

SLEEP IN PARKINSON'S DISEASE

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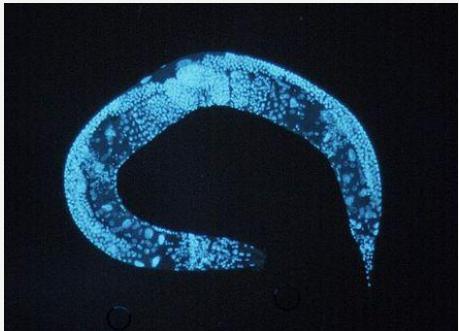
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OVERVIEW

- Why do we sleep
- What are key ideas and features of sleep
- Why to care about sleep
- Case review of sleep disorders in those with Parkinson's disease
 - Sleep Apnea
 - Restless Leg Syndrome
 - REM sleep behavior disorder
 - Insomnia
 - Excessive Sleepiness (hypersomnia)



ALL ANIMALS THAT HAVE BEEN INVESTIGATED HAVE A SLEEP STATE



C. Elegans



Komodo Dragon



Cuckoo Bee



Macaques



Flamingo

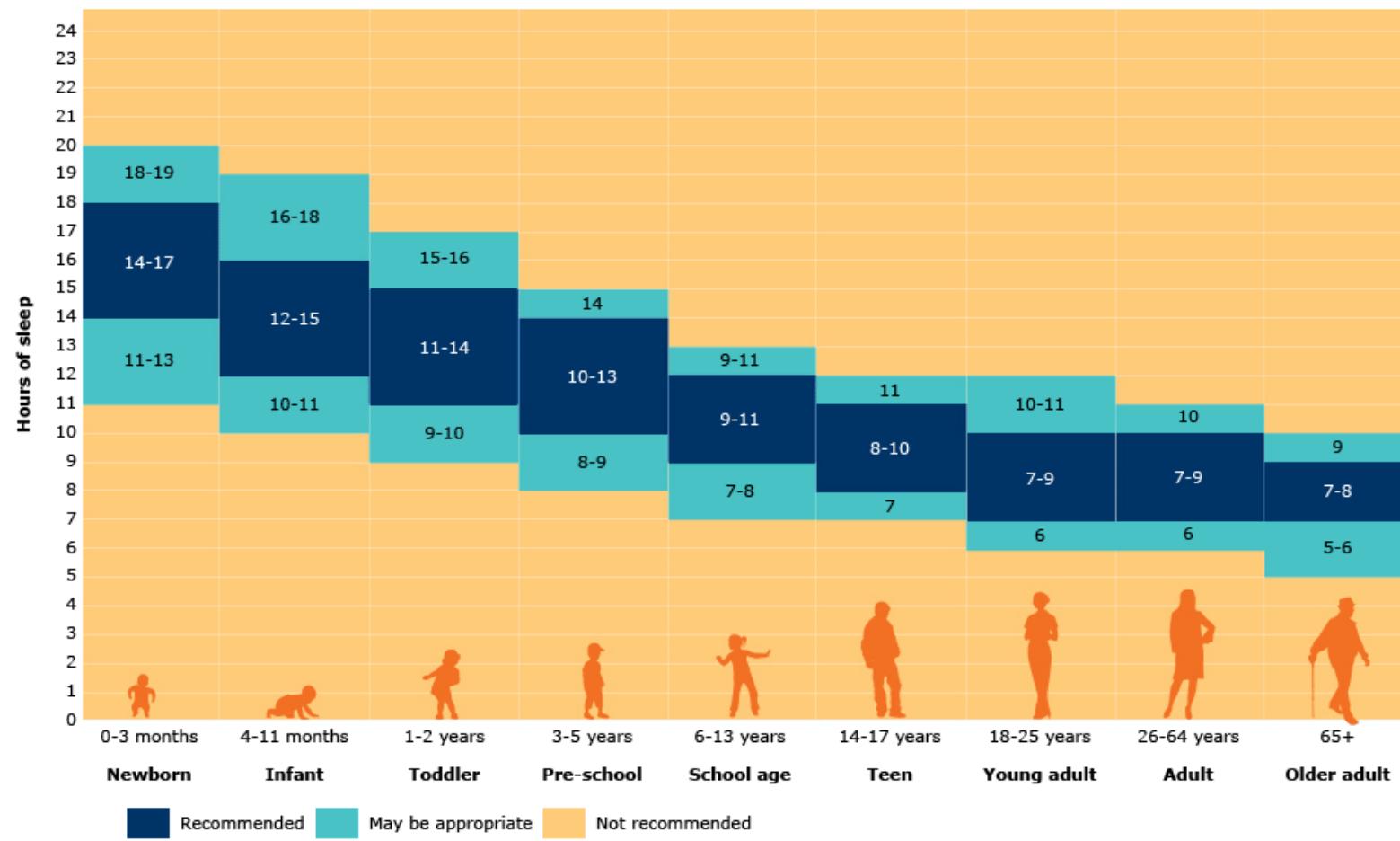


Bats



Seal

Sleep duration recommendations by age from the National Sleep Foundation*

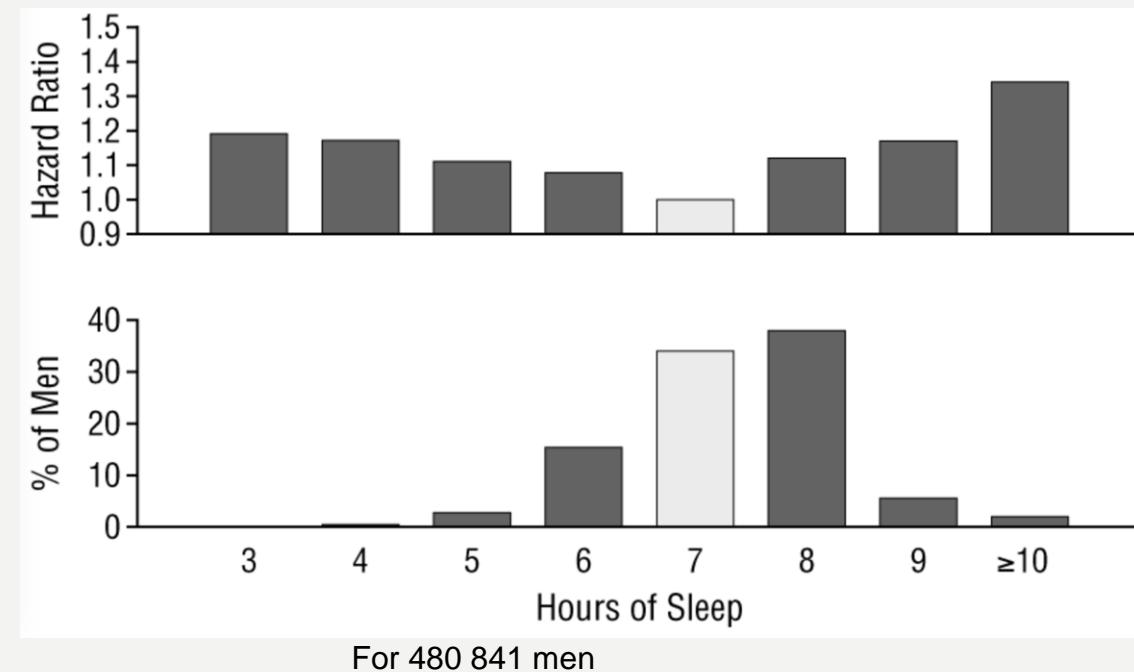
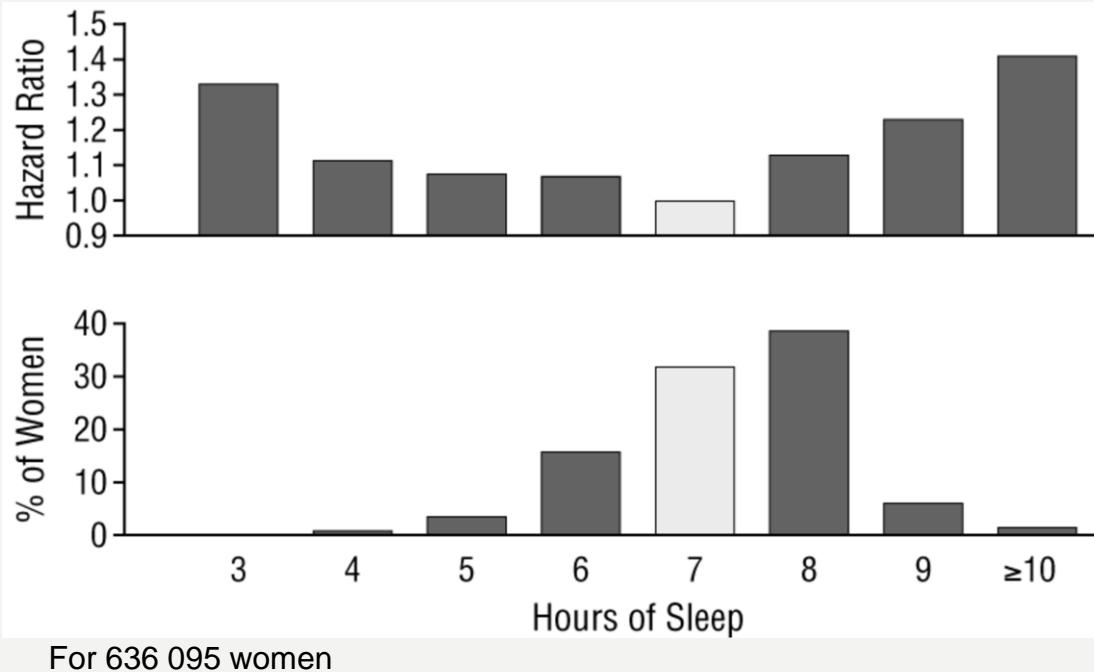


* These recommendations are very similar, but not identical to those from the American Academy of Sleep Medicine (AASM).^[1,2]

1. Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: A statement of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2016; 12:785.
2. Consensus Conference Panel, Watson NF, Badr MS, et al. Recommended amount of sleep for a healthy adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *J Clin Sleep Med* 2015; 11:591.

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U SHAPED SLEEP DURATION CURVE AND MORTALITY

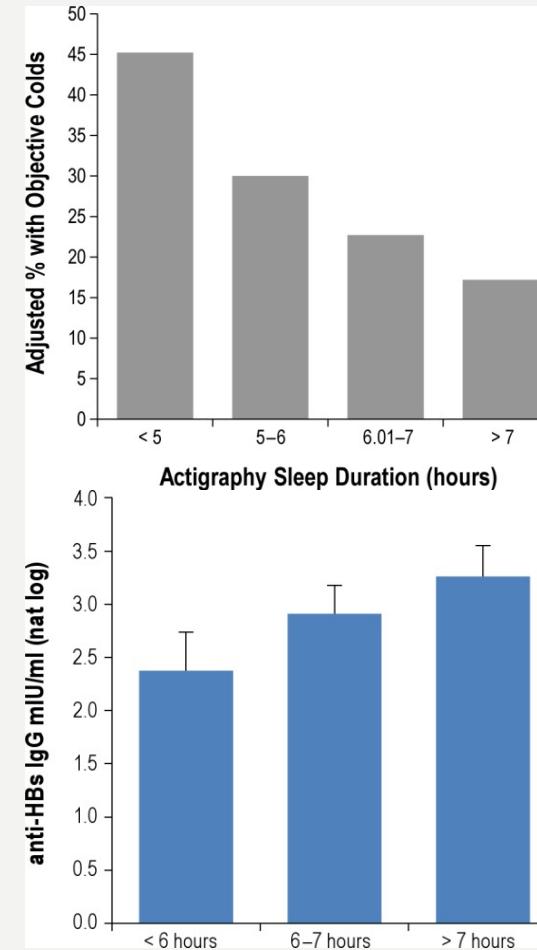


SLEEP DEPRIVATION

- Associated with impaired
 - Glucose tolerance – can lead to diabetes
 - Emotional regulation
 - Impaired attention and memory
 - divergent thinking and originality
 - flexible decision-making
 - increased risk taking
 - Immune function

SLEEP HOURS: IMMUNE FUNCTION

- **Increased risk for colds:** Fewer hours of sleep by sleep diary/actigraphy over seven days prior to exposure to cold virus leads to increased risk of getting a cold (Prather et al, 2015)
- **Reduced response to vaccines:** shorter actigraphy-based sleep duration is associated with a lower secondary antibody response to Hep B vaccine (Prather et al, 2012)



SLEEPINESS AND DRIVING

- Drowsy driving is the cause of
 - 2.5% of fatal motor vehicle crashes (approximately 730 in 2009)
 - 2.0% of all crashes with nonfatal injuries (approximately 30,000 in 2009)
 - Some estimate 15% to 33% of fatal crashes might involve drowsy drivers
- Fatalities and injuries are more likely with drowsy driving
- Among 147,076 respondents in 19 states and DC, 4.2% report having fallen asleep while driving at least one time during the previous 30 days
 - Risk factors for falling asleep while driving:
 - sleeping \leq 6 hours per day
 - Snoring
 - Unintentionally falling asleep during the day

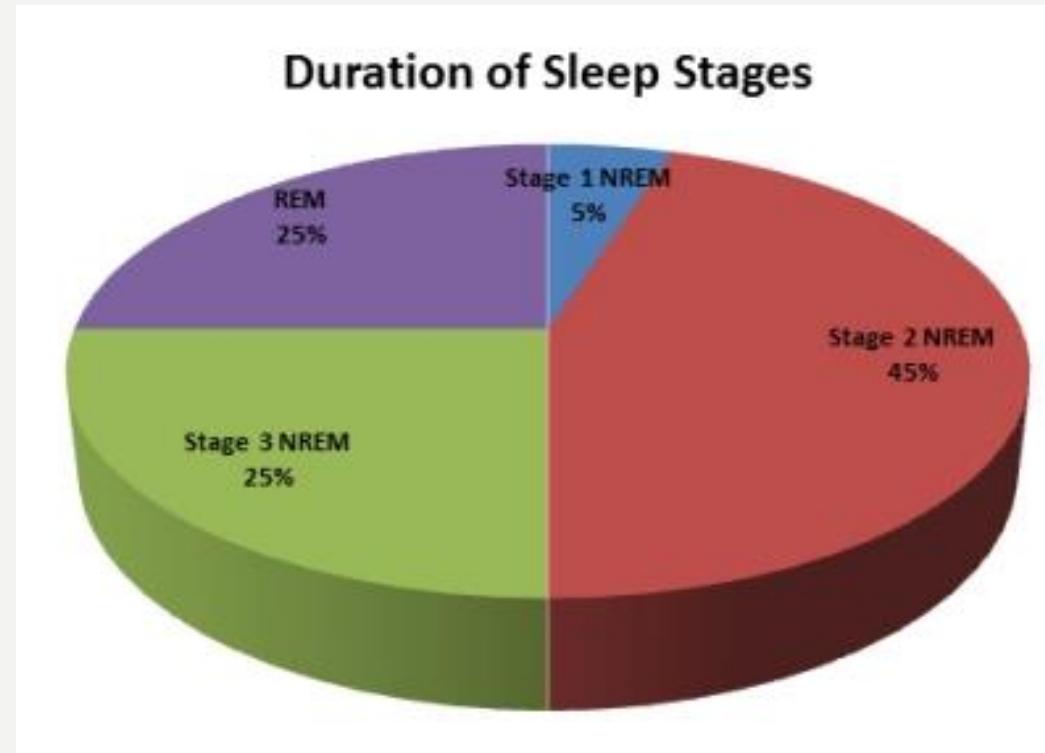
THE FUNCTION OF SLEEP

- To cure sleepiness!

Also

- Memory consolidation and pruning
- Mood and emotional homeostasis – “sleep on it”
- Emerging: glymphatic function by removing toxic byproducts

STAGES OF SLEEP



Awake – low voltage – random, fast



Drowsy – 8 to 12 cps – alpha waves



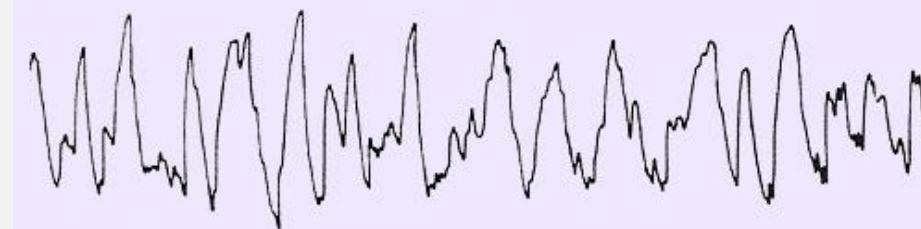
Stage 1 – 3 to 7 cps – theta waves



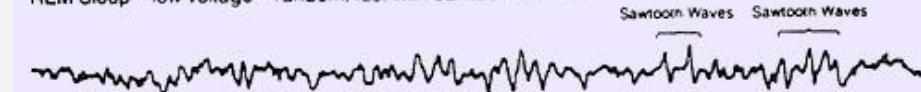
Stage 2 – 12 to 14 cps – sleep spindles and K complexes



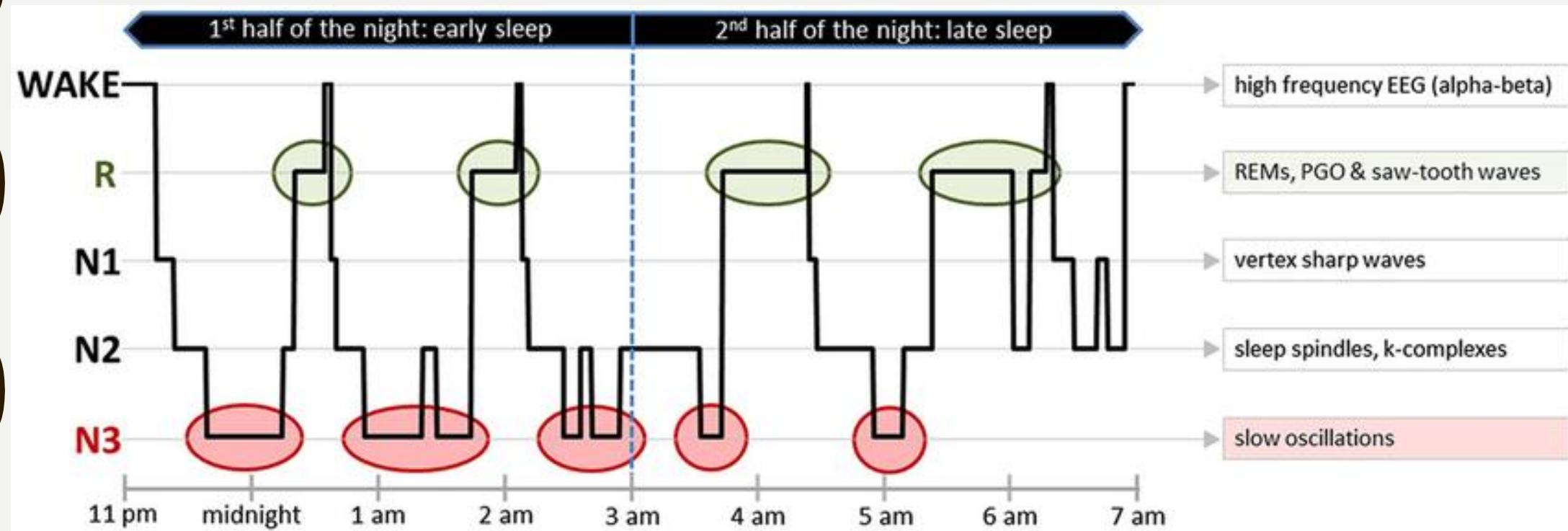
Delta Sleep – ½ to 2 cps – delta waves > 75 μ V



REM Sleep – low voltage – random, fast with sawtooth waves

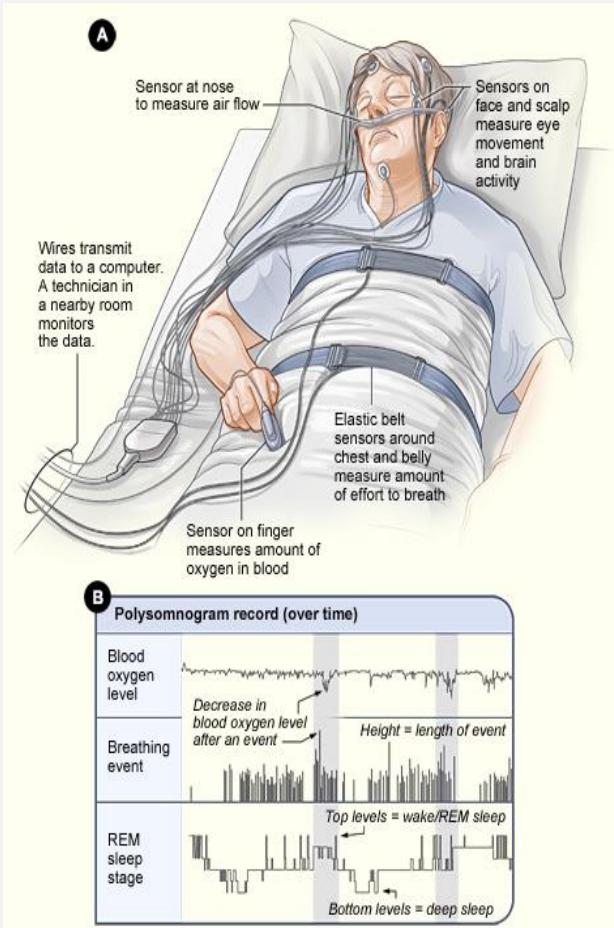


THE CYCLES OF SLEEP

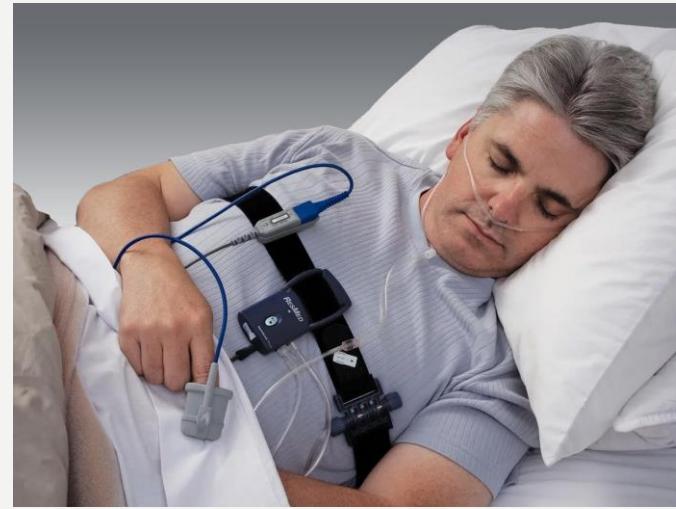


HOW IS SLEEP STUDIED?

Polysomnography (PSG)

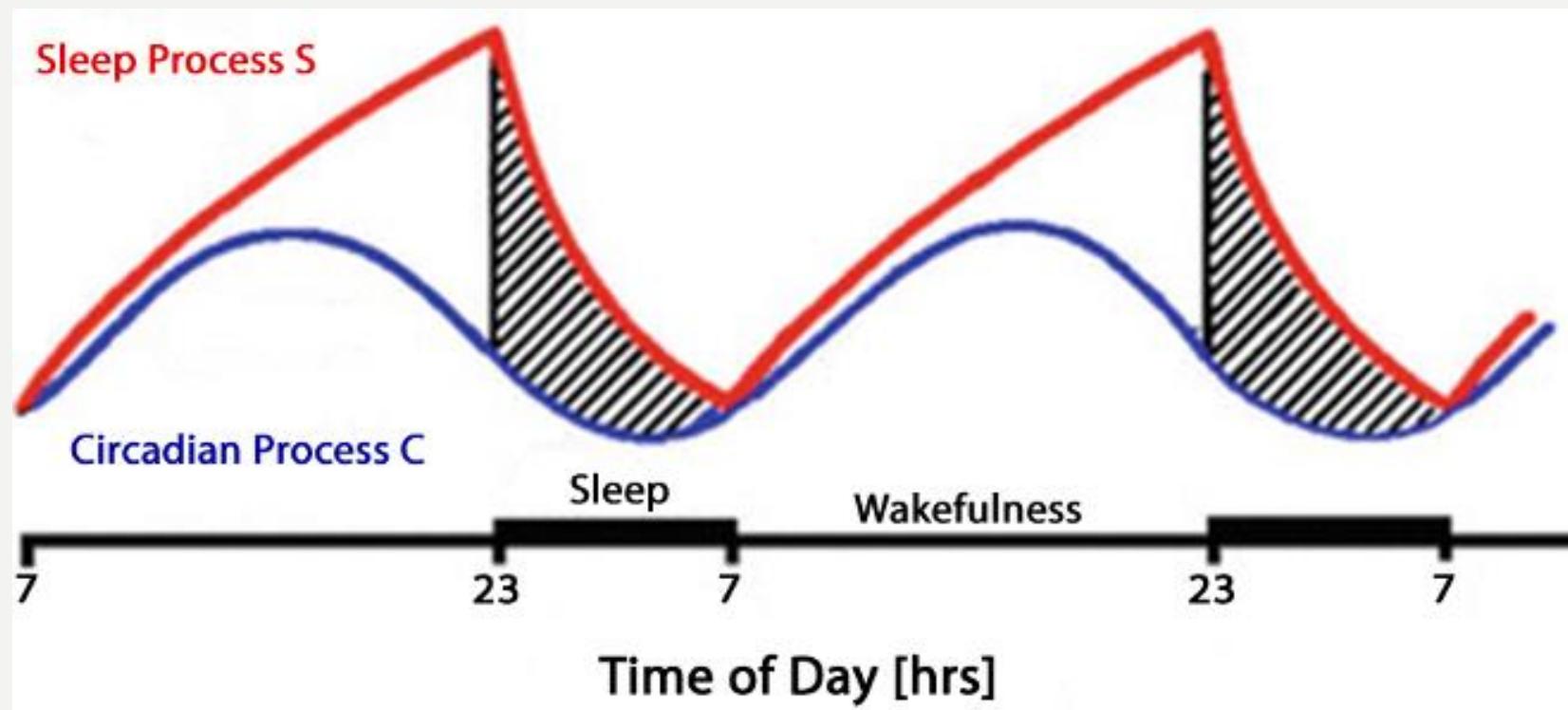


Home sleep test



WHAT MAKES YOU SLEEPY AT ONLY CERTAIN TIMES OF DAY?

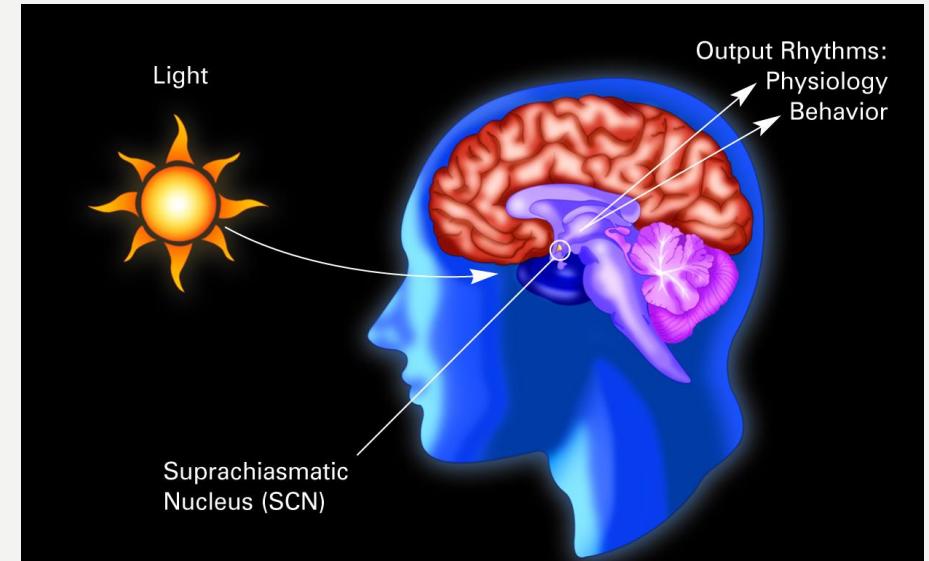
- Circadian forces = Process C
- Sleep homeostatic pressure = Process S



THE CIRCADIAN SYSTEM



- The brain keeps an internal clock of about 24 hours
- This allows the brain to know when it should expect to sleep, eat, and be active
- Suprachiasmatic nucleus (SCN): central time keeper in the brain
- The main input is sunlight
- The SCN send out information to the rest of the body to tell it when to sleep and when to expect to process food or fast overnight



INTRODUCTION: WHY TO CARE ABOUT SLEEP IN PARKINSON'S

- 55 - 80% of patients with Parkinson's complain of sleep trouble
- May be discussed less than motor and other non-motor symptoms
- One of the most bothersome non-motor symptoms of Parkinson's disease
- About 40% of Parkinson's patients take medication for sleep, far greater than the general population

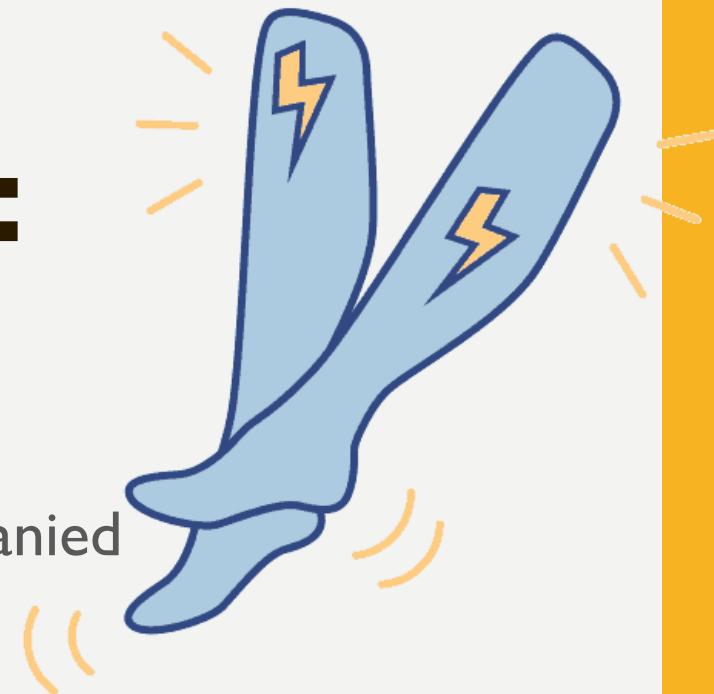


CASE 1

- A 64 year old woman who was diagnosed three years ago with Parkinson's disease reports **trouble falling asleep and staying asleep 1-2 nights per week**
- Since she was a child she has experienced an "**electric shock**" or "**creepy crawly**" sensation in her legs and feel it is **impossible following this to hold her legs still**. When worst she has to get up and it is hard to sleep all night. In the early morning she can finally sleep for three hours

RESTLESS LEG SYNDROME (RLS): WHAT IS IT?

1. An urge to move the legs usually but not always accompanied by uncomfortable/unpleasant sensations in the legs
2. Symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
3. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity
4. Symptoms only occur or are worse in the evening or night than during the day



RESTLESS LEG SYNDROME : ETIOLOGY

- Central iron deficiency
 - Autopsy studies (substantia nigra)
 - Cerebral spinal fluid analysis
 - Brain imaging using gradient echo and transcranial ultrasound
- Significance of iron
 - Iron is a cofactor for tyrosine hydroxylase, the catalyst for the rate limiting step of dopamine synthesis

RESTLESS LEG SYNDROME TREATMENT

- Supplemental Iron
- Avoid triggering medications including:
 - Many antidepressants, antipsychotics, dopamine blocking antiemetics (antinausea medications), antihistamines
- Moderate regular exercise
- Avoid excessive caffeine
- Avoid sleep deprivation
- Hot shower
- Leg massage/pneumatic compression
 - Restifffic
 - Relaxis Pad



RLS MEDICATIONS

Dopamine Agonists

- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro)

Gabapentinoids

- Pregabalin (Lyrica)
- Gabapentin (Neurontin)
- Gabapentin enacarbil (Horizant)

Rarely: iron infusion, opioids such as methadone

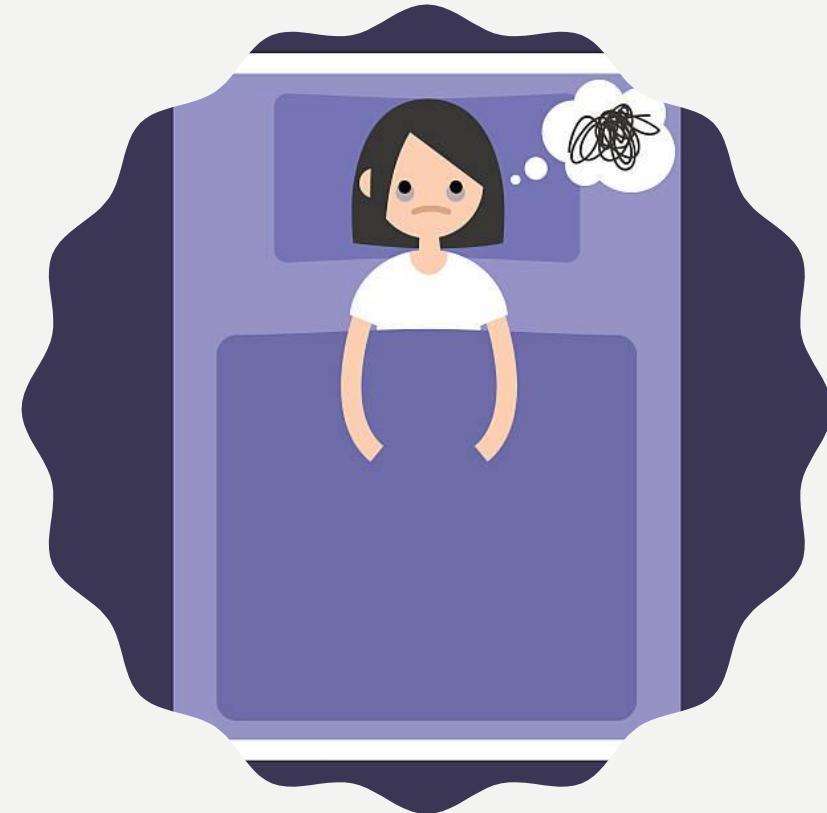


CASE 2

- A 54 year old woman with Parkinson's disease and depression reports since pregnancy 14 years ago she has had trouble falling asleep
- She complains her **right arm and leg feel stiff at night**
- She is thinking about deep brain stimulation (DBS) surgery which is **causing anxiety**
- Bedtime: **variable**
- Sleep latency: one hour
- Awakenings overnight: 1-2 times, may have trouble going back to sleep
- Final awakening: **variable**, 7-9 a.m.
- She may use her **phone** in bed if not sleeping
- She does not snore or report restless leg symptoms

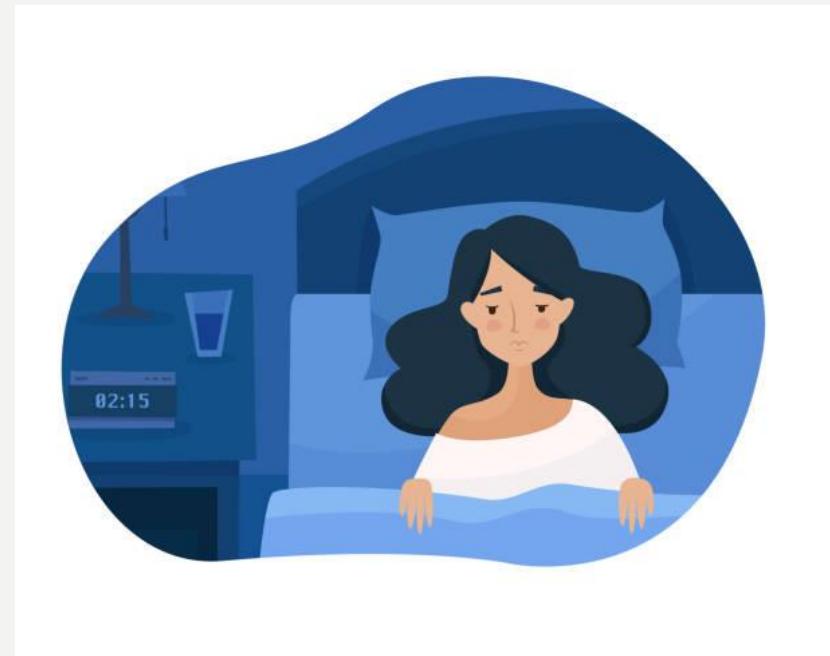
INSOMNIA

- 60% of those with Parkinson's have insomnia
- More likely to occur in females, those with a longer duration of disease, depression or anxiety, memory complaints
- Sleep maintenance insomnia (staying asleep)
 > sleep initiation insomnia (falling asleep)



INSOMNIA – COMMON CAUSES IN PARKINSON'S DISEASE

- dystonia
- Akinesia (internal restlessness)
- restless legs
- painful cramps
- tremor
- difficulty turning in bed
- circadian clock disruption
- Nocturnal urination
- urinary incontinence



INSOMNIA – TREATMENT 1

- **Optimize motor symptoms**
 - Long acting dopaminergic medications such as controlled-release carbidopa/levodopa or rotigotine transdermal patches have been shown to significantly improve subjective sleep quality, onset, and maintenance
 - DBS improves subjective sleep quality
- For **urination** overnight consider medication or botox
- Make sure another sleep disorder such as restless leg, sleep apnea are the the underlying cause of the insomnia

INSOMNIA TREATMENT 2: “SLEEP HYGIENE”

- Avoid practices that hurt sleep: caffeine, alcohol, nicotine
- Create a good sleep environment
 - Keeping the room dark during the sleep period
 - Ensure a quiet sleep environment
 - Keep room cool (65-68 degrees ideal for most people)
- Start practices that help sleep
 - Exercise
 - Bedtime routine
 - Avoiding bright lights in the two hours before sleep



INSOMNIA TREATMENT 3: COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA (CBTI)

- Typically 5 or 6 sessions at 1-2 week intervals
- Consistency in the wake time, no matter what
- Use the bed only for sleep and sex
 - Go to bed only when sleepy
 - Get out of bed if awake
- Cognitive therapy, relaxation/stress reduction techniques to address anxiety around sleep

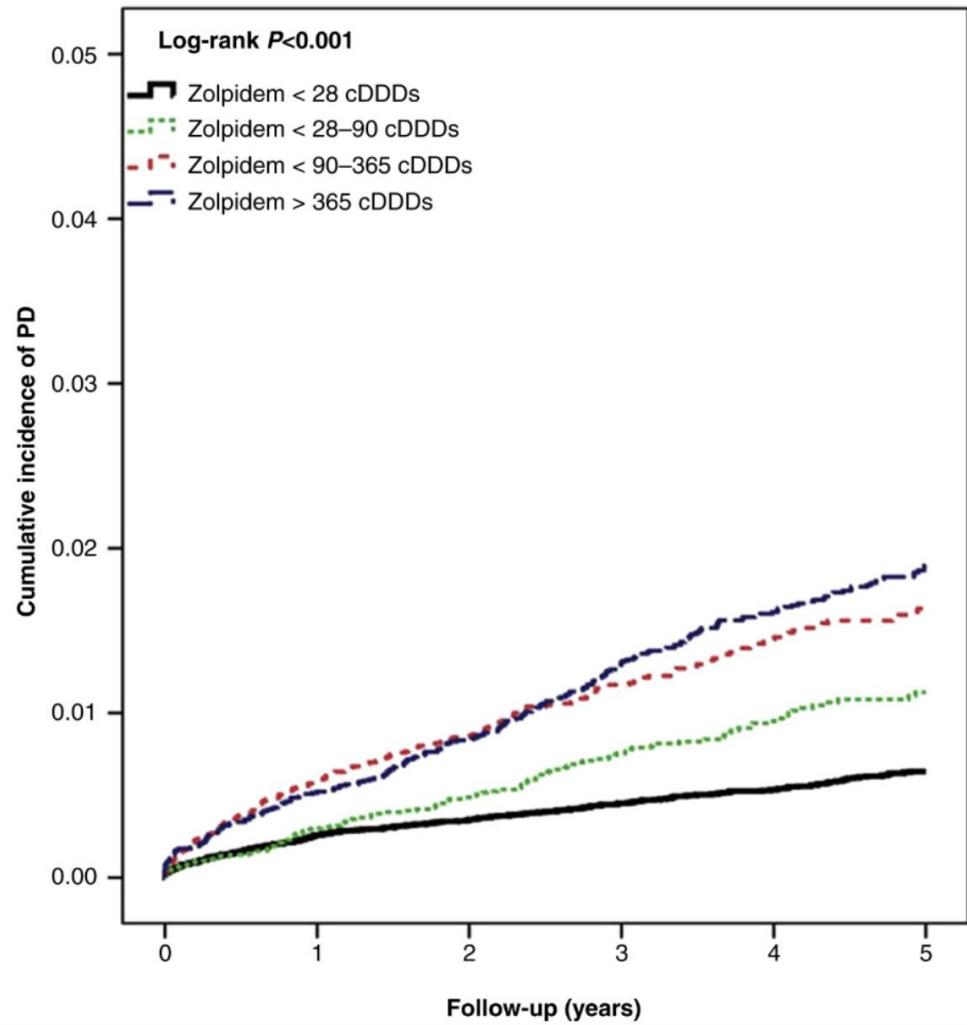


INSOMNIA TREATMENT 4: MEDICATIONS

- Very limited research data
- What has been studied improves patient report on sleep but not numbers on the sleep study
 - Melatonin: may help subjective (patient report) of sleep
 - Doxepin (Silenor): may help subjective (patient report) of sleep
 - Eszopiclone (Lunesta): may help subjective (patient report) of sleep
- Other medications used for insomnia: Ambien, Sonata, Trazodone, Mirtazepine, Suvorexant

RISKS OF SLEEP AID

- Sleep aids are habit forming, sedating, increase fall risk overnight
- Study: Large retrospective cohort study
- Who: 59,548 Taiwanese patients on zolpidem vs 42,171 matched for age, insomnia not on zolpidem
- Outcome:
 - 30–40% increased risk of developing Parkinson's in the group treated with zolpidem when compared to age-matched controls over a 5-year period.
- Causative or is insomnia a marker for future Parkinson's disease?



CASE 3:

- 74 year old man with Parkinson's disease complains of **increased daytime sleepiness**. He now has to take an **afternoon nap** and recently fell asleep at a stop light while driving.
- He does not snore but does report fragmented sleep with frequent awakenings. He does not know what is disturbing his sleep.

PARKINSON'S DISEASE AND SLEEPINESS

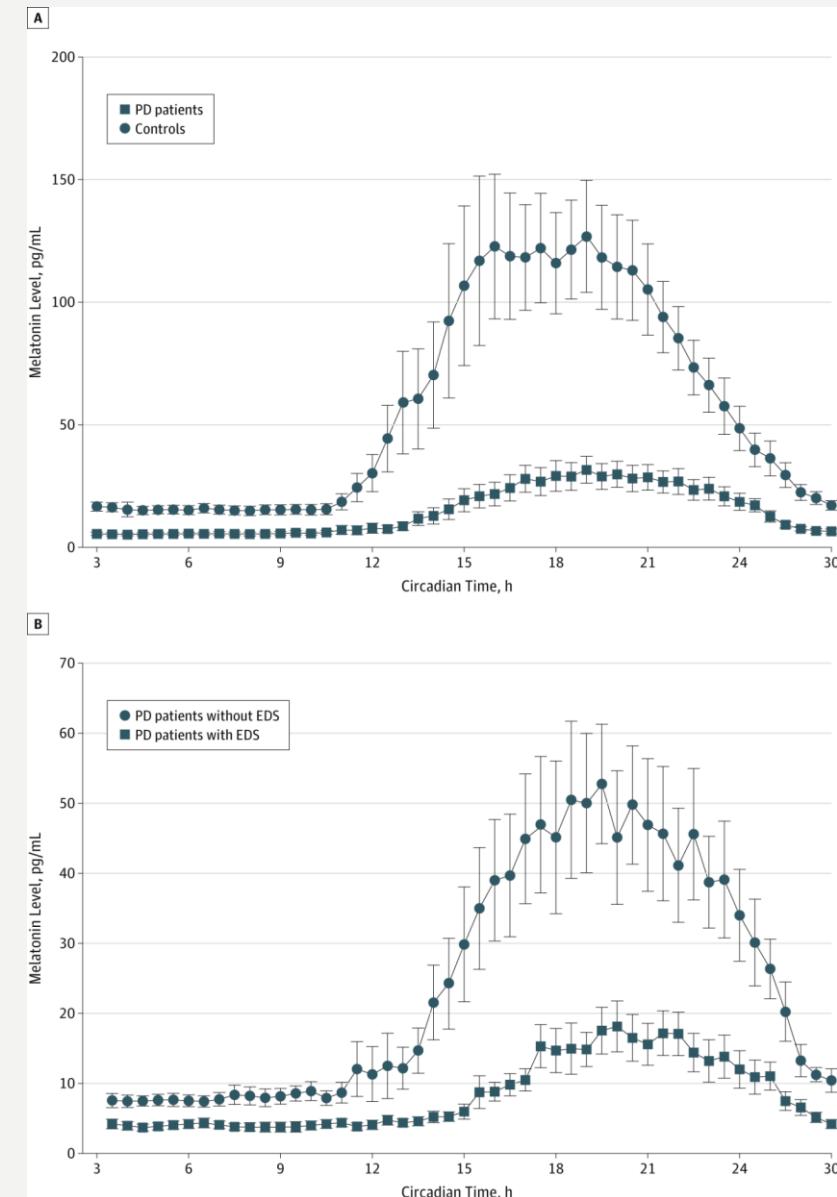
- Excessive daytime sleepiness 5–50% of people with Parkinson's, compared to 2–20% of matched people without the disease
- More common in men, longer duration of illness, greater severity of disease, pain, depression
- Typical test for sleepiness do not match well with the complaints of those suffering with sleepiness

CAUSES OF DAYTIME SLEEPINESS

- Disrupted sleep at night
- The underlying disease and damage to wake promoting area of the brain
- Medications
- Circadian disruption

ONE POSSIBLE CAUSE: BLUNTED CIRCADIAN SYSTEM

- Those with Parkinson's have a blunted melatonin curves
- Peak melatonin levels only 25% as high as those of control subjects
- Severity of melatonin impairment correlates with daytime sleepiness



TREATMENT OF SLEEPINESS IN PARKINSON'S

- Very limited research data
- Sun light or light box (10,000 Lux is common strength)
 - One research study used 1 hour of bright light (10,000 Lux) or dim-red light in the morning (9-11 AM) and in the afternoon (5-7 PM) daily for 2 weeks.
 - Bright light reduced excessive daytime sleepiness, sleep fragmentation, ease of falling asleep

Stimulants during the daytime:

- Caffeine
- Modafinil

Attempts to improve overnight sleep , ie sleep consolidation:

- Clonazepam
- Sodium oxybate (a medication for narcolepsy)

SLEEP ATTACKS

- Sleep attacks are sudden, irresistible bouts of sleep
- Sleep attacks are estimated to occur in 1–6% of patients
- May be related to multiple dopamine agonist medications
- In up to 1 in 5 patient on one study did not have excessive daytime sleepiness despite sleep attacks
- If you have sleep attacks, you should not drive until this symptom is effectively treated.

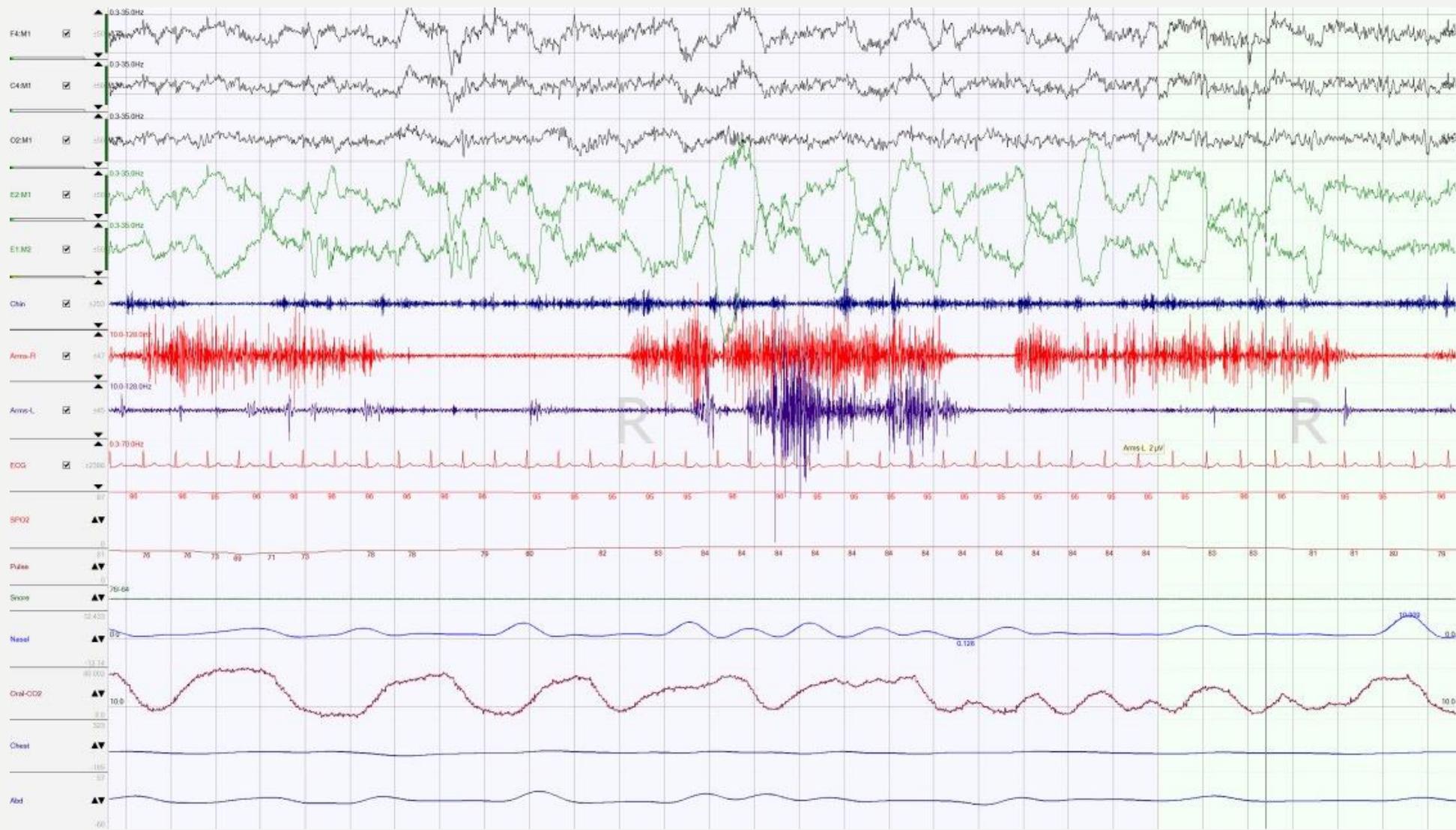
CASE 4

- 69 year old man with Parkinson's disease diagnosed three years ago comes to sleep clinic with his wife. His wife reports he is **swinging his arms** in his sleep and **kicking**. He has hit her on occasion.
- He does not always recall this, but can recount lunging out of bed recently and awakening feeling he was **running to save his wife** from a fire. He has **broken a rib** from this activity.
- Looking back, he started **mumbling** in his sleep 20 years and this progressed to **talking and yelling**, then he **started acting out his dreams** 10 years ago

REM SLEEP BEHAVIOR DISORDER (RBD)

- During REM sleep (our vivid dream sleep) we are typically paralyzed
- However in RBD this paralysis is lost, leading to dream enactment
- 0.5% of the general population and 2% of those over 60-years-old
- May be more common in men
- Typically associated with Parkinson's disease and related disorders (α -synucleinopathies such as multiple systems atrophy, Dementia with Lewy Bodies)
 - 15– 44% of patients with Parkinson's disease
 - 30–83% of patients with Dementia with Lewy Bodies
 - 85–100% of patients with Multiple Systems Atrophy

LOSS OF REM ATONIA



REM SLEEP BEHAVIOR DISORDER (RBD) TREATMENT

- Safe sleeping environment: move breakable objects from bedside, consider mattress on the floor or separate bed from bed partner
- Melatonin 3-12 mg
- Clonazepam
- Consider stopping medications that worsen it such as some antidepressants if safe to stop

CASE 5

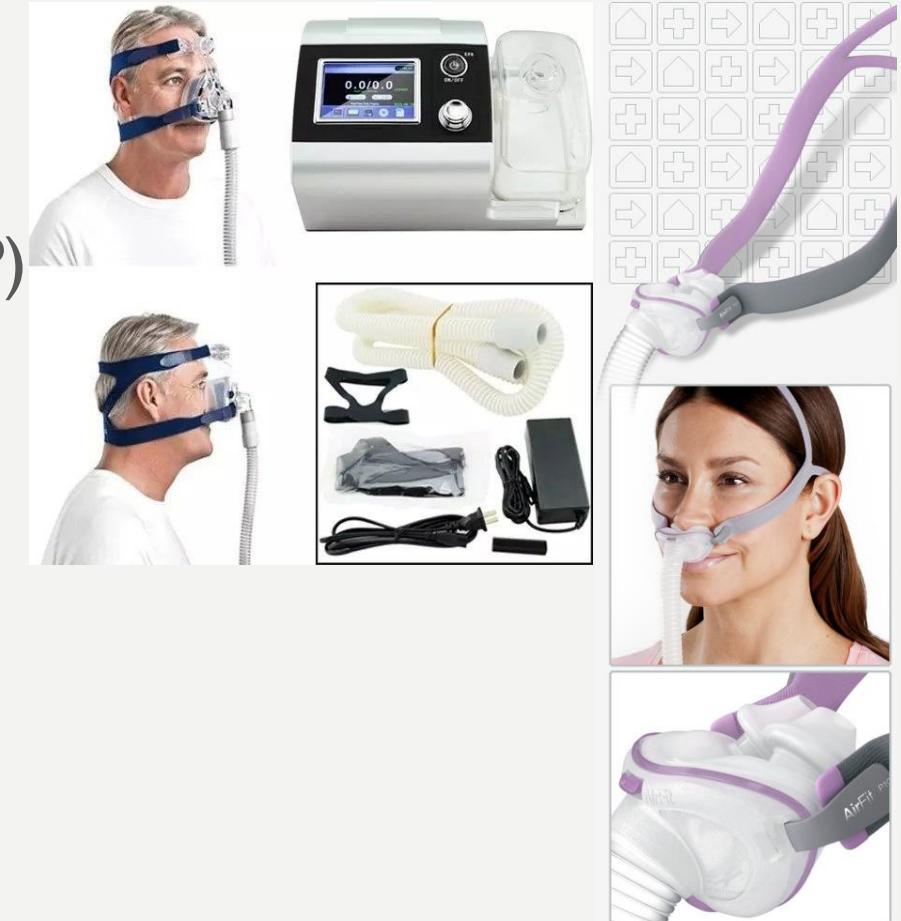
- A 75 year old man with Parkinson's disease comes to sleep clinic with **frequent awakenings overnight, feeling unrefreshed** when he awakens in the morning, and **sleepiness** during the daytime.
- He recently shared a room with a friend while traveling who complained that he gasped and had **breathing pauses** overnight

OBSTRUCTIVE SLEEP APNEA (OSA)

- OSA is characterized by recurrent collapse of the upper airway
- Similar incidence in Parkinson's disease compared to the general population
- Very common, about 25% of older adults
- Diagnosis: Sleep study (at home or in lab)
- May be less linked to weight in Parkinson's
- Usually worse laying on the back and those with Parkinson's may sleep more on the back due to movement trouble

SLEEP APNEA TREATMENT

- Continuous positive airway pressure (CPAP)
- Oral Appliance
- Surgery
- Weight loss



IF YOU ARE HAVING SLEEP TROUBLE WHAT WILL YOUR DOCTOR WANT TO KNOW?

- Bedtime
- Wake time
- Sleep latency - long it takes to fall asleep
- Overnight awakenings and time to return to sleep
- Snoring or other abnormal breathing sounds
- Excessive daytime sleepiness (EDS), fatigue, concentration trouble
- Nocturnal motor and sensory symptoms
 - including rigidity, dystonia and restless legs
- Nocturnal behaviors such as dream enactment

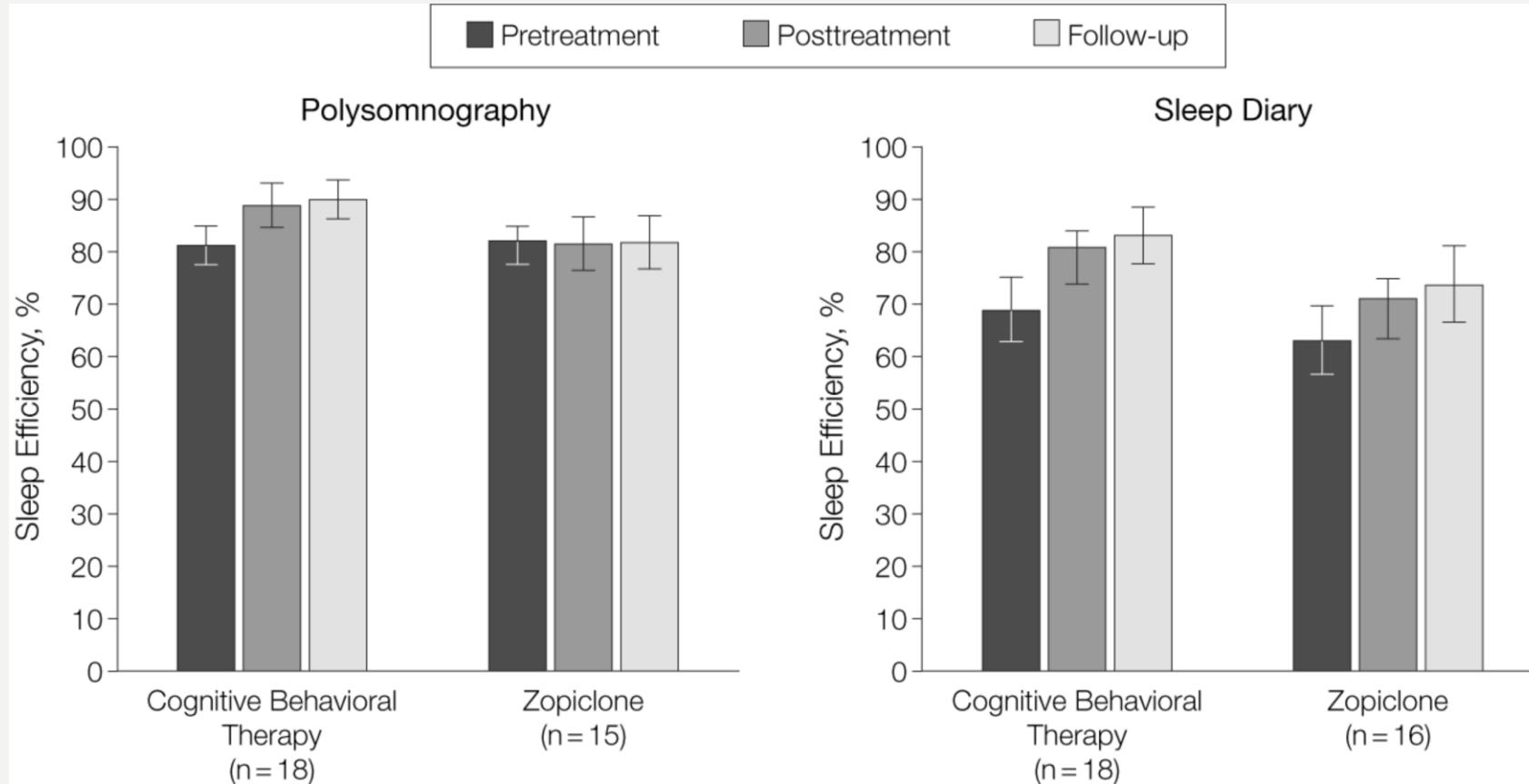
SUMMARY

- Sleep is important for memory consolidation, emotional processing, decreasing sleepiness
- Sleep problems are very common in Parkinson's disease and can be very bothersome
- Common sleep disorders in Parkinson's include
 - Restless Leg syndrome
 - Insomnia
 - Hypersomnia
 - REM sleep behavior disorder
 - Obstructive sleep apnea
- Many of the treatment approaches mirror those on the general population
- Important pearls for healthy sleep:
 - Daily exercise
 - Adequate sunlight
 - Stable wake up time

THANK YOU

- Questions?
- If you have sleep concerns and are interested in being seen at our UCSF clinic, ask your doctor for a referral to the Neuro/Psych Sleep Clinic at UCSF. We are within the neurology department.
- Phone 415-353-2273
- Fax 415-353-2892

TREATMENT: CBTI VS ZOPICLONE



From: Cognitive Behavioral Therapy vs Zopiclone for Treatment of Chronic Primary Insomnia in Older Adults: A Randomized Controlled Trial JAMA. 2006;295(24):2851-2858. doi:10.1001/jama.295.24.2851