and epilepsy in children and adolescents

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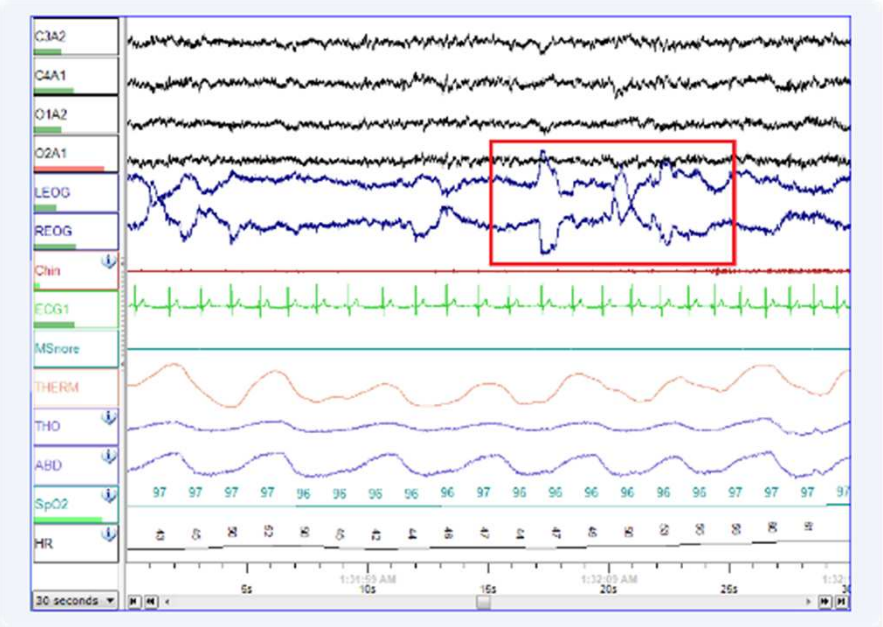
ABSTRACT

Epilepsy and sleep disorders are considered by many to be common bedfellows. Several sleep phenomena may occur during nighttime taking a wide variety of forms and which can mimic seizures. Although most seizure sub-types have the potential to occur during sleep or wakefulness, sleep has a well-documented and strong association with specific epilepsy syndromes. Seizures in sleep also tend to occur during lighter stages of non-REM (NREM) sleep. The neurophysiologic process involved in the deepening of NREM sleep may also facilitate both seizures and IEDs. Epilepsy per se and/or seizures themselves promote sleep disruption and significantly affect the quality, quantity, and architecture of sleep. There are many causes of sleep disruption in patients with epilepsy, including inadequate sleep hygiene, coexisting sleep disorders, and circadian rhythm disturbances. Seizures themselves can disrupt sleep, even when they occur during wakefulness. Anti-epileptic drugs (AEDs) can also alter sleep in positive and negative ways, and these effects are independent of anticonvulsant actions. The end result of sleep disruption is excessive daytime sleepiness, worsening seizures, and poor quality of life. Screening for sleep disorders in the epilepsy population and appropriate intervention strategies will lead to overall improved quality of life and seizure control.

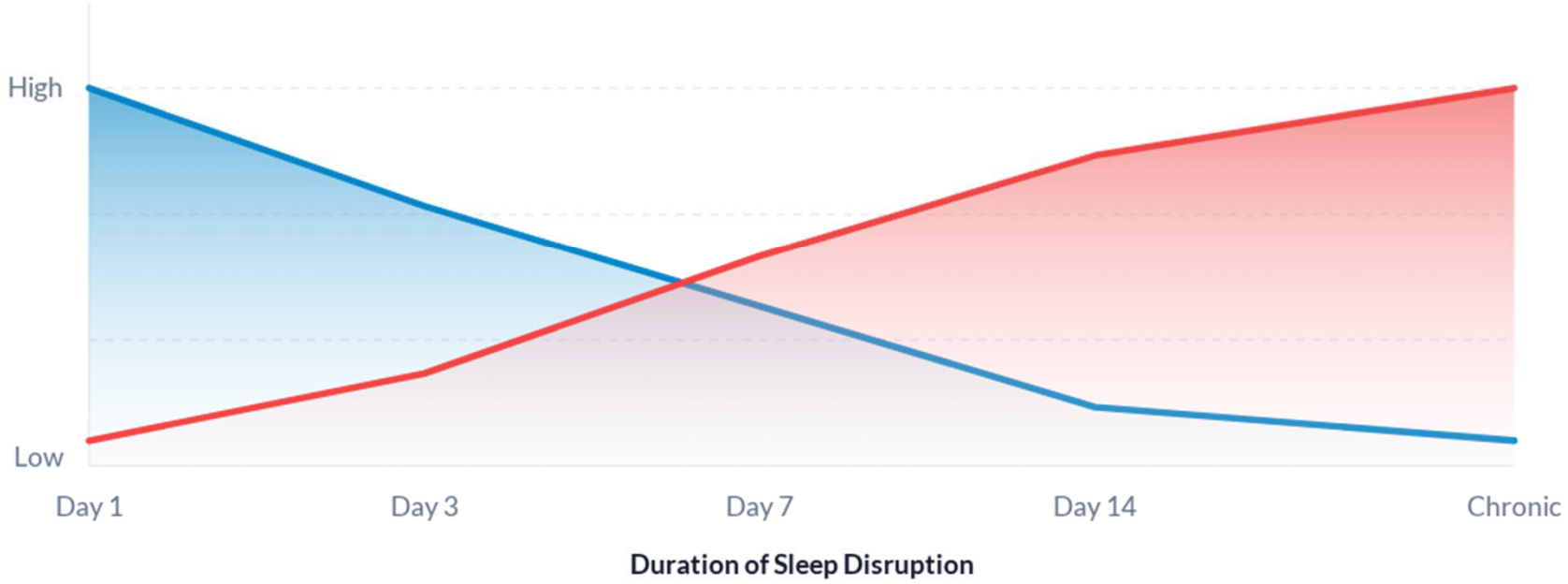
Adults: Impact of Epilepsy on Sleep Architecture

- **High Prevalence of Poor Sleep:** Adults with epilepsy report a significantly high prevalence of poor sleep quality, often quantified by the Pittsburgh Sleep Quality Index.
- **Objective Disruption via PSG:** Polysomnography reveals frequent nighttime arousals directly correlated with epileptiform discharges and nocturnal seizures.
- **Sleep Fragmentation:** These disruptions prevent patients from reaching restorative slow-wave and REM sleep, severely degrading sleep architecture.
- **Clinical Manifestation:** Leads to highly prevalent chronic insomnia and excessive daytime sleepiness (EDS).



Ref: Sivathamboo et al. (2023). Sleep and respiratory abnormalities in adults with developmental and epileptic encephalopathies using polysomnography and video-EEG monitoring. Epilepsia Open.

Adults: Provocative Effect of Sleep Deprivation



Mechanistic Link: *Chronic sleep deprivation induces neuroinflammation (**Red**), which synergizes with existing epileptic networks to lower the seizure threshold (**Blue**), worsening neurological outcomes.*

Ref: Bonilla-Jaime et al. (2021). Sleep Disruption Worsens Seizures: Neuroinflammation as a Potential Mechanistic Link. Int J Mol Sci.

The Role of Obstructive Sleep Apnea (OSA) in Adults

Pathophysiological Synergy

OSA and epilepsy are highly comorbid in the adult population.

Recurrent upper airway collapse causes intermittent hypoxia (oxygen deprivation) and hypercapnia.
These periodic respiratory events independently decrease the seizure threshold and can trigger nocturnal or daytime seizures.

Therapeutic Intervention

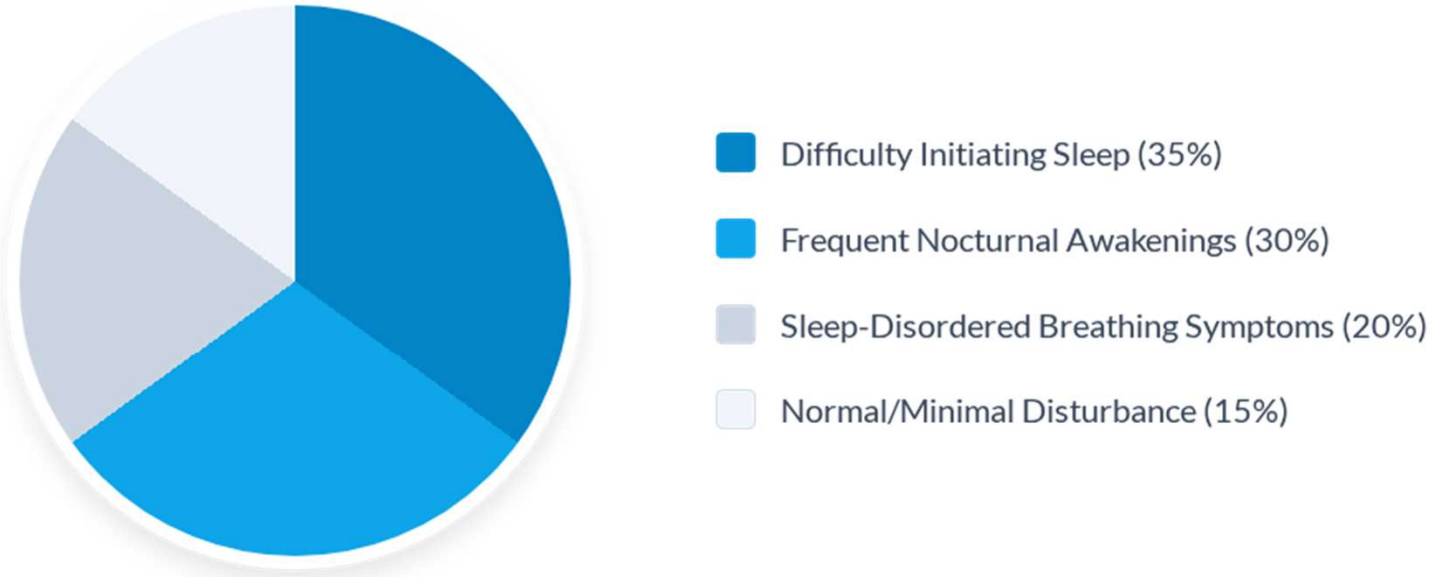
OSA is a critical, **reversible driver** of epilepsy severity.

Treating OSA with Continuous Positive Airway Pressure (CPAP) has been shown to frequently improve seizure control, especially in patients with drug-resistant epilepsy (DRE).

Screening for OSA in adult epilepsy clinics is strongly recommended.

Ref: Ma & Wu (2023). Intermittent hypoxia: linkage between OSAS and epilepsy. Frontiers in Pharmacology.
Sivathamboo et al. (2023). Sleep and respiratory abnormalities in adults... Epilepsia Open.

Pediatric Profiles: Early-Life Epilepsies & Sleep



Conceptual representation based on Gupta et al. In severe developmental encephalopathies, pervasive sleep difficulties significantly disrupt circadian rhythms, with daytime sleepiness exceeding that of typically developing peers.

Ref: Gupta et al. (2022). Parent-Reported Sleep Profile of Children With Early-Life Epilepsies. Pediatric Neurology.
Bricker & Vaughn (2024). Rett syndrome: a review... Frontiers in Sleep.

Pediatrics: Sleep Deprivation & Seizure Provocation

- **Seizure Provocation:** Similar to adults, sleep deprivation and fragmentation are major provocateurs of seizures in children, further destabilizing developing neural networks.
- **Cognitive Impact:** The dual burden of frequent epileptiform discharges during sleep (e.g., CSWS) and disrupted sleep architecture severely impairs daytime cognition, memory consolidation, and behavior.
- **Therapeutic Target:** Interventions that successfully diagnose and treat pediatric sleep disorders can decrease both the frequency and severity of seizures.
- **Clinical Imperative:** Active, rigorous sleep management must be integrated into standard pediatric neurology care, rather than treated as a secondary symptom.

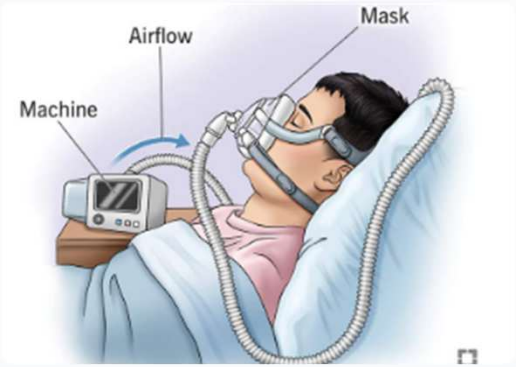
Ref: Gupta et al. (2022). Parent-Reported Sleep Profile of Children With Early-Life Epilepsies. Pediatric Neurology.

OSA in Epilepsy: Adult vs. Pediatric Nuances

Parameter	Adult Epilepsy Patients	Pediatric Epilepsy Patients
Primary Etiology	Obesity, upper airway anatomy, loss of muscle tone.	Adenotonsillar hypertrophy (peaks in early childhood).
Cortical Arousal Threshold	Lower; airway obstruction frequently fragments sleep.	**Higher**; sleep architecture may be better preserved despite obstruction.
Prevalence vs. Controls	Statistically higher prevalence and severity of OSA.	Parents report higher symptoms, but PSG studies suggest actual OSA prevalence may not be statistically higher than healthy controls.
Treatment Approach	CPAP is primary; highly effective for seizure control.	Adenotonsillectomy is often first-line; CPAP as secondary.

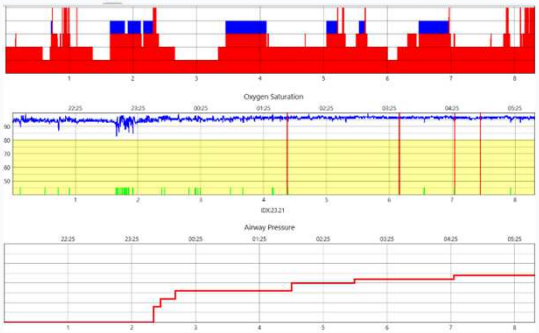
Ref: Chang & Chae (2010). Obstructive sleep apnea syndrome in children. Korean J Pediatr.
Urquhart et al. (2024). A case-control study... OSA in children and young people with epilepsy. JCSM.

Key Clinical Takeaways for Epileptologists



Aggressive OSA Screening

Particularly in adult drug-resistant epilepsy, screening for and treating OSA via CPAP can substantially improve seizure control.



Pediatric PSG/EEG Utilization

Utilize overnight polysomnography with expanded EEG montages to accurately differentiate nocturnal seizures from parasomnias and SDB.

Holistic Neurological Care

Treating insomnia and poor sleep quality is not merely symptomatic relief; it alters the neuroinflammatory environment and raises seizure thresholds.