

Overview of Sleep Medicine



Rodney Smith. New York Times 11-18-2007

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What is Sleep?

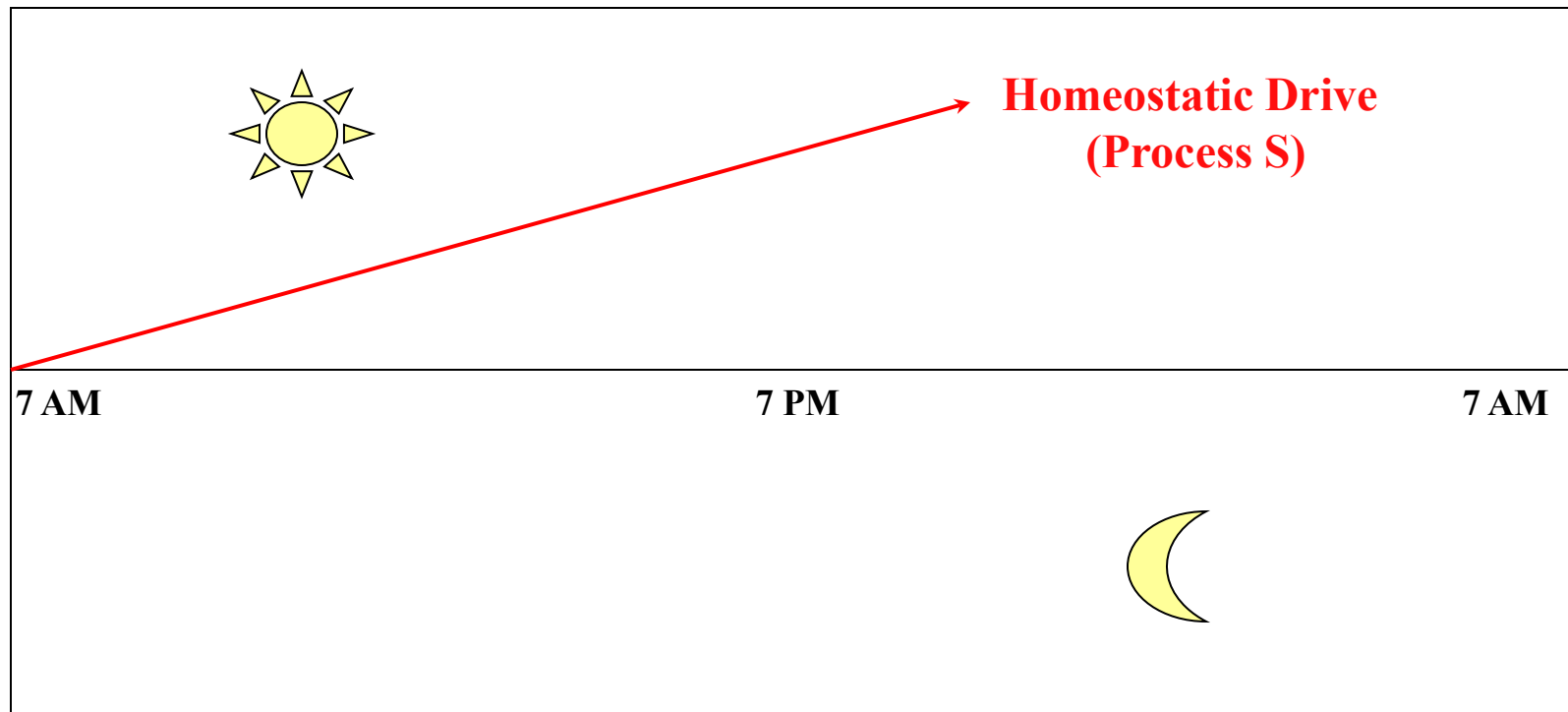
- Reversible state
- Perceptual disengagement
- Relative unresponsiveness to the environment
- Behavior



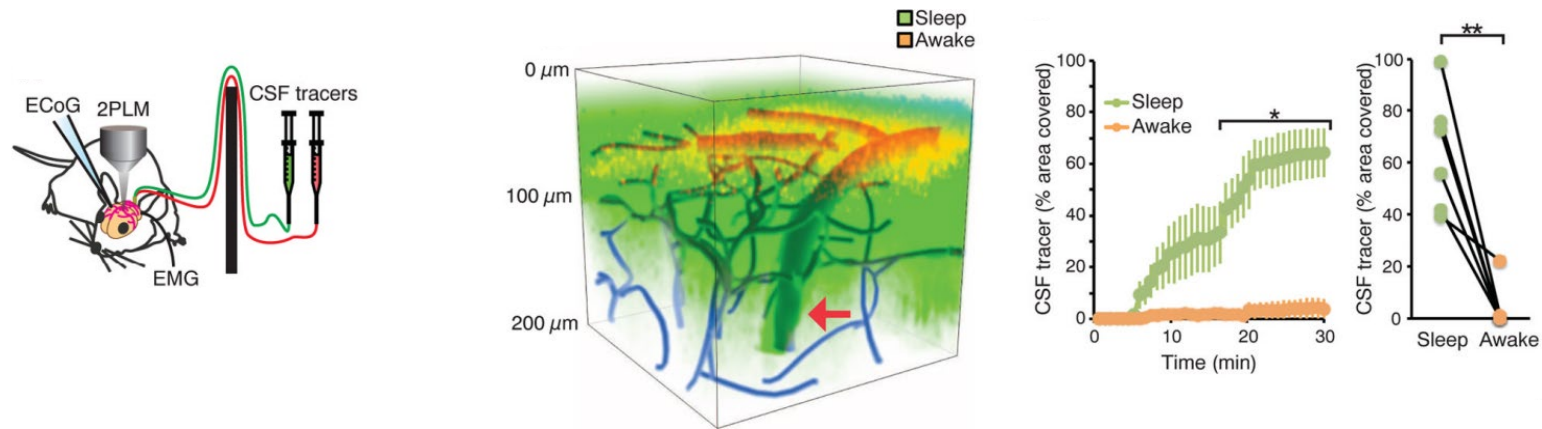
Sleep is driven by a physiologic need.

- Analogous to hunger.
- Can be quantified by
 - Time to sleep onset (latency)
 - Arousal threshold from sleep
 - Duration of sleep
- Can be modulated by environment, motivation, and stimulation.

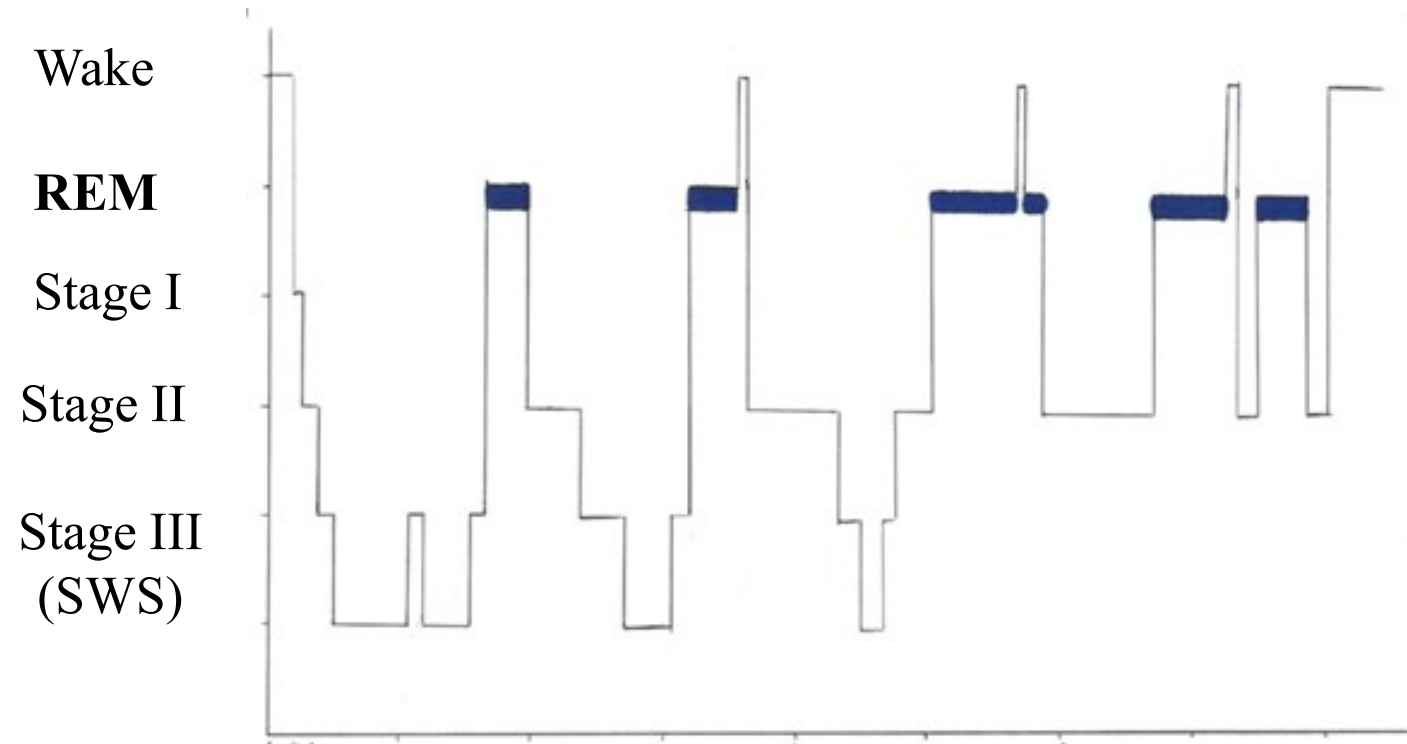
As the day wears on, adenosine accumulates from metabolism of ATP



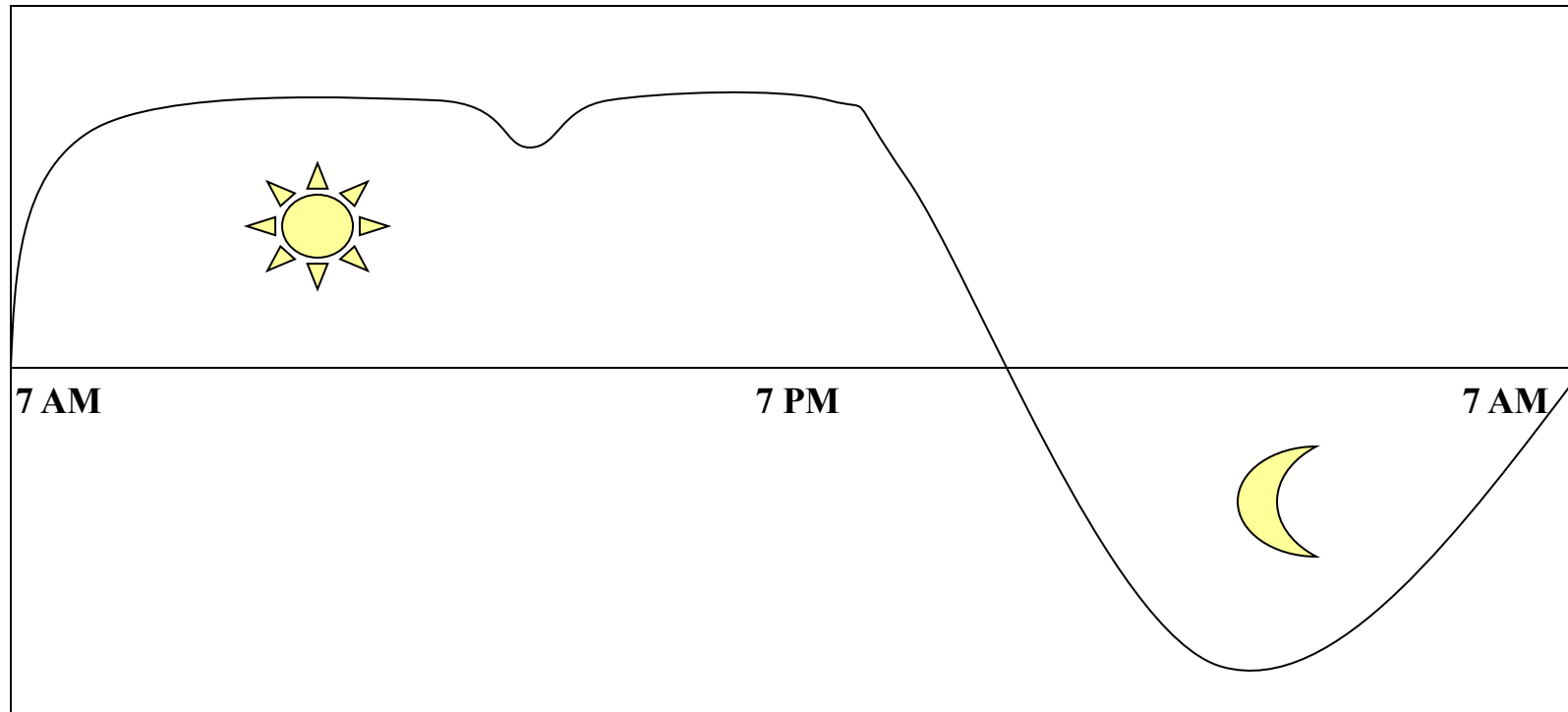
Increase in the interstitial space during sleep drives metabolite clearance and dephosphorylation



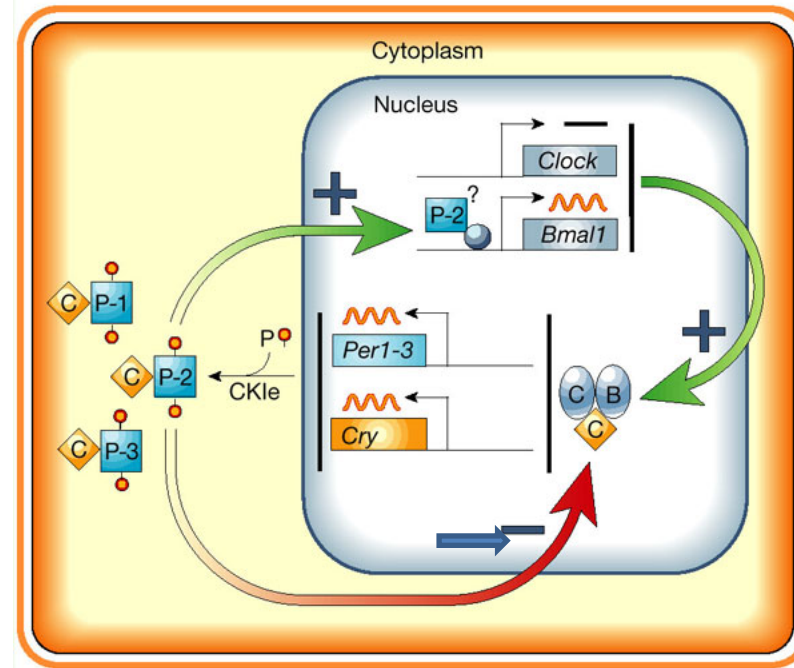
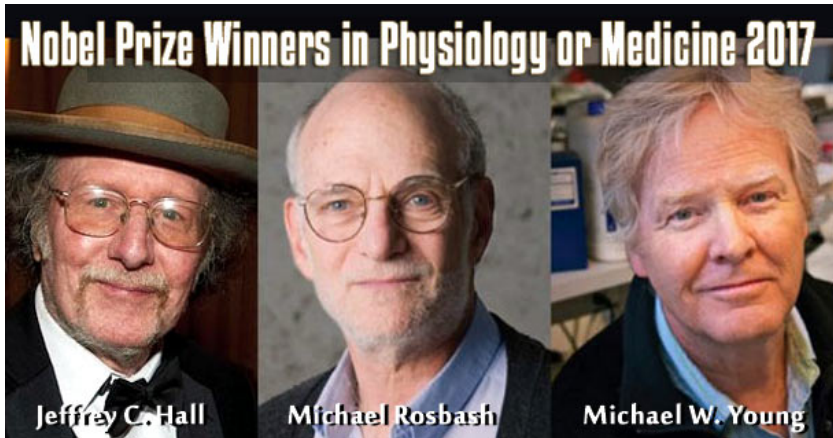
Hypnogram



Circadian rhythm results in a
“biological” day and night

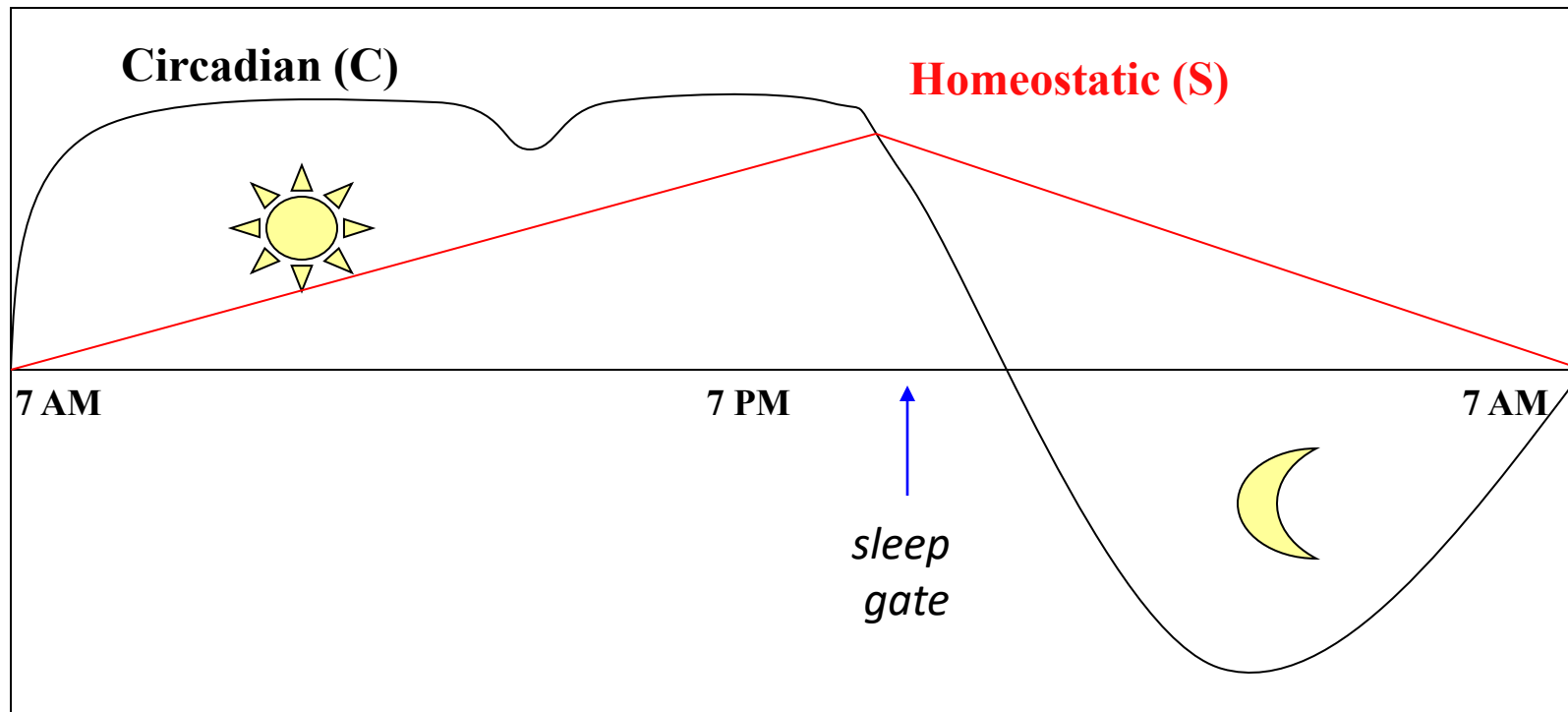


Transcription, translation, and regulation of circadian clock genes generates a 24-hour cycle through nocturnal accumulation of PER

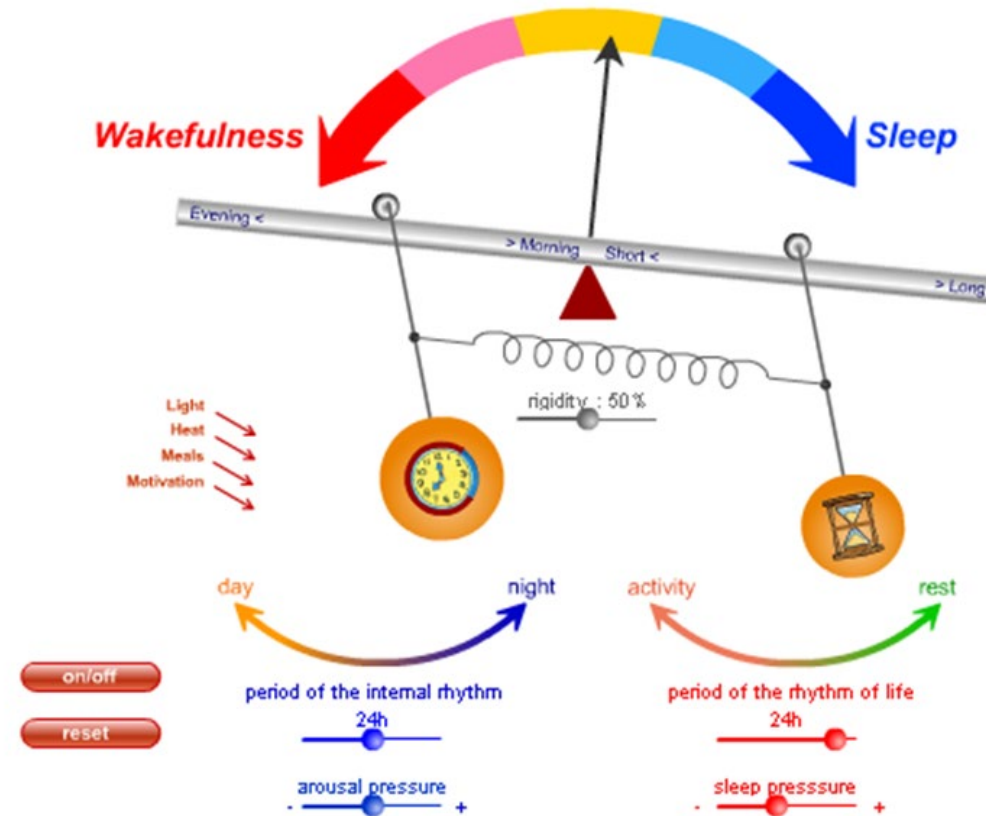


Reddy P, et al. *Cell* 1984; 38(3): 701-710
Clayton JD, et al. *Nature* 2001; 409: 829-831

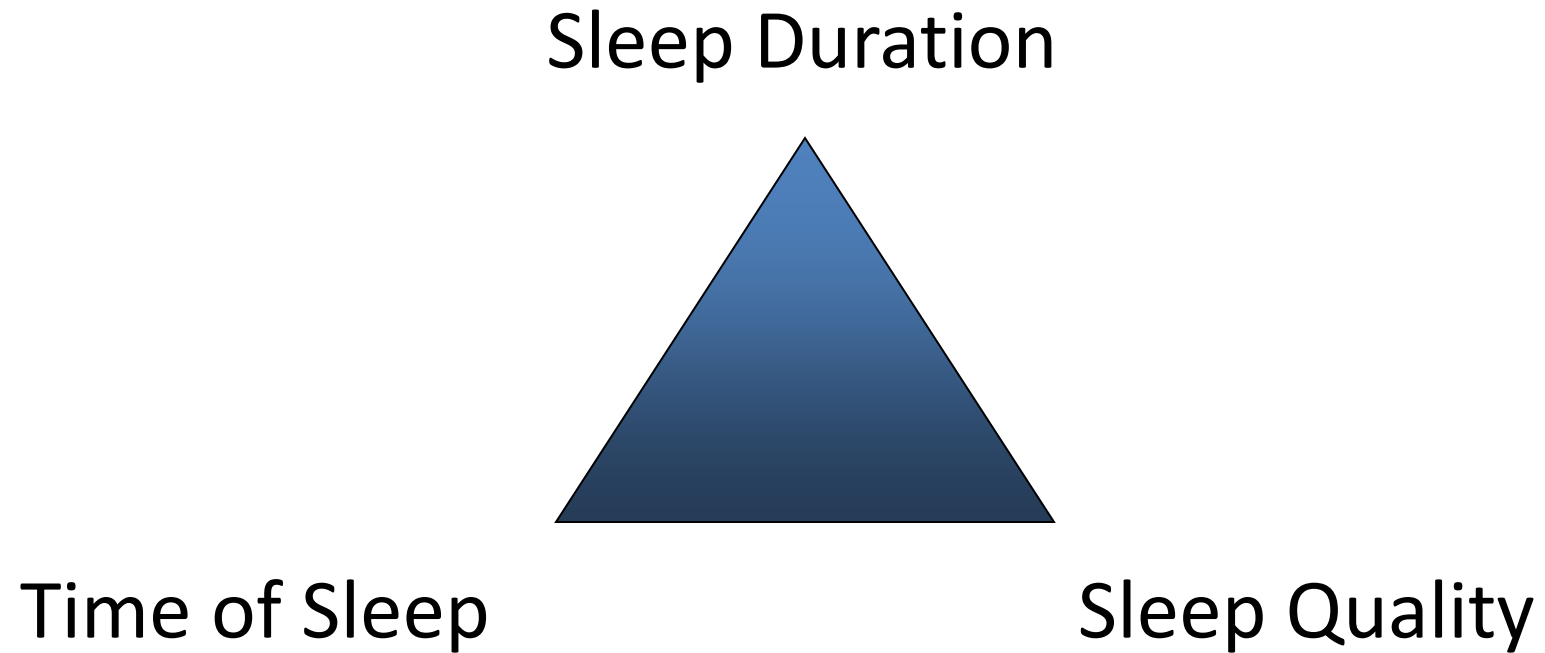
Sleep occurs when the circadian and homeostatic drives collide.



The balance between wake and sleep states is fragile.



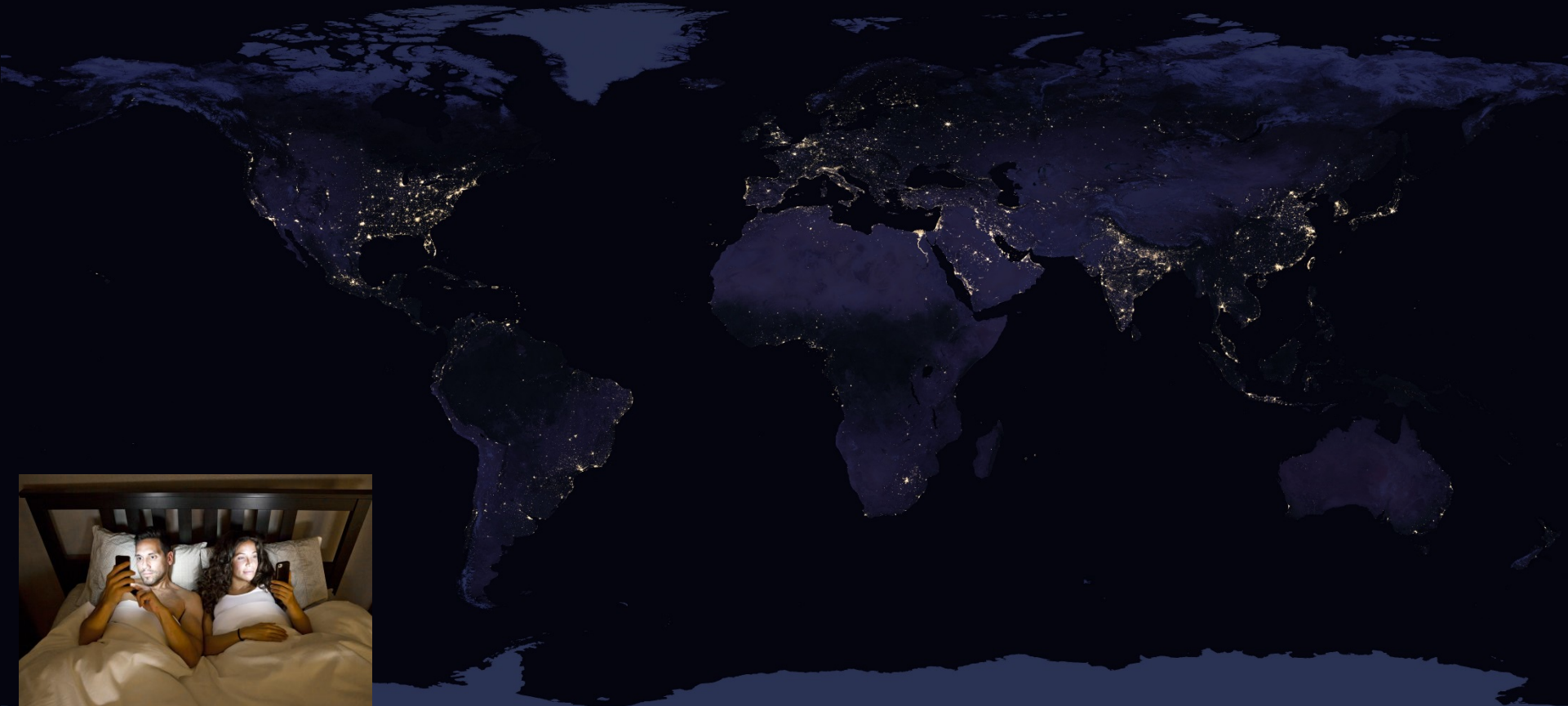
Cornerstones of Good Sleep



Insufficient sleep is becoming the norm

- Surveys demonstrate rising percentages of adults obtaining less than 6 hours sleep (Knutson KL et al. *Sleep* 2010; 33: 37 – 45).
 - American Cancer Society (1959): 2%
 - Alameda County, CA (1972): 14%
 - American Cancer Society (1982): 20%
 - NIH survey (2004): 30%
- National Sleep Foundation polls in 2017 reported only 28% sleep more than 8 hours.

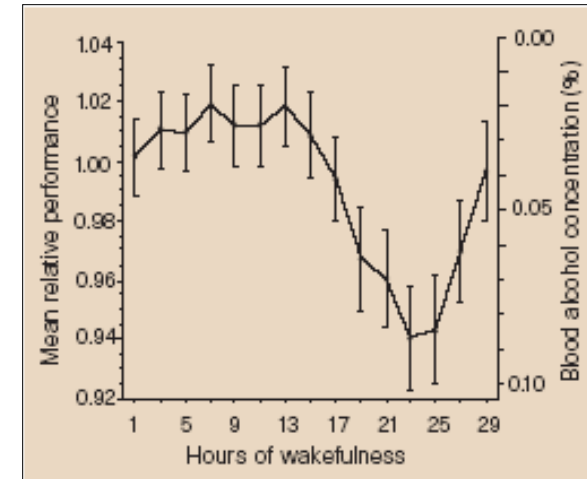
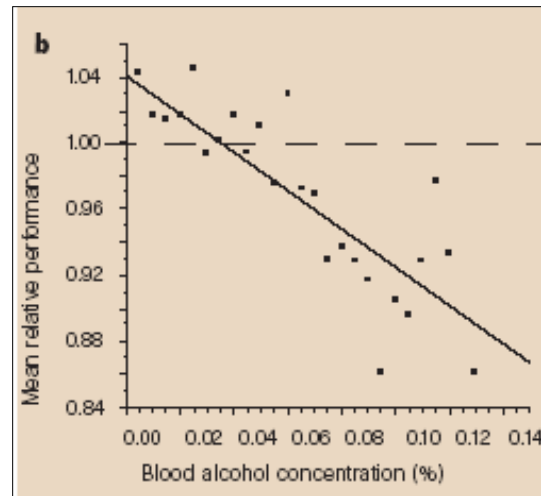
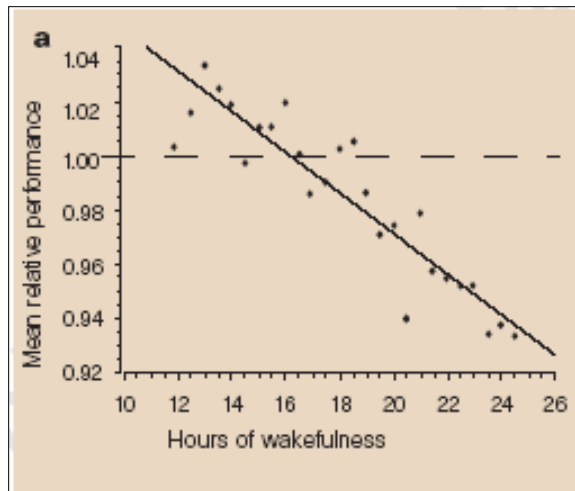
Light impacts melatonin secretion and alertness



<https://www.ucsf.edu/news/2016/11/404886>

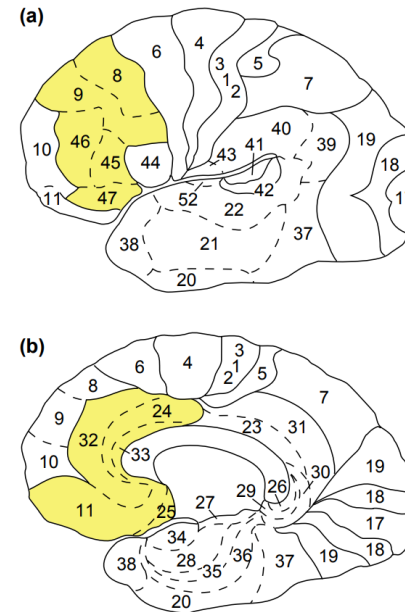
https://www.nasa.gov/specials/blackmarble/2016/globalmaps/BlackMarble_2016_3km.jpg

Like alcohol, sleep deprivation from prolonged wakefulness leads to decreased alertness

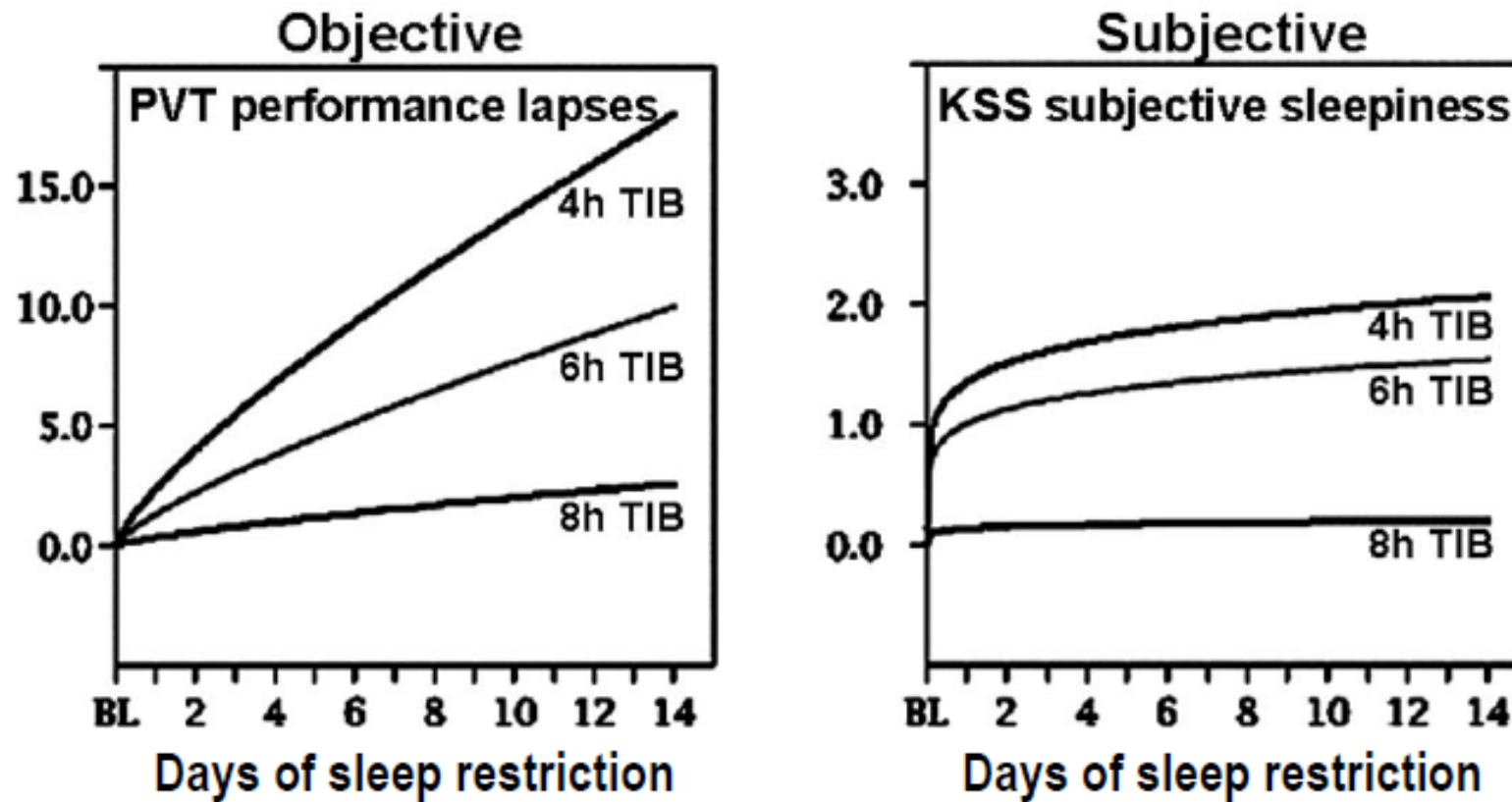


Sleep deprivation can impact prefrontal (executive) function

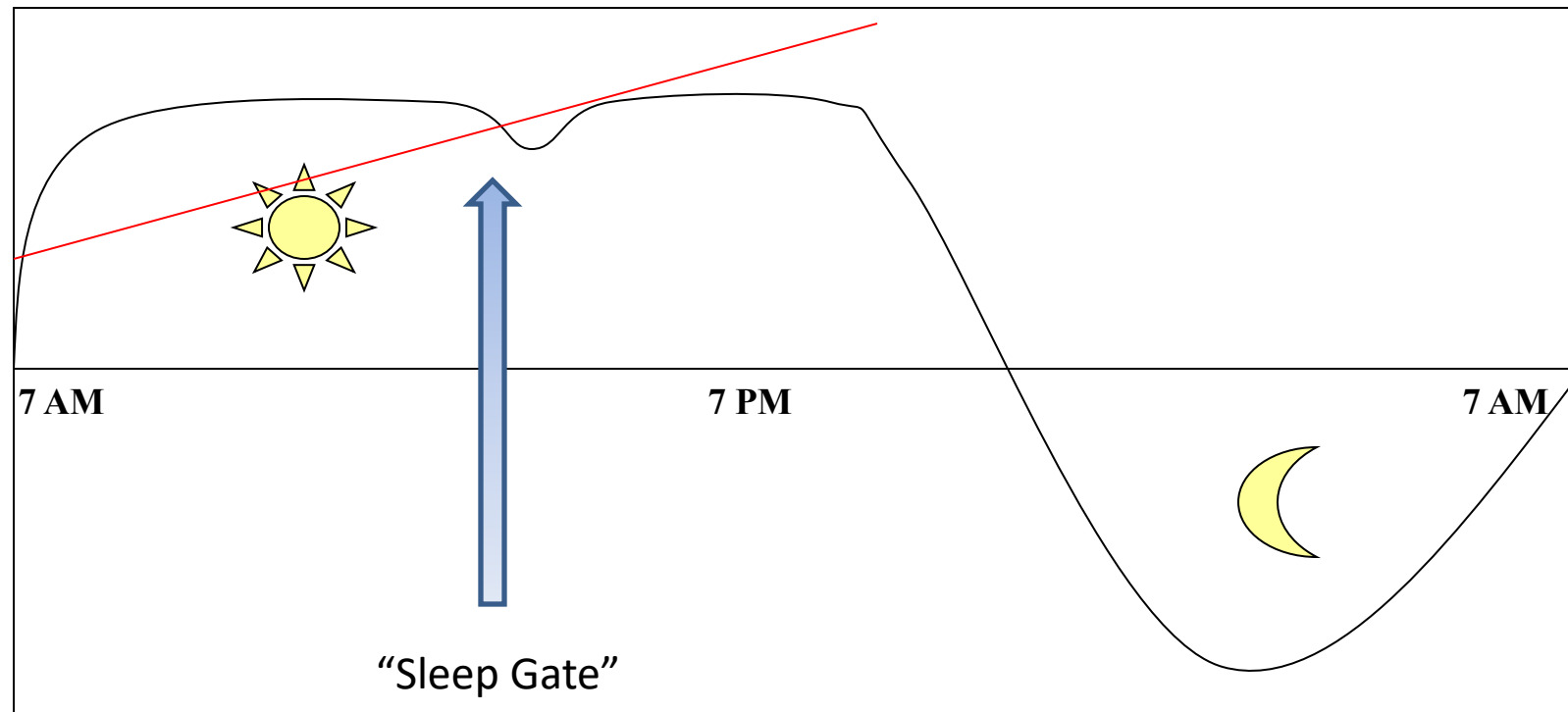
- Verbal fluency
- Temporal memory
- Logical reasoning
- Working memory
- Planning
- Decision making



Sleep deprivation has a cumulative effect,
which is *not* perceived by subject

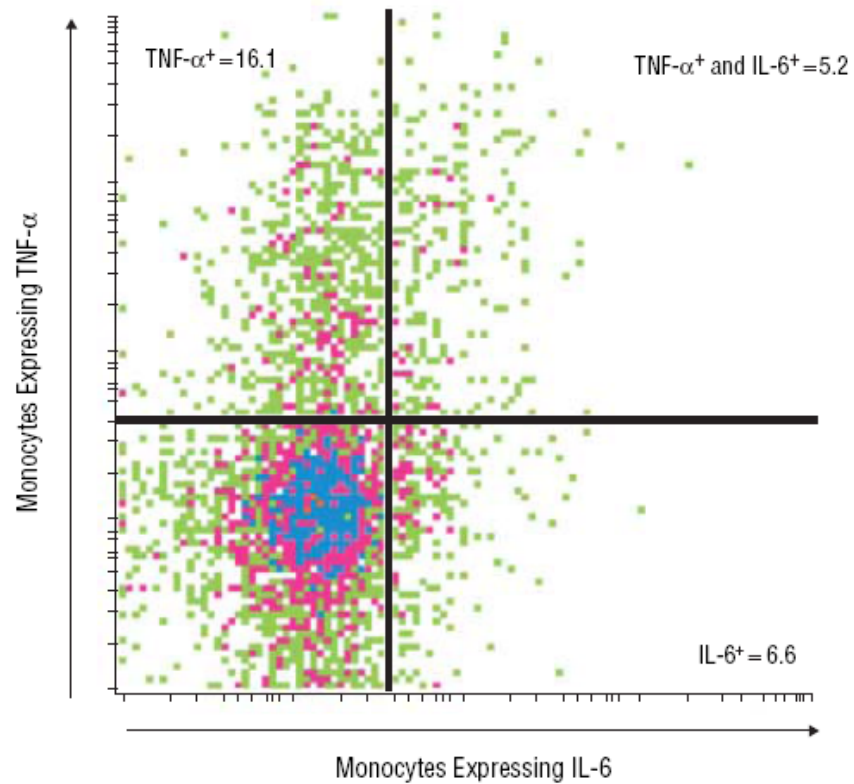


Insufficient sleep may result in prominent “dips” with sleep intrusions during your biological day.

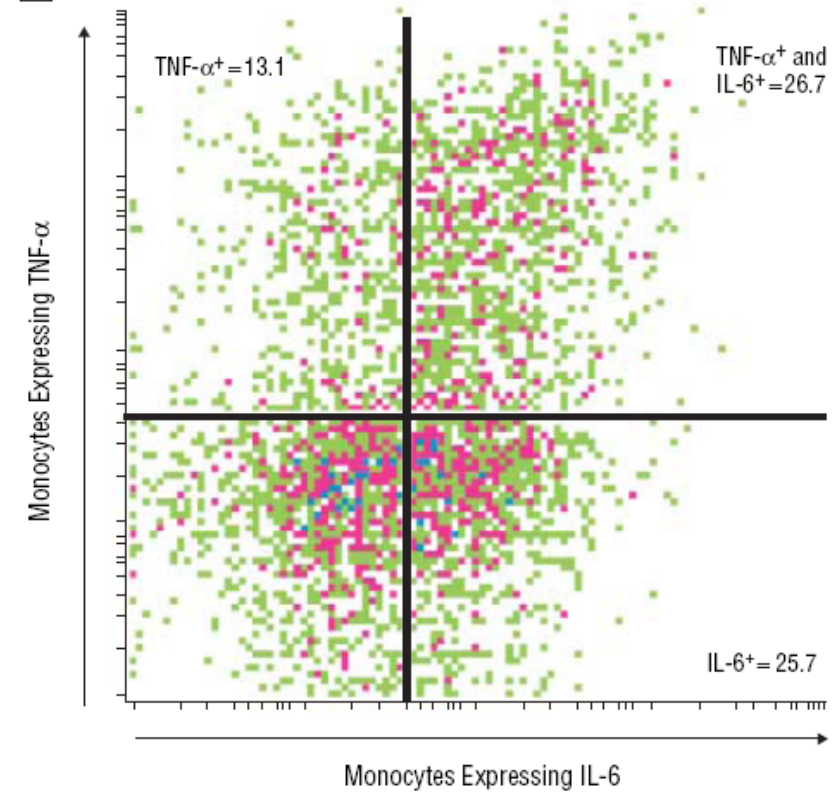


After a single night of sleep loss, monocytes demonstrate irritability

A Baseline

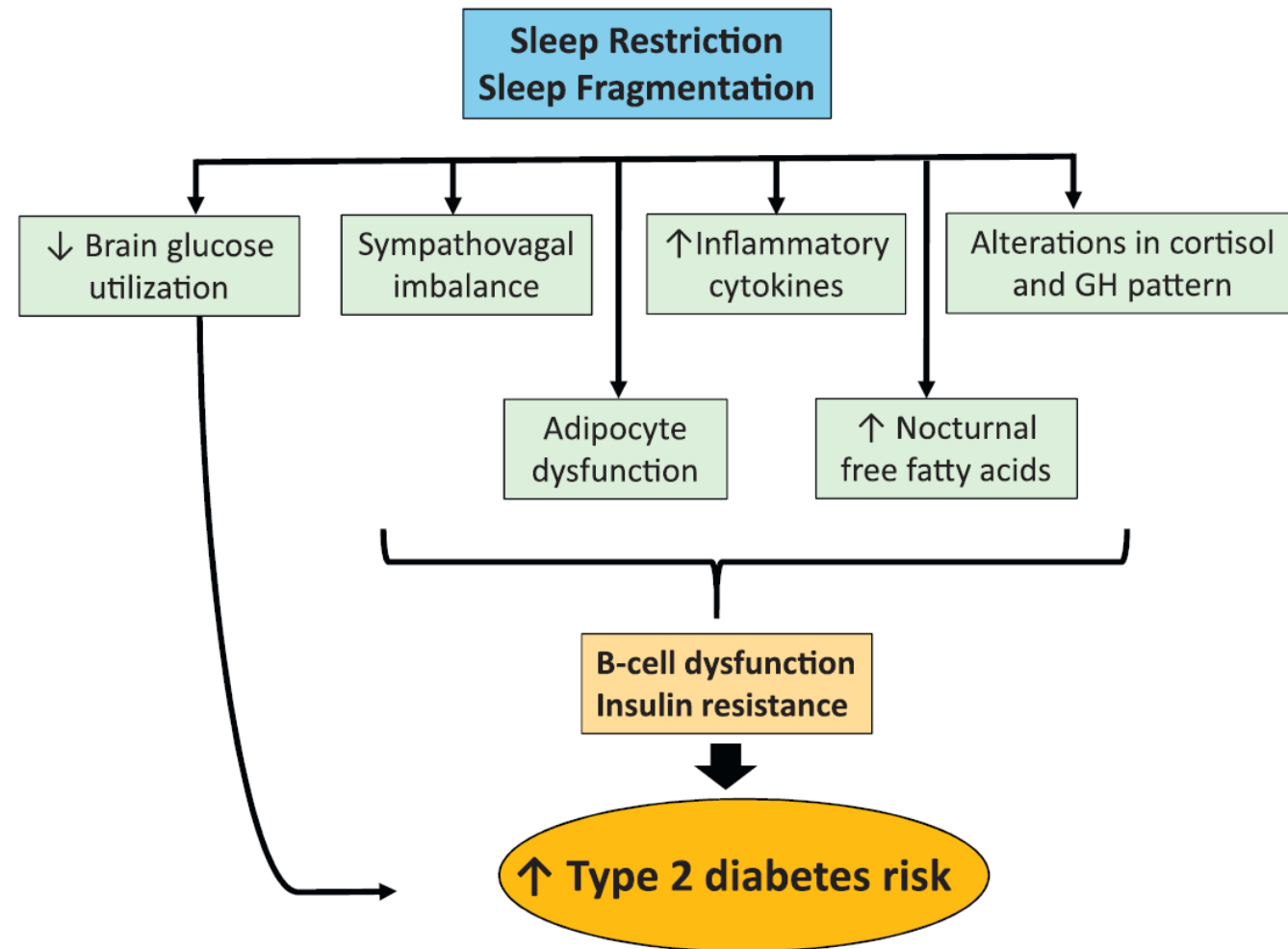


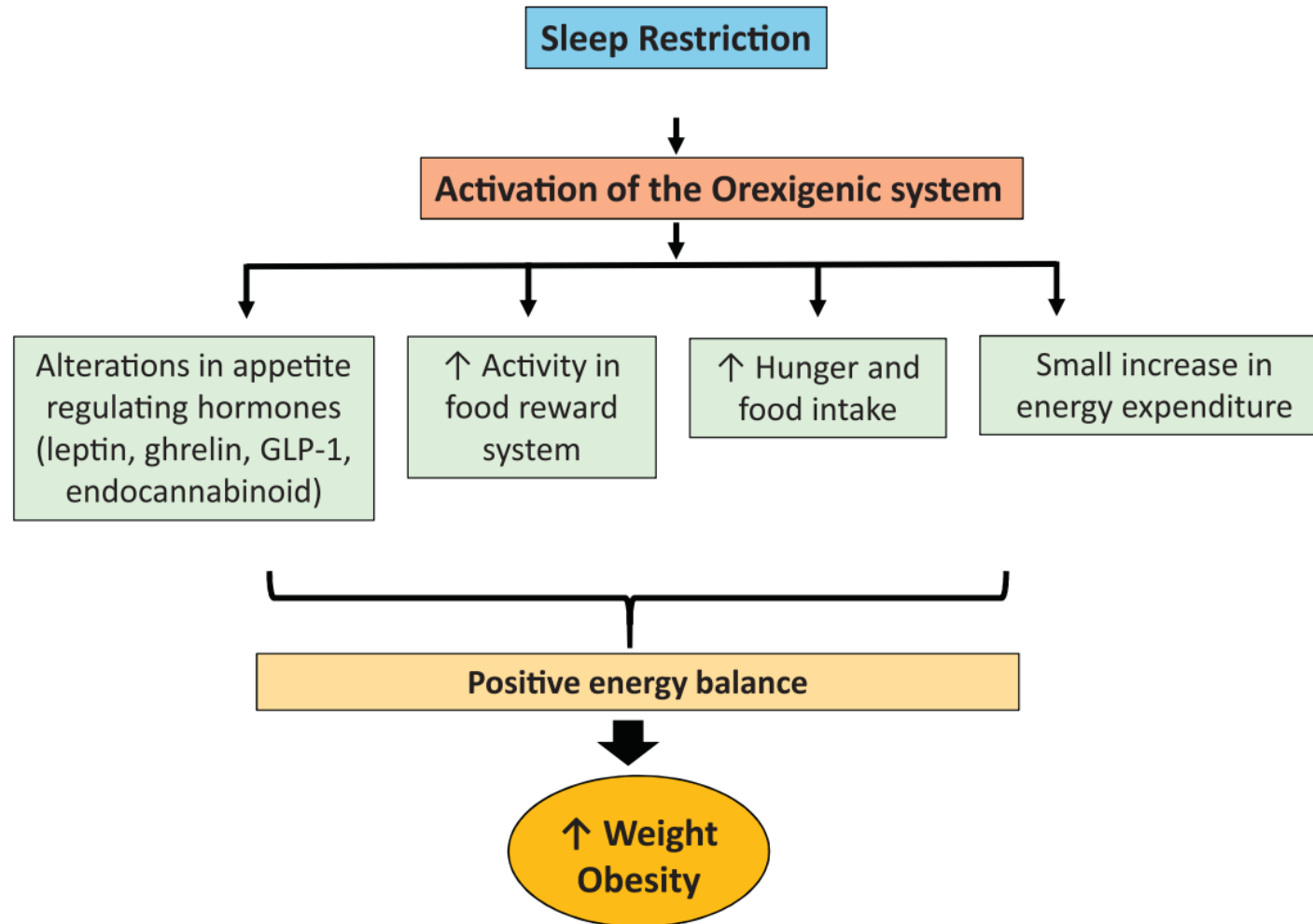
B Partial Sleep Deprivation



Sleep duration may impact immunity based on risk of pneumonia at extremes

	Hours of Sleep per Day				
	≤ 5	6	7	8	≥ 9
Age < 45 y	2.04 (1.32-3.16)	1.49 (1.11-2.02)	1.26 (0.96-1.66)	1.00	1.77 (1.16-2.73)
Age ≥ 45 y	1.52 (1.08-2.14)	1.17 (0.92-1.49)	1.08 (0.87-1.35)	1.00	1.30 (0.88-1.91)
BMI < 25 kg/m ²	1.31 (0.83-2.06)	1.38 (1.05-1.80)	1.12 (0.88-1.43)	1.00	1.47 (0.96-2.23)
BMI ≥ 25 kg/m ²	1.88 (1.34-2.65)	1.18 (0.91-1.54)	1.18 (0.92-1.50)	1.00	1.47 (0.99-2.17)
Not current smoker	1.63 (1.21-2.19)	1.25 (1.02-1.53)	1.11 (0.92-1.33)	1.00	1.33 (0.97-1.83)
Current smoker	1.95 (0.96-3.93)	1.57 (0.88-2.78)	1.60 (0.93-2.77)	1.00	3.19 (1.51-6.71)
Inadequate sleep	1.52 (1.04-2.24)	1.10 (0.78-1.54)	1.14 (0.82-1.59)	1.00	1.37 (0.73-2.56)
Adequate sleep	0.20 (0.03-1.40)	0.98 (0.68-1.39)	0.97 (0.77-1.20)	1.00	1.55 (1.12-2.14)



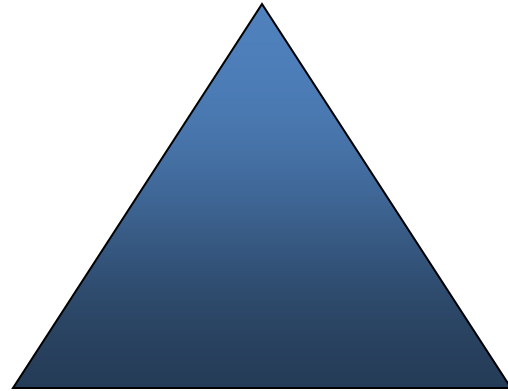


Insufficient sleep leads to

- Fatigue, excessive daytime sleepiness, and reduced quality of life
- Reduced cognitive and motor performance acutely with increased risk of memory disorders long-term
- Behavioral / emotional disturbance with impulsivity and mood disruption acutely and mood disorders chronically
- Weight gain with increased risk of obesity
- Immune disruption with increased risk of infections

Cornerstones of Good Sleep

How Much Sleep Do You Need?

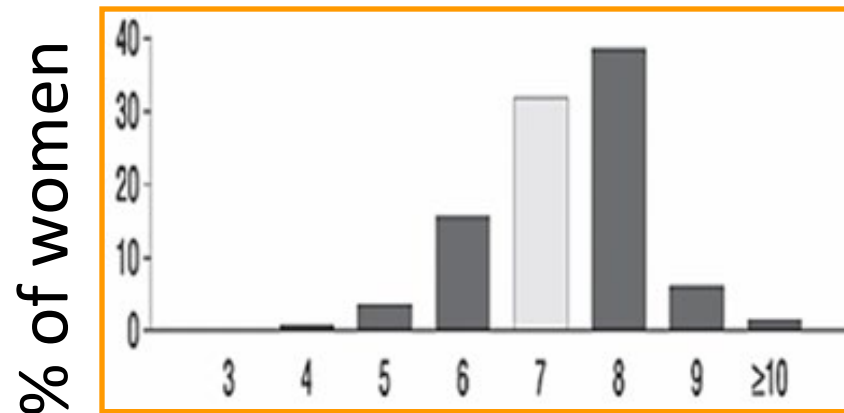


Time of Sleep

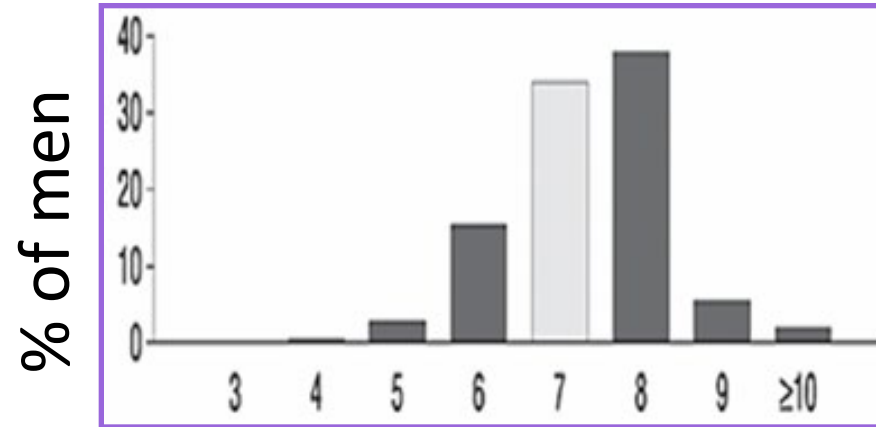
Sleep Quality

Healthy adults appear to require 7 to 8 hours of sleep per day, but we need more “field studies”.

N = 636,095

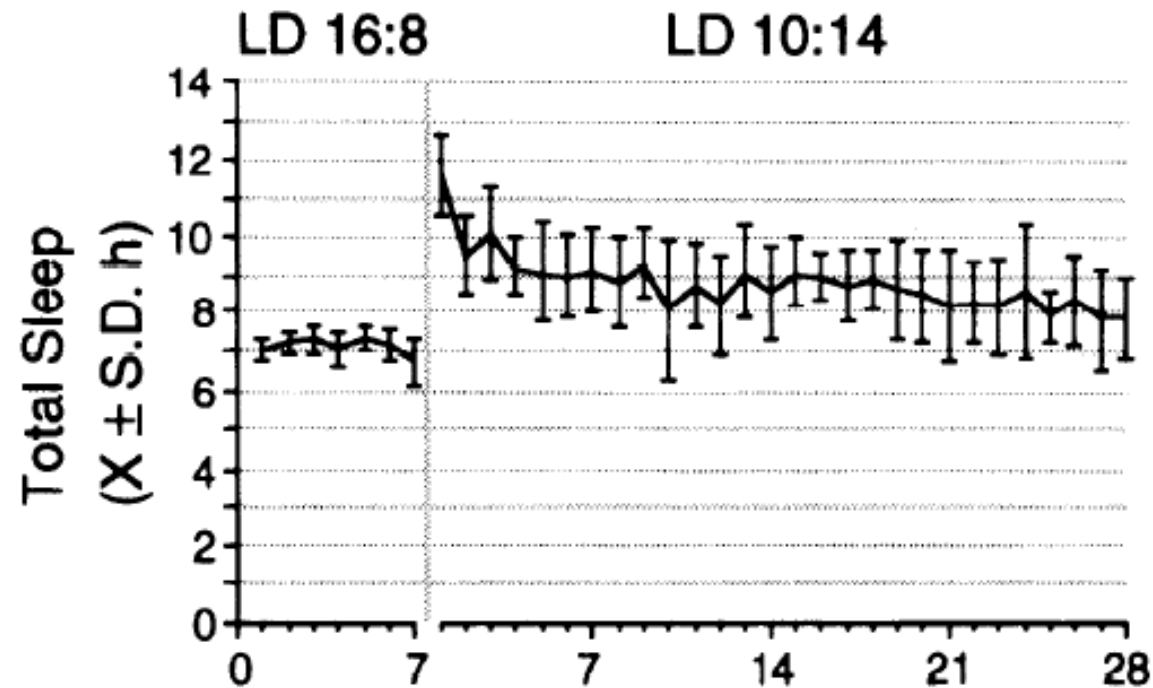


N = 480,841



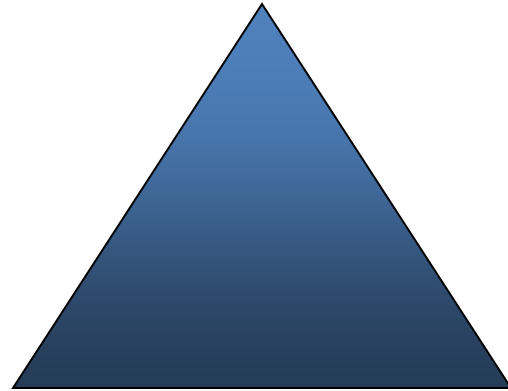
Daily hours of sleep

After sleep restriction, healthy adults appear to settle on 7 to 8 hours of sleep per day.



Cornerstones of Good Sleep

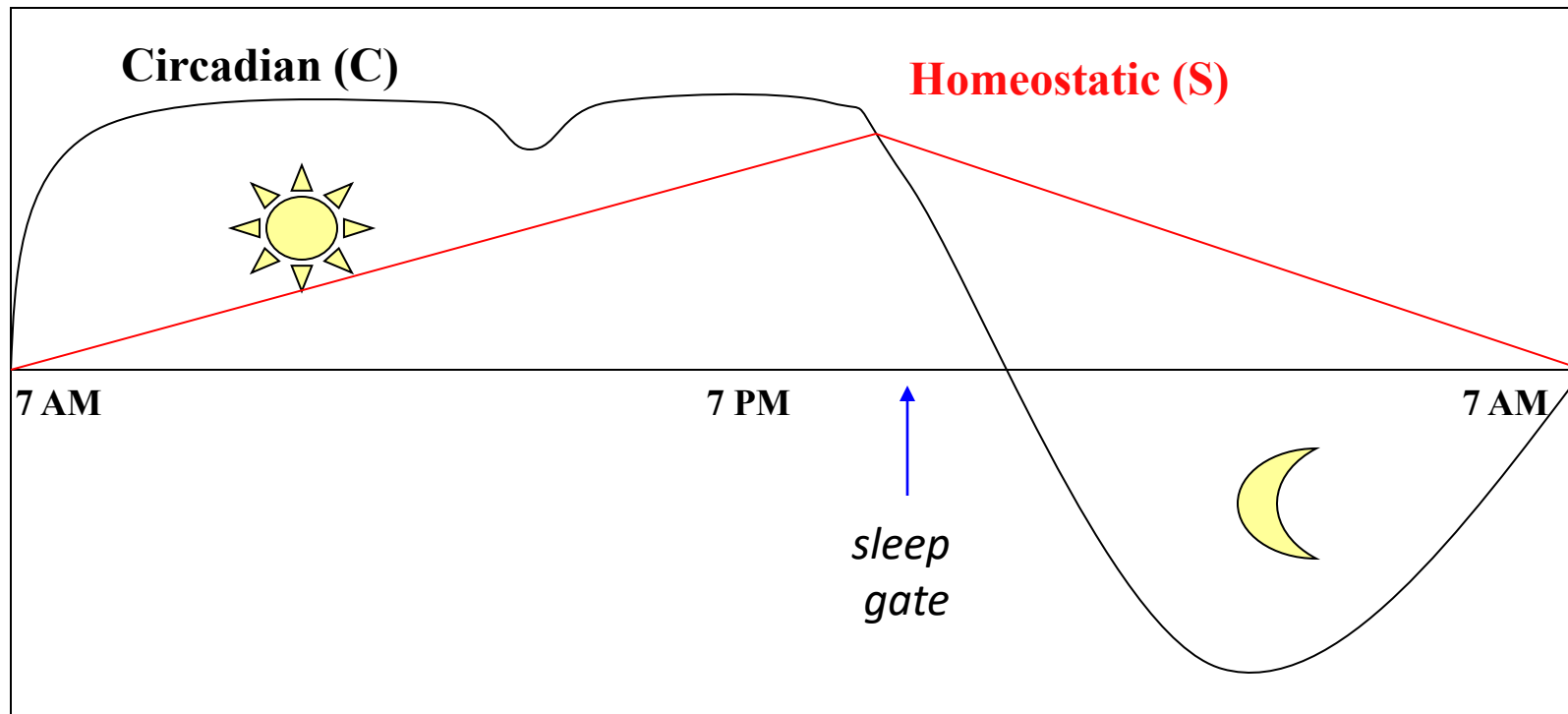
Sleep Duration



When should I sleep?

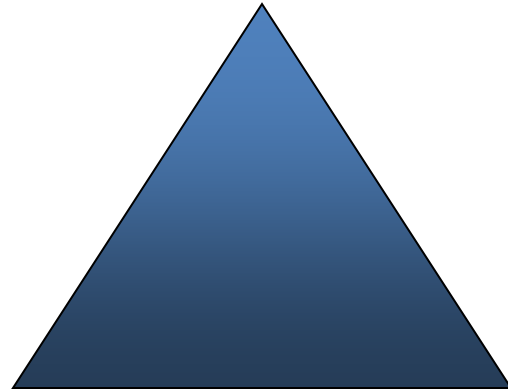
Sleep Quality

Sleep during your biological night,
when you are sleepy and tired.



Cornerstones of Good Sleep

Sleep Duration



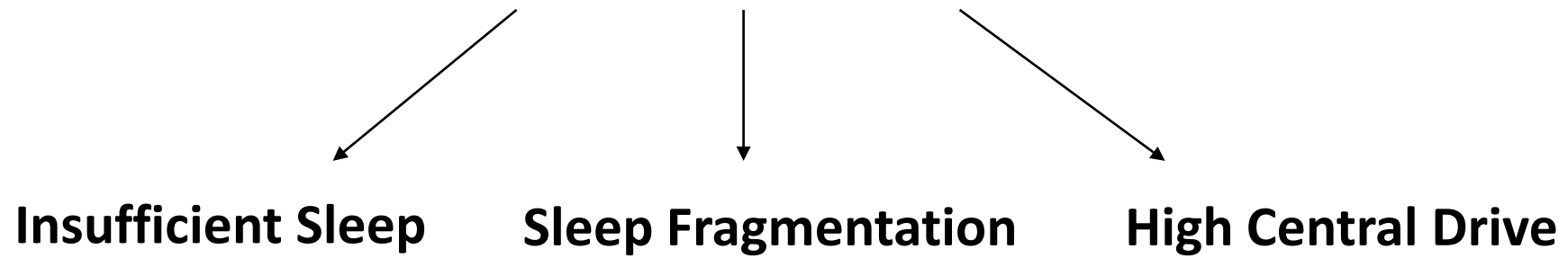
Time of Sleep

How are you sleeping?

Key Elements of a Sleep History

- Is there a problem with your sleep?
- When and how does your sleep take place?
- Any signs or symptoms of sleep-related phenomenon?
 - Snoring
 - Frequent awakenings
 - Gasping / choking awakenings
 - Morning headaches
 - Restless sleep
 - Dream enactment

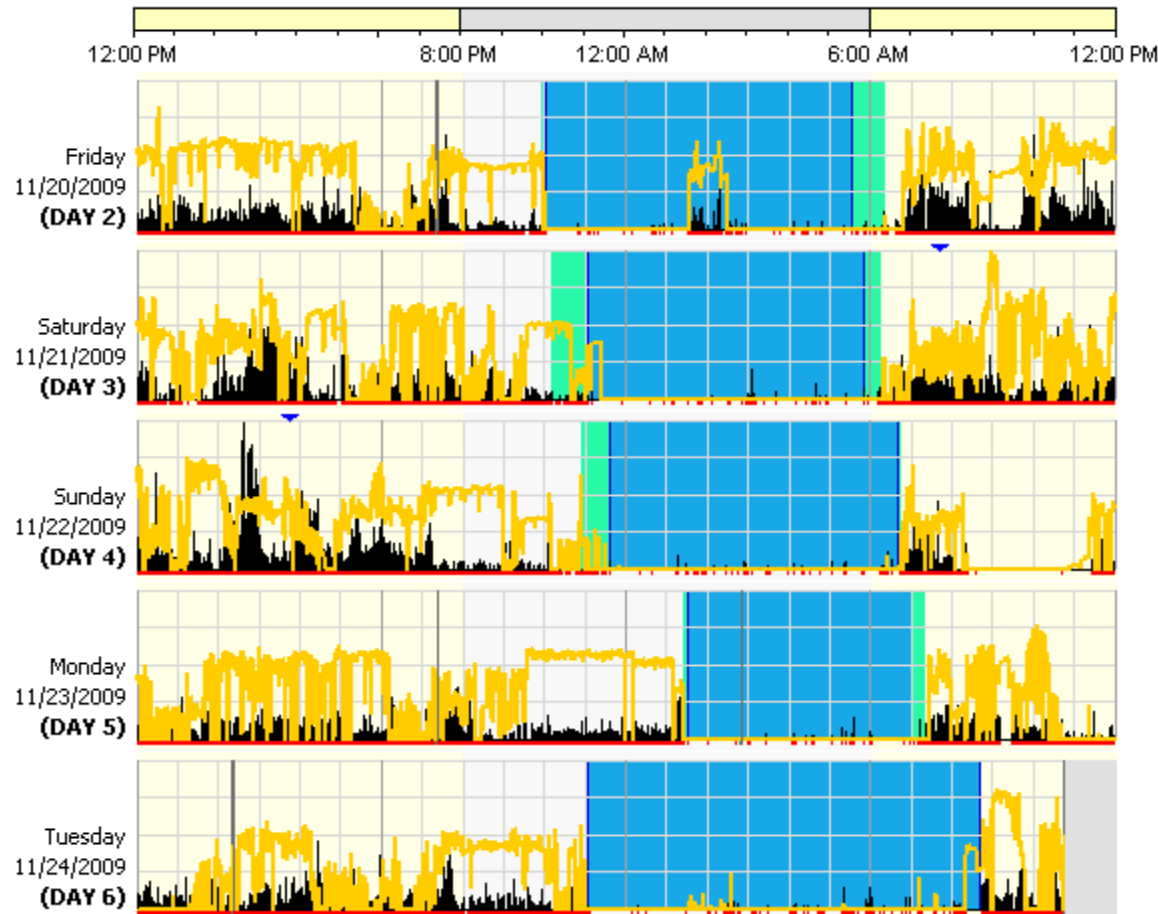
Common Sleep Disorders



Circadian disorders reflect a misalignment between internal and external clocks (e.g., “jet lag”) that lead to insufficient and/or inappropriate sleep



Actigraphy may provide objective information about the sleep period.



Treatment of Circadian Disorders

- Consistent bed/wake times.
- Light therapy (usually blue light) for 20-30 minutes on awakening
- Melatonin (3 – 5 mg) around bedtime



Restless Legs Syndrome (RLS)

- Uncomfortable / unpleasant sensation in the legs accompanied by an urge to move them.
- Occurs in the evenings, near bedtime.
- Sensation worsens with inactivity
- Partial to complete relief with movement

Diagnosis of RLS

No recognized objective test

This is a clinical diagnosis that
does *not* require a sleep study

Brain iron deficiency causes RLS in many patients

- Iron deficient states increase the risk of RLS
 - Iron deficiency anemia
 - End-stage renal disease
 - Pregnancy
 - Repeat blood donors (esp. female)
- Brain MRI show reduced iron content in substantia nigra
- Autopsy analyses demonstrate reduced transferrin receptor in substantia nigra

Therapies for Restless Legs Syndrome and Periodic Limb Movement Disorder

- Behavioral / Exercise
- Iron replacement +/- Vitamin C
- Pregabalin or Gabapentin
- Dopamine agonists (ropinirole or pramipexole)
- Opioids in refractory cases

“Prescribing” sleep may not be enough

- Insomnia symptoms are common ~ 30%
- Moderate symptomatic insomnia ~ 10%
- Risk factors include advanced age, female sex, shift work, comorbid disorder, and lower socioeconomic status/unemployment.
- Hallmark of mood disorders (OR in depression 5.5), but carries a broad differential diagnosis.

Sleep Hygiene

- Consistent sleep schedule
 - Allow time to “wind down”
 - Go to bed when sleepy
 - Allow 6-8 hours
- Conducive environment (dark, quiet, cool)
- Avoid
 - Stimulants in the afternoon (caffeine, alcohol, nicotine)
 - Naps (or limit to 15 minutes after lunch)
 - Bright light (smartphone, TV)
 - Heavy meals at night
 - Staying awake in bed for more than 20 minutes

Cognitive Behavioral Therapy for Insomnia (CBT-I)

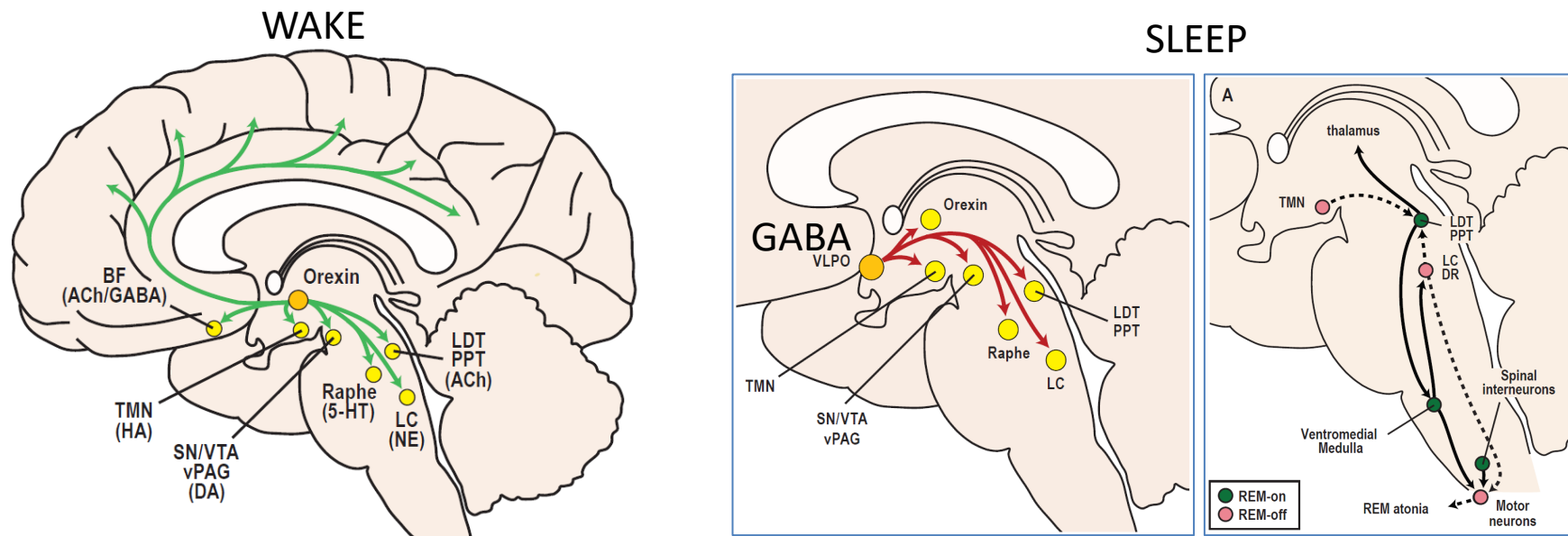
- Specialized subset of CBT provided by a certified sleep PhD or validated online services
- Includes:
 - Sleep education (self-management)
 - Stimulus control (reduce anxiety response)
 - Sleep restriction (improve efficiency)
 - Cognitive control (reduce intrusions)
 - Imagery and relaxation
 - Cognitive restructuring (correct inaccuracies)
 - Paradoxical intention (performance anxiety)

The ideal sleeping pill?



A drug that would make you agree to pursue
Cognitive Behavioral Therapy for Insomnia!

Inhibition of activating centers by GABA (γ -aminobutyric acid) induces sleep



Sedative-Hypnotics

- Short to intermediate acting benzodiazepine (BZD or BZD receptor agonist “Z”-drugs) or ramelteon (melatonin receptor agonist)
- Sedating antidepressants next line, especially if comorbid depression/anxiety
- Next line, combine BzRA / ramelteon with a sedating antidepressant
- AASM recommends against: over-the-counter antihistamines, melatonin, valerian and trazodone

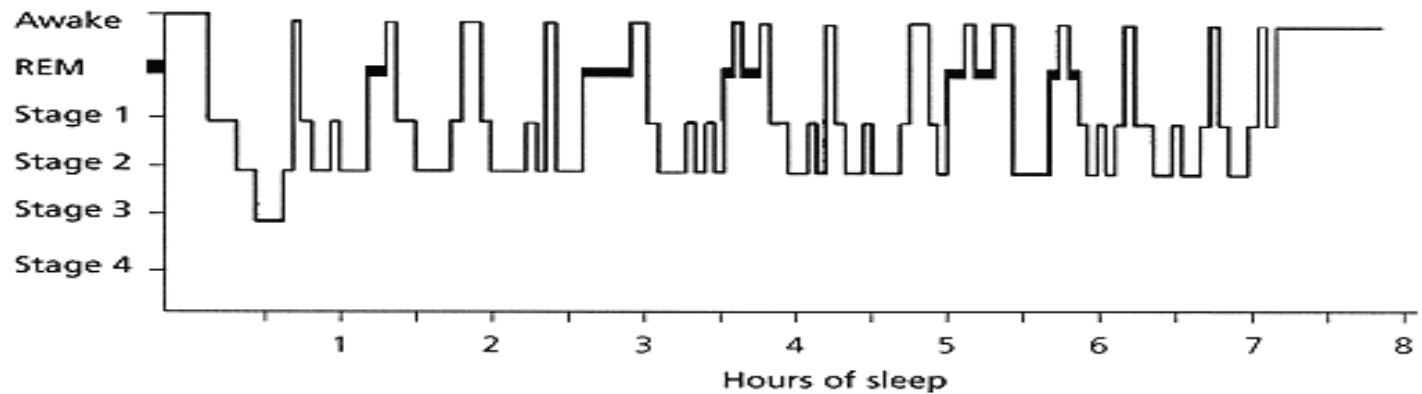
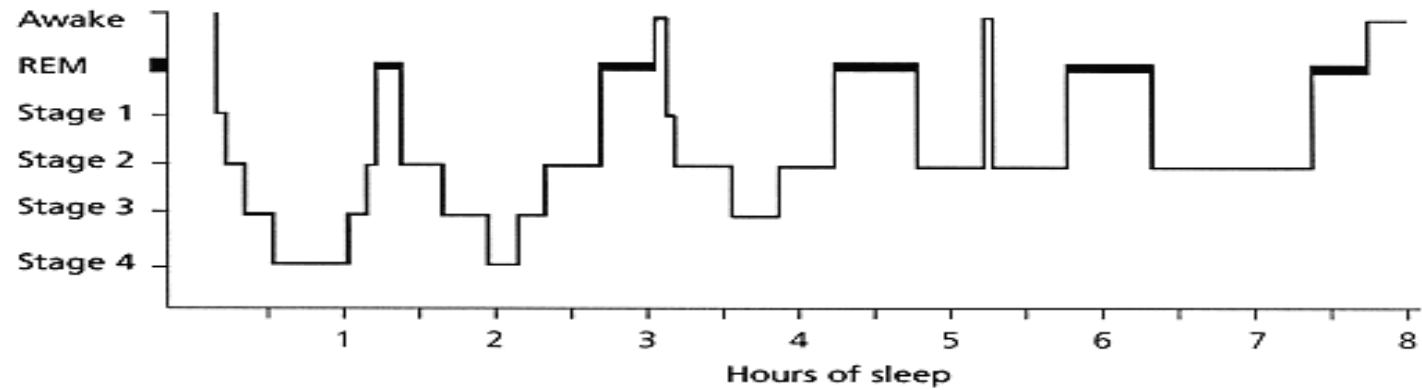
Nonbenzodiazepines are FDA approved for short-term management of insomnia

- Not related to benzodiazepines (BZD) but bind GABA-A receptor
- Shorter duration and less “next day” side effects compared to BZD
- Can be used to help correct an irregular sleep pattern and/or as bridge to CBT for Insomnia (CBT-I)
- Zaleplon (Sonata) – shortest
- Zolpidem (Ambien) – short
- Eszopiclone (Lunesta) – intermediate
- Zolpidem ER (Ambien CR) - intermediate

Trazodone

- Serotonin antagonist and reuptake inhibitor (SARI) also with antihistamine and alpha-1 receptor blockade.
- One of the most frequently prescribed agents for insomnia, but a single large-scale placebo-controlled trial *failed* to show sustained effect compared to placebo (1983).
- Can be metabolized to a wake-promoting molecule (mCPP) and cause anxiety.

Fragmentation of the sleep architecture results in non-restorative sleep.



Periodic Limb Movement Disorder (PLMs during Sleep, *not* wake)

- Phasic, repetitive, and myoclonic movements occurring during Non-REM sleep.
- Regularly spaced (series of four within 90 seconds of each other).
- Unilateral or Bilateral
- Polysomnogram diagnosis

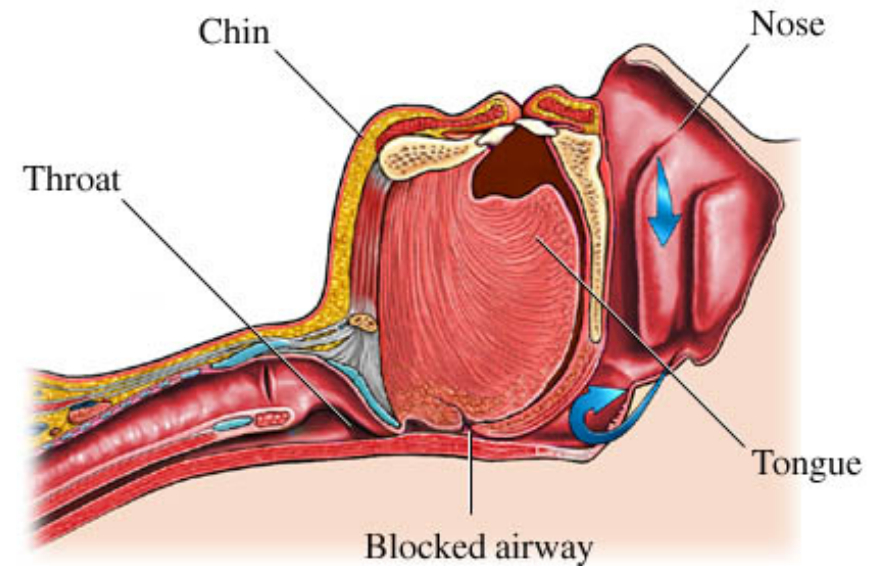


Differential for PLM Disorders

- Primary / Idiopathic / Familial
- Iron deficiency (ferritin under 50 ng per mL)
- Vitamin deficiencies (folate, B12)
- Chronic renal insufficiency
- Peripheral neuropathy / radiculopathy
- Medications (e.g., SSRIs)
- Pregnancy
- Restless Legs Syndrome

Obstructive Sleep Apnea

- Partial to complete upper airway obstruction
- Frequency of respiratory events (Apnea Hypopnea Index or AHI) helps define severity
 - Normal: AHI < 5 per hour
 - Mild: AHI 5 to 15 per hour
 - Moderate: AHI 15 to 30 / hour
 - Severe: AHI > 30 per hour (with upper range of ~ 120 per hour)
- OSA with excessive daytime sleepiness = “OSA syndrome”



OSA can be obvious to a bed partner, but will escape the clinician

- Only half of the patients with OSA will report symptoms on history, such as subjective sleepiness.
- Clinical exam carries poor sensitivity and specificity, regardless of subspecialty training
- Only half of the patients with OSA will demonstrate objective sleepiness based on a questionnaire (e.g., Epworth Sleepiness Scale) or daytime nap study (i.e., multiple sleep latency testing (MSLT))

Symptoms of sleep apnea are *not* sufficient for screening or diagnosis

Symptom	Sensitivity (95% CI)	Specificity (95% CI)	Positive Pred Value	Negative Pred Value
Snoring	90% (77% - 96%)	19% (9.7% - 35%)	15	8.9
Daytime Sleepiness	50% (41% - 60%)	61% (52% - 71%)	18	12
Morning headache	22% (12% - 32%)	85% (82% - 88%)	20	13
Witnessed apnea	80% (73% - 87%)	42% (33% - 51%)	19	7.1
Choking or gasping during sleep	52% (34% - 70%)	84% (77%-92%)	35	8.5

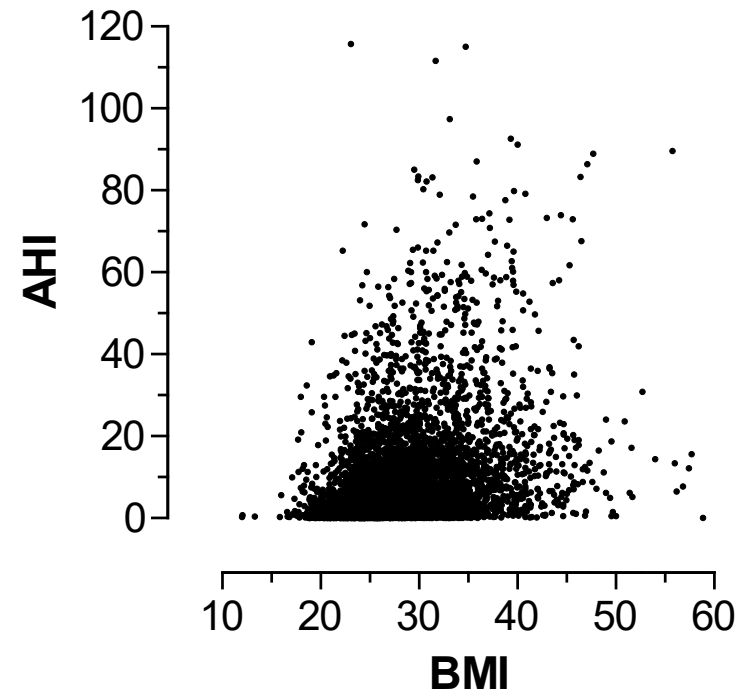
Modified from Myers KA et al. JAMA 2013; 310(7): 731

The sleep community appropriated the Mallampati, but that also lacks accuracy

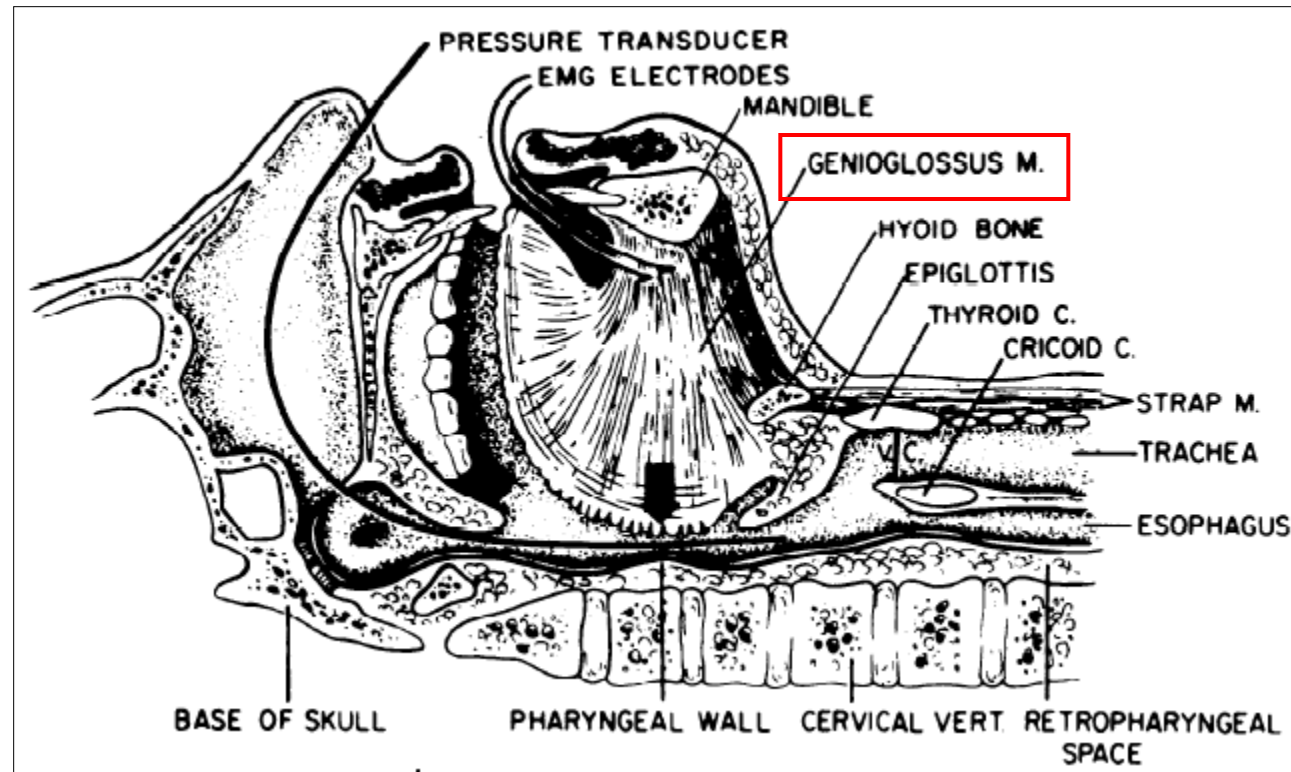
Finding	AHI Threshold (Events/Hour)	Sensi- tivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI) I ² , %, R ² , %	LR- (95% CI) I ² , %, R ² , %	Probability of Sleep Apnea, % (95% CI)	
						Positive Predictive Value (Baseline Prevalence) ^b	Negative Predictive Value (Baseline Prevalence) ^b
						6	6
						14	14
Signs							
Mallampati class ^e							
	≥5 ⁶⁴	65 (54-75)	60 (47-72)	1.6 (1.1-2.3)	0.60 (0.41-0.85)	9.3 (6.6-13)	3.7 (2.6-5.1)
						21 (15-27)	8.9 (6.3-12)
	≥15 ³¹	55 (40-69)	65 (57-72)	1.6 (1.1-2.2)	0.68 (0.47-0.98)	9.3 (6.6-12)	4.2 (2.9-5.9)
						21 (15-26)	10 (7.1-14)



Body Mass Index does not have a clear correlation with AHI



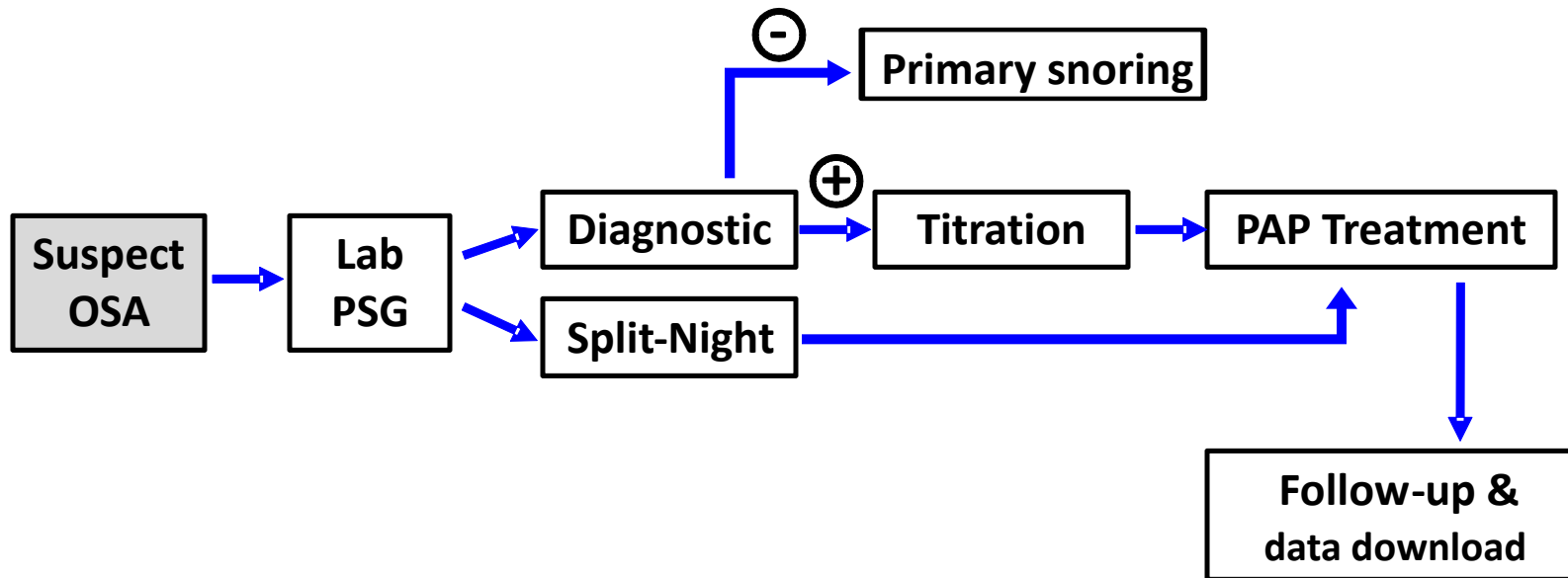
Genioglossus muscle can play an important and “hidden” role in the pathogenesis of OSA



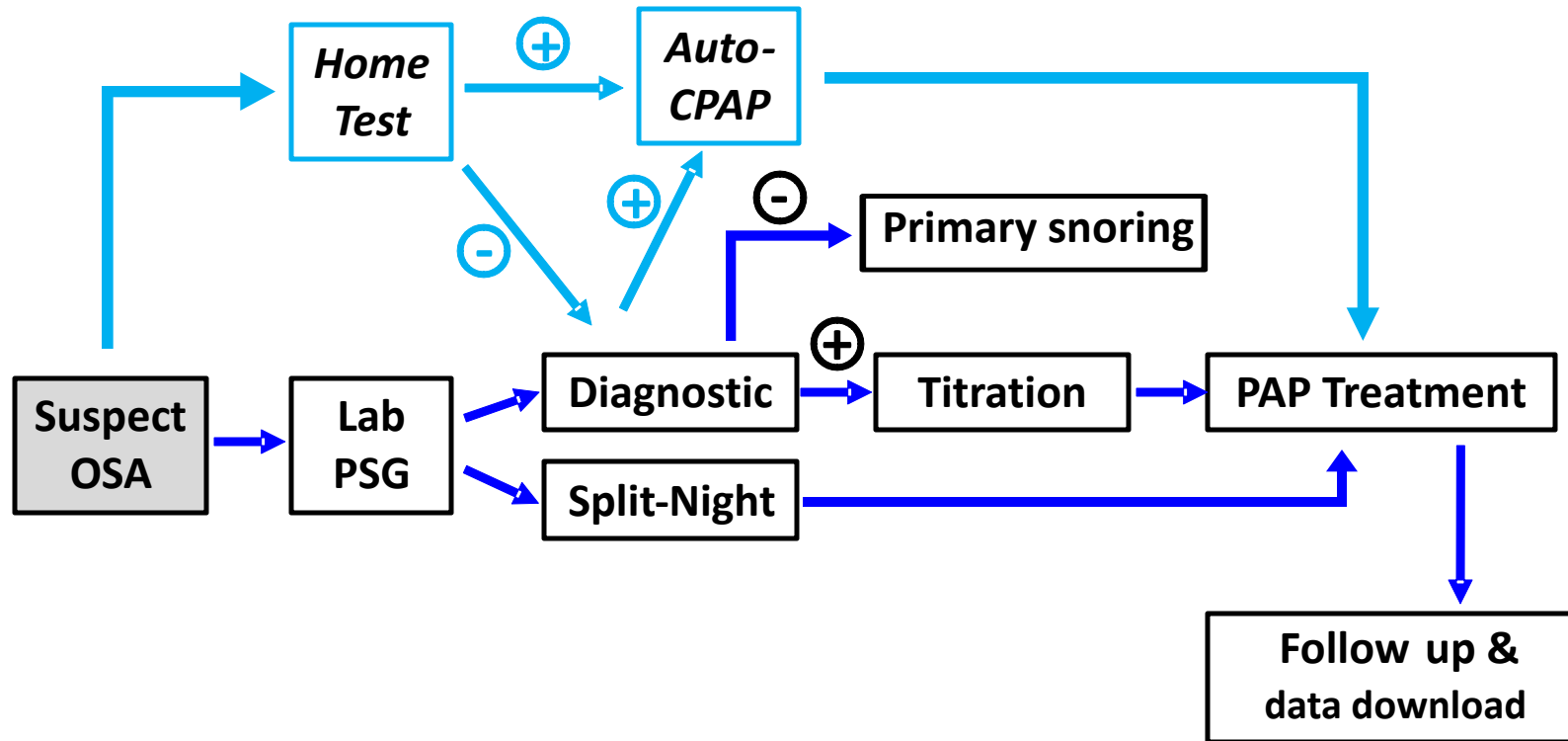
Sleep apnea is diagnosed with either a laboratory-based or home-based study



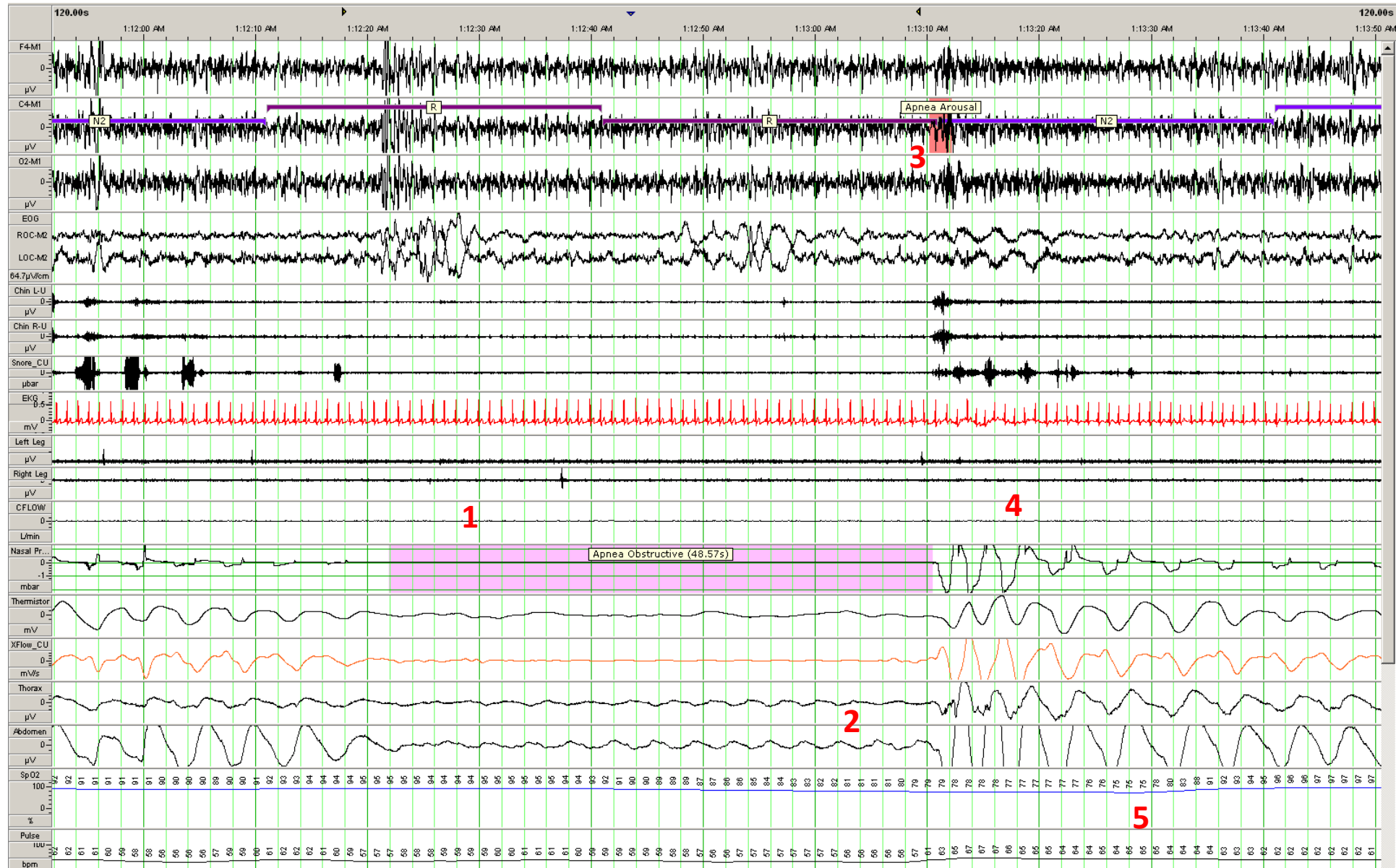
Lab-based diagnosis / treatment of OSA



Home-based diagnosis & management of OSA

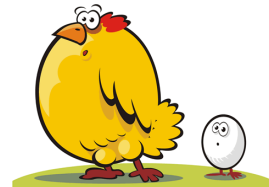


Features of an obstructive apnea recorded during polysomnography



Expanding list of complications from untreated OSA may be related to hypoxemia and/or sleep disturbance

- Hypersomnia
- Cognitive dysfunction
- Mood disorders
- Impaired work performance
- Accidents (MV/Work)
- Decreased QOL
- Hypertension
- Coronary disease
- Stroke
- Diabetes
- *Venous thrombo-embolism?*
- *Malignancy?*
- *Dementia?*

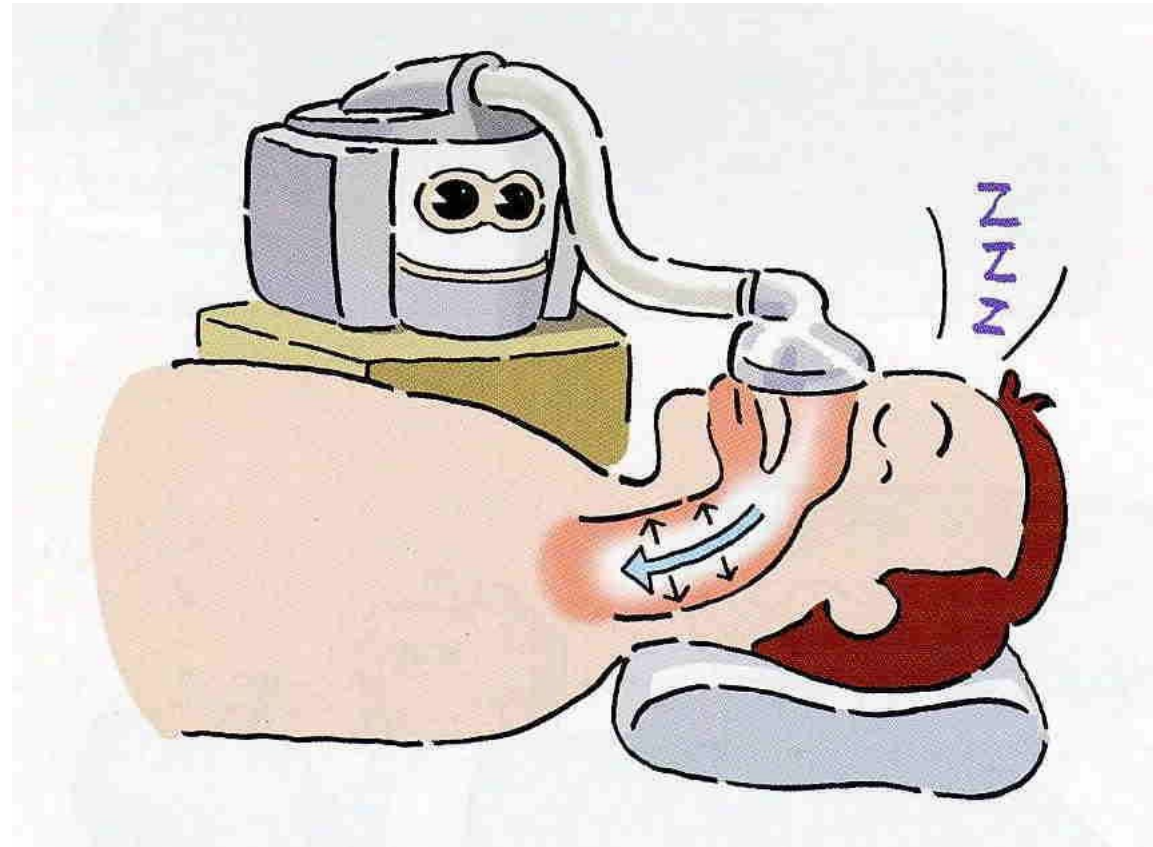


Management of sleep apnea is based on its severity and associated symptoms.



- Weight loss
- Positional therapy
- Nasal appliance
- Oral appliance
- Surgery
- **Positive airway pressure**
- ? *Medications*
- ? *Upper airway stimulators*

PAP remains gold standard therapy
for moderate to severe OSA.



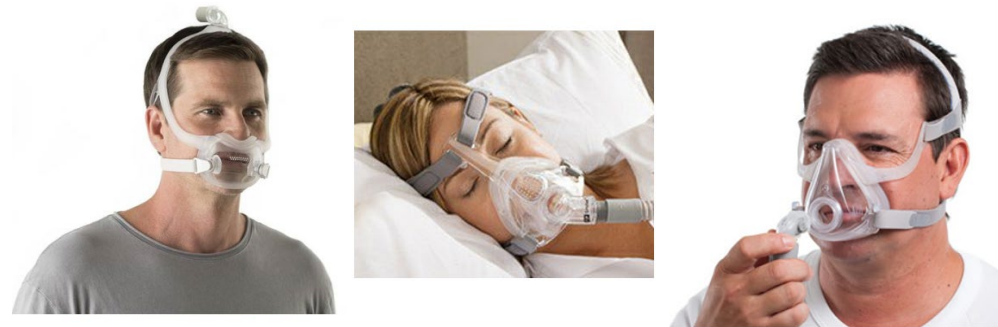
Sullivan CE, Issa FG, Berthon-Jones M, Eves L; *Lancet* 1981; 1: 862–865.

Range of PAP masks

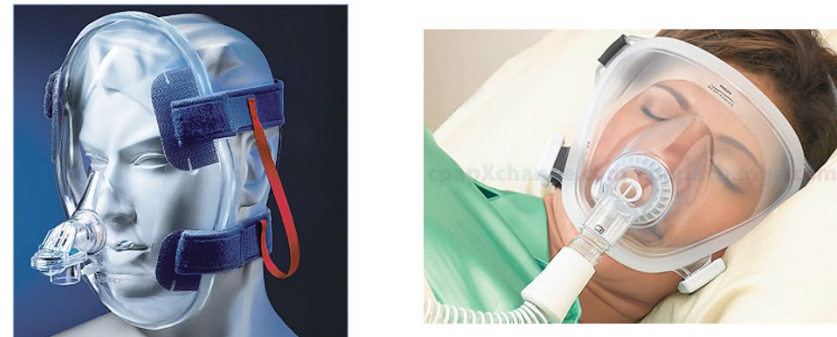
Nasal masks



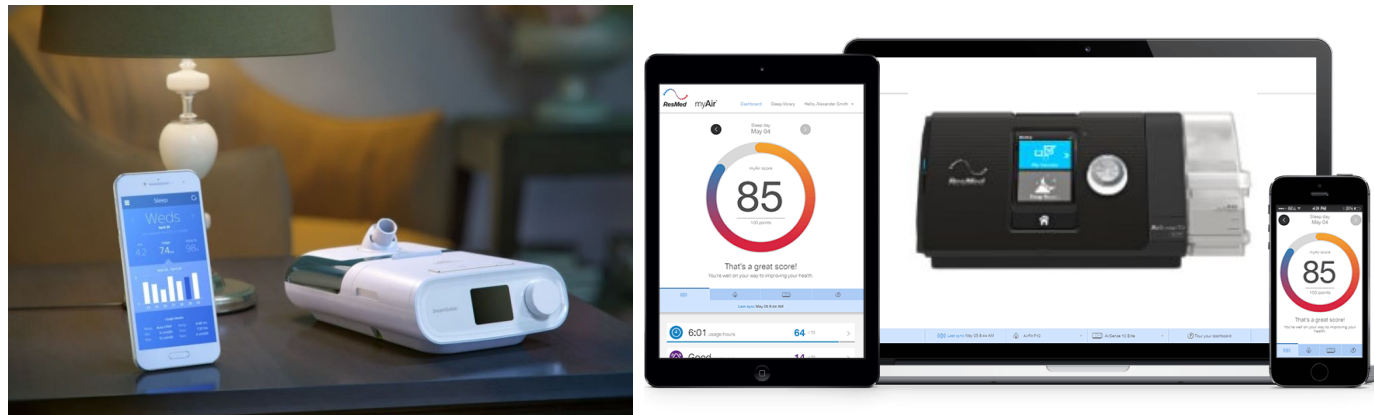
Oronasal full face masks



Total face masks



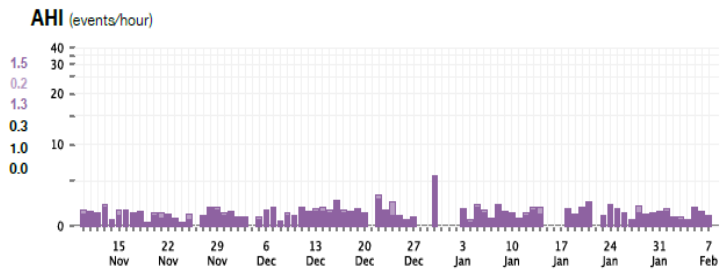
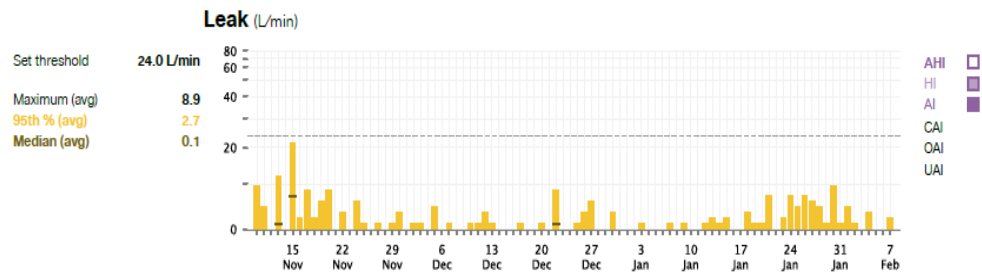
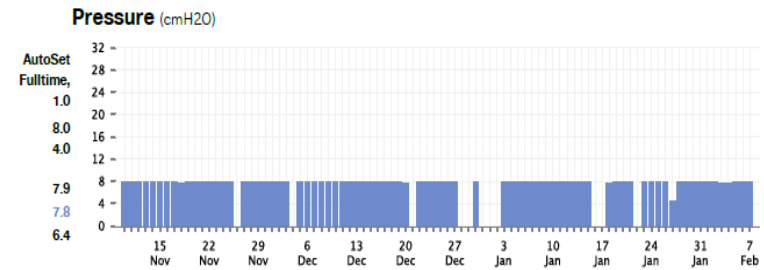
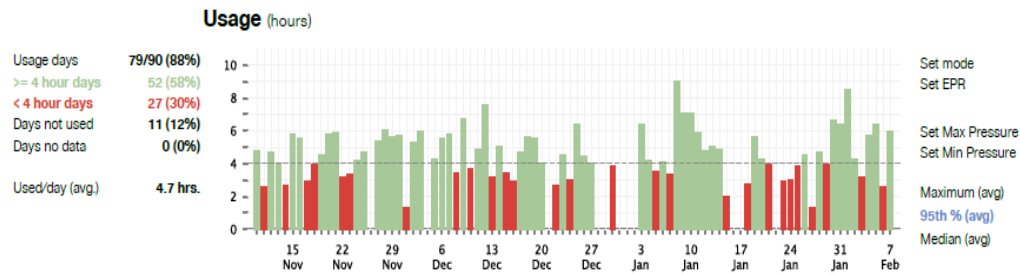
PAP devices can also provide direct feedback to the patient and have improved adherence



Fox N, et al. *Sleep* 2012; 35: 477-481

Kuna ST, et al. *Sleep* 2015; 38: 1229 - 1236

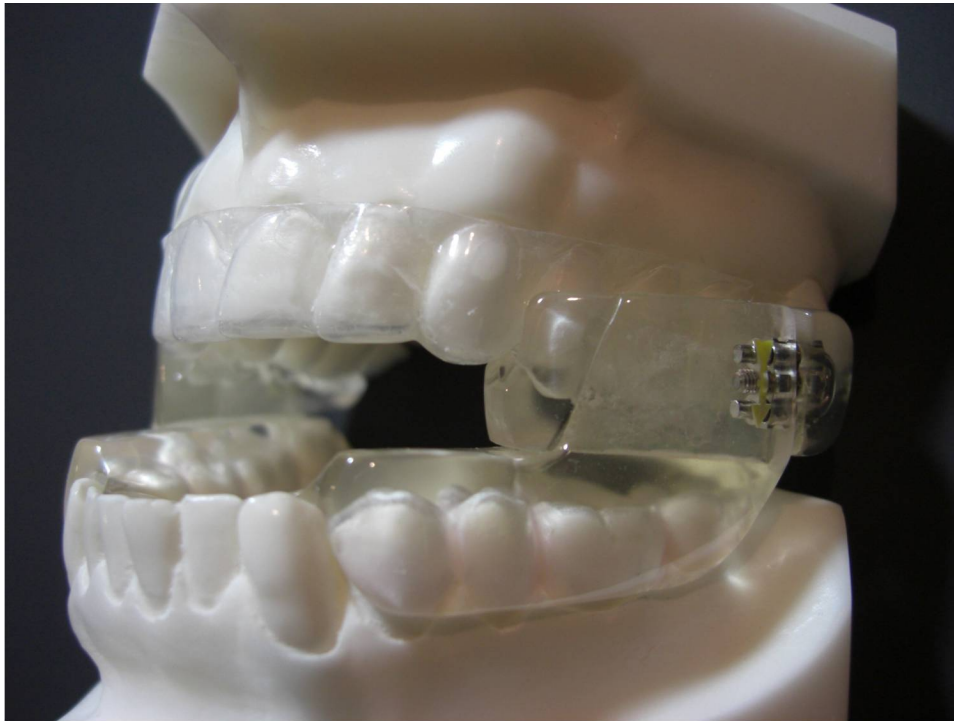
Clinicians can interrogate devices to obtain usage, leaks, and machine-estimated AHI



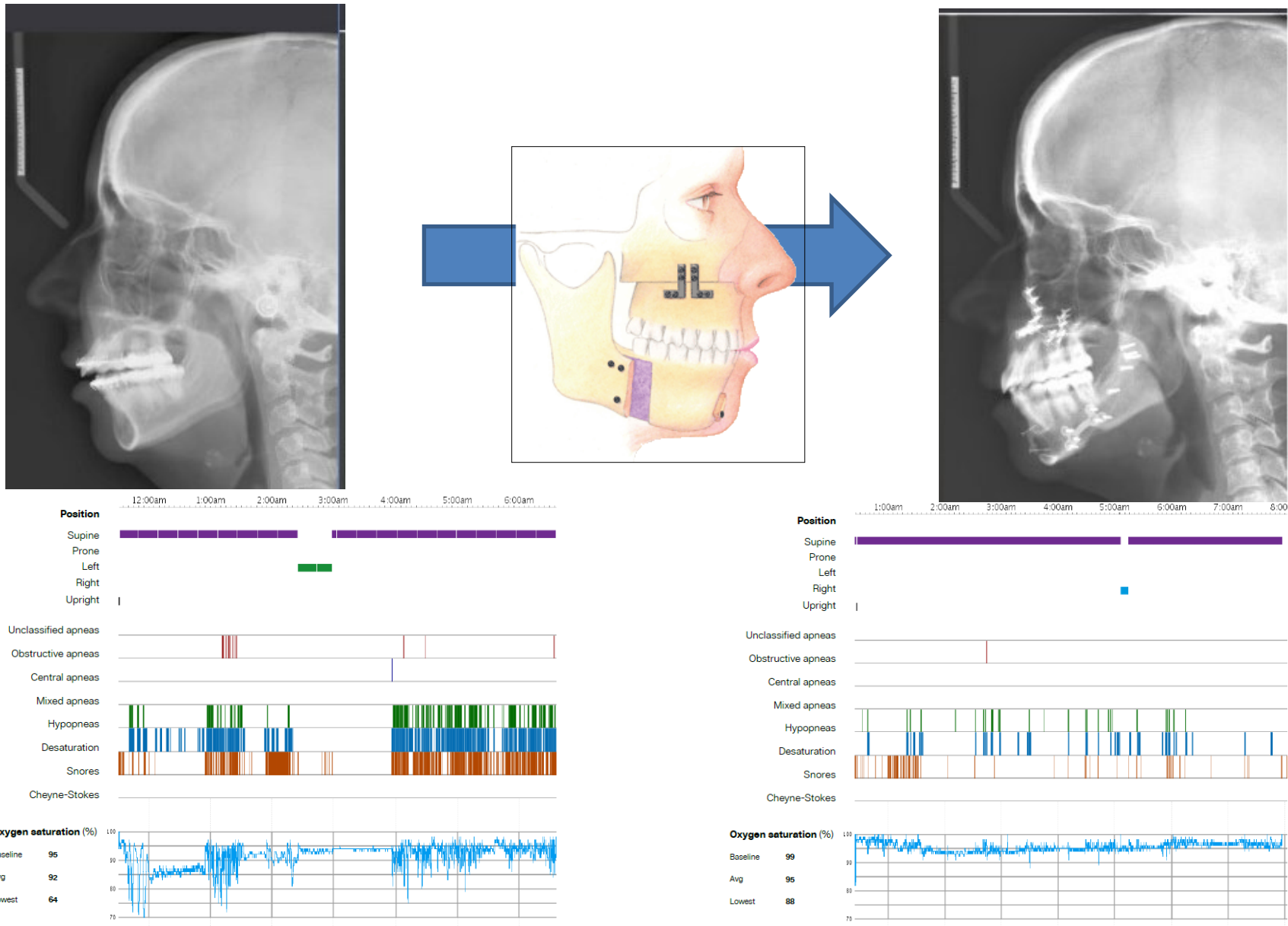
Common CPAP issues and solutions

- Mask leaks / aerophagia
 - Oral dryness
 - “Rain out”
 - Nasal congestion
 - Lack of control
 - Pressure intolerance
- ✓ Mask fitting
 - ✓ Heated humidification
 - ✓ Heated tubing
 - ✓ Nasal steroid spray
 - ✓ Pressure relief on CPAP or change to Bilevel PAP

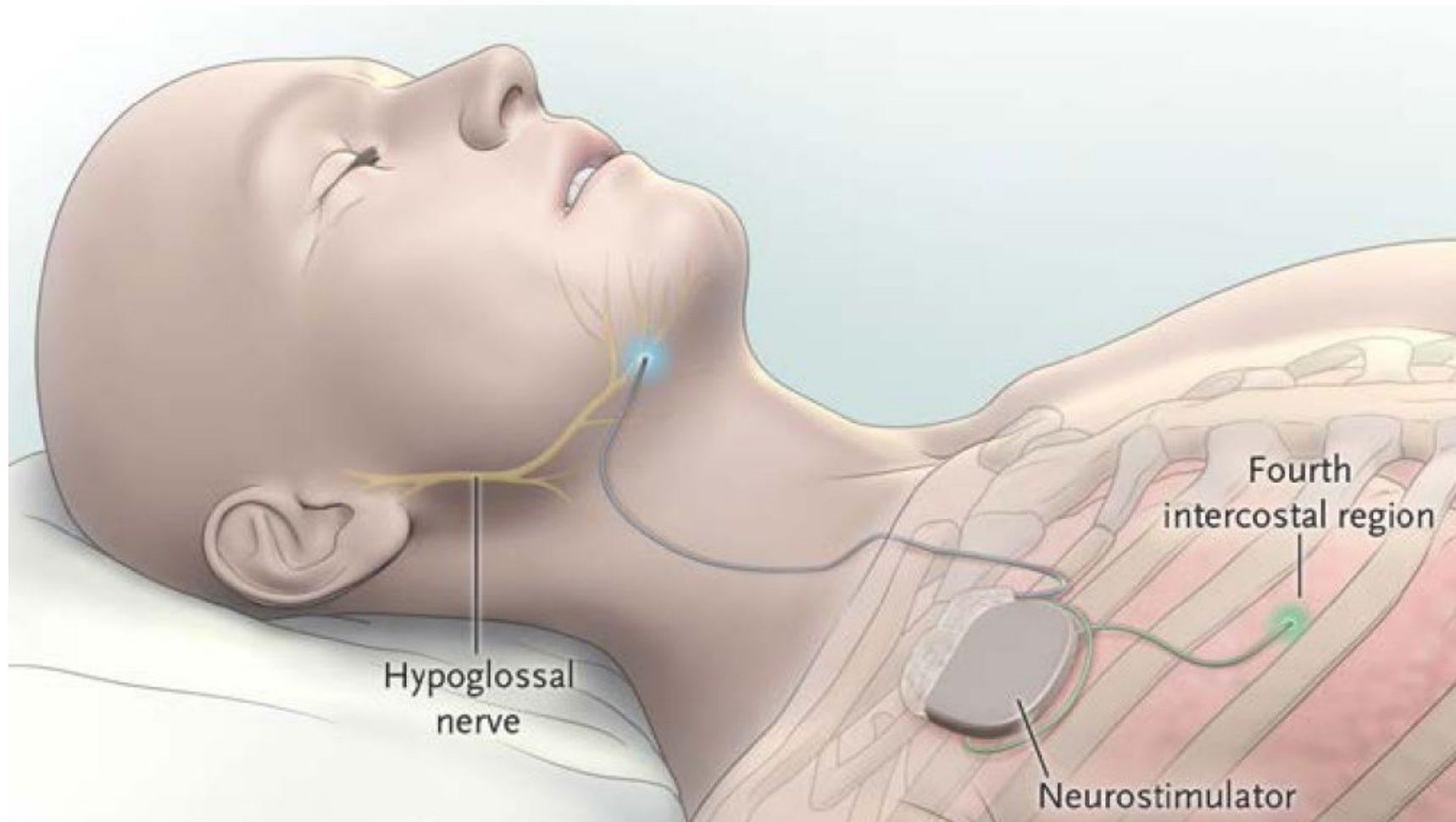
Dental / Oral appliances can be used for mandibular advancement to treat OSA



Maxillomandibular Advancement (MMA)

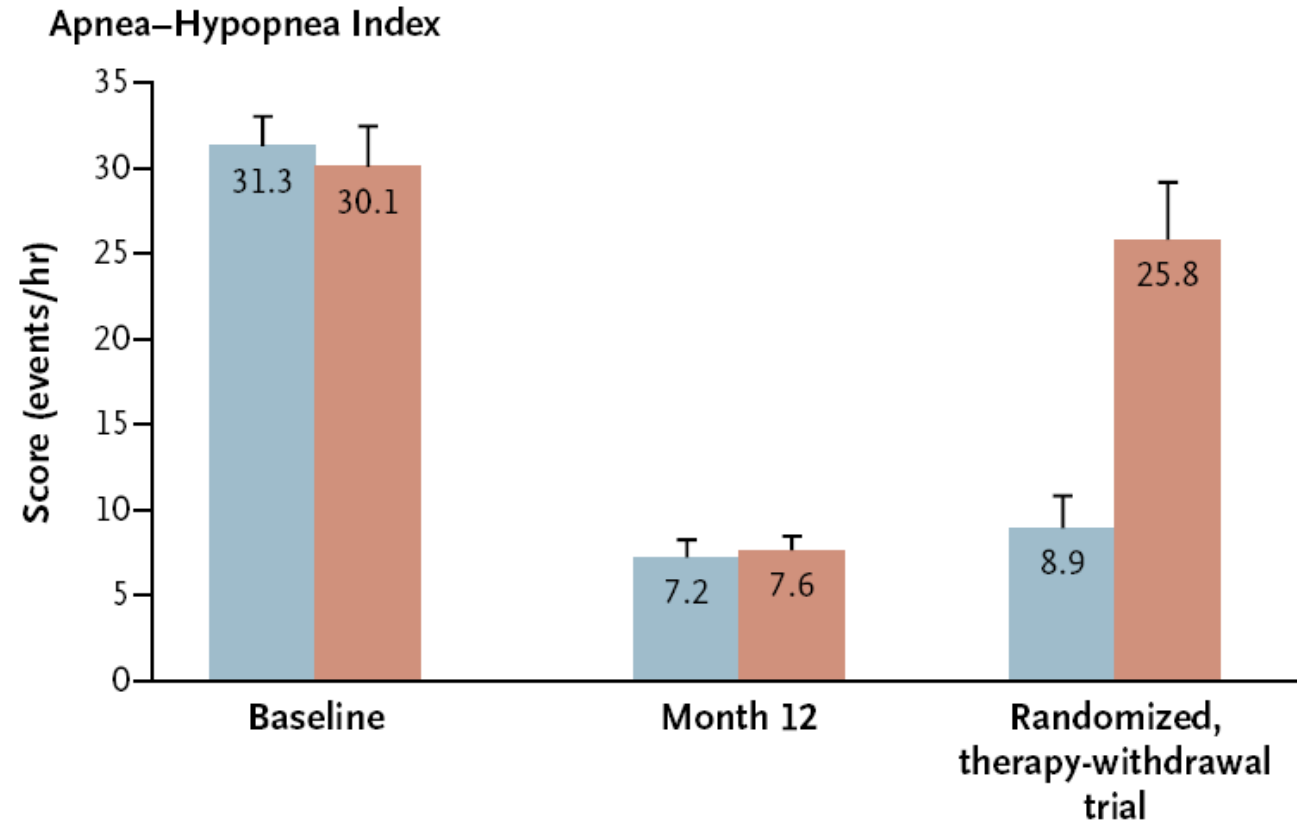


Upper Airway Stimulators may address “hidden” etiology of OSA

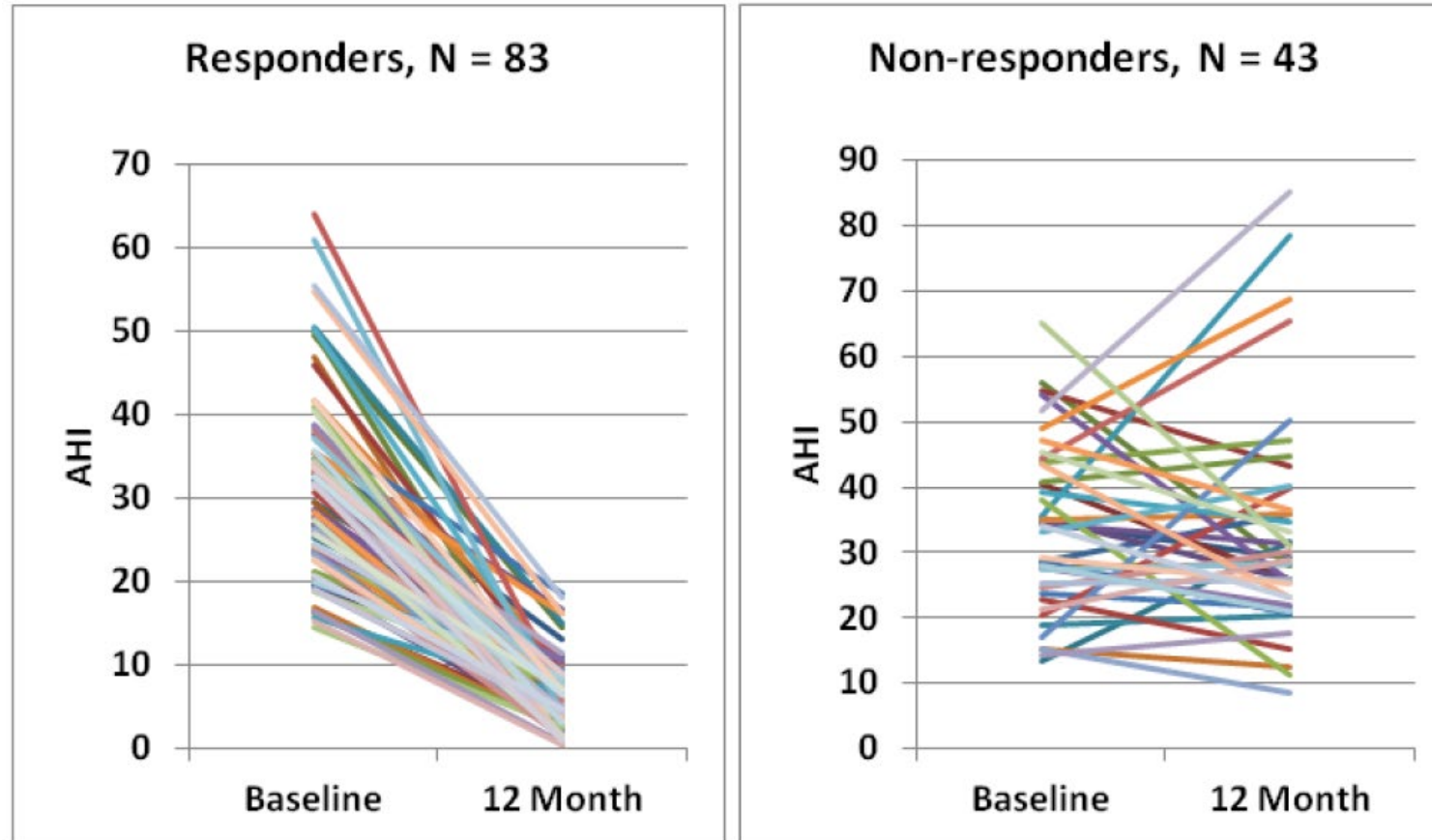


Strollo PJ et al. *NEJM* 2014; 370: 139-149

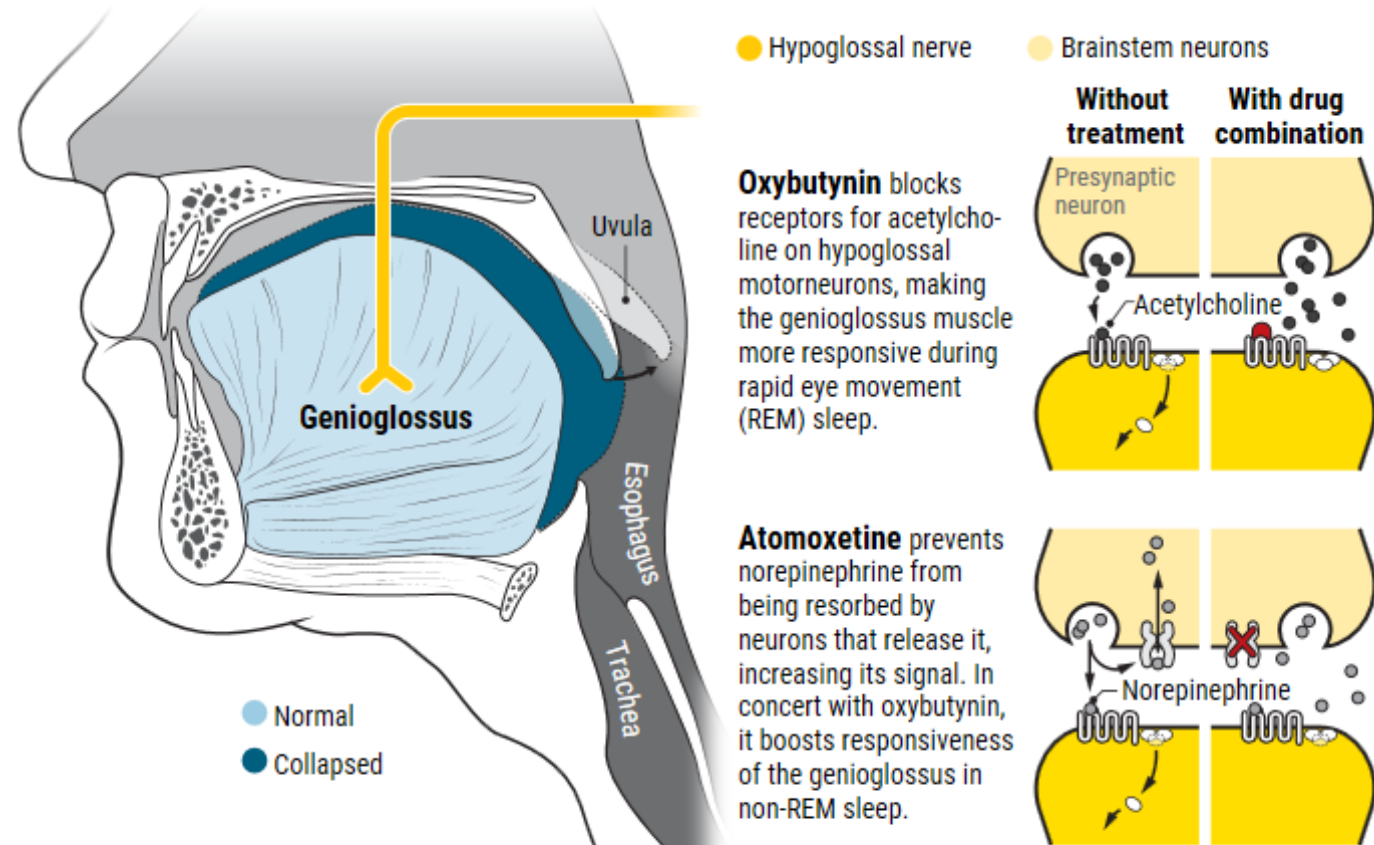
Hypoglossal stimulator reduced frequency of respiratory events, improved saturations, and reduced sleepiness



19 of the 126 participants had worsening of their sleep apnea



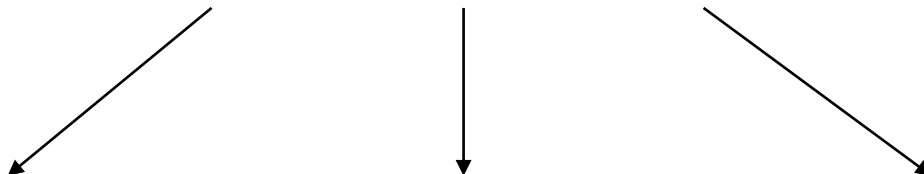
Pharmacologic activation of upper airway muscles? (ATOSA trial; PI: Wellman)



V. ALTOUNIAN/SCIENCE

doi:10.1126/science.aav4379

Common Sleep Disorders



Insufficient Sleep

- Behavioral
- Medications
- Insomnia
- Altered sleep-wake cycle

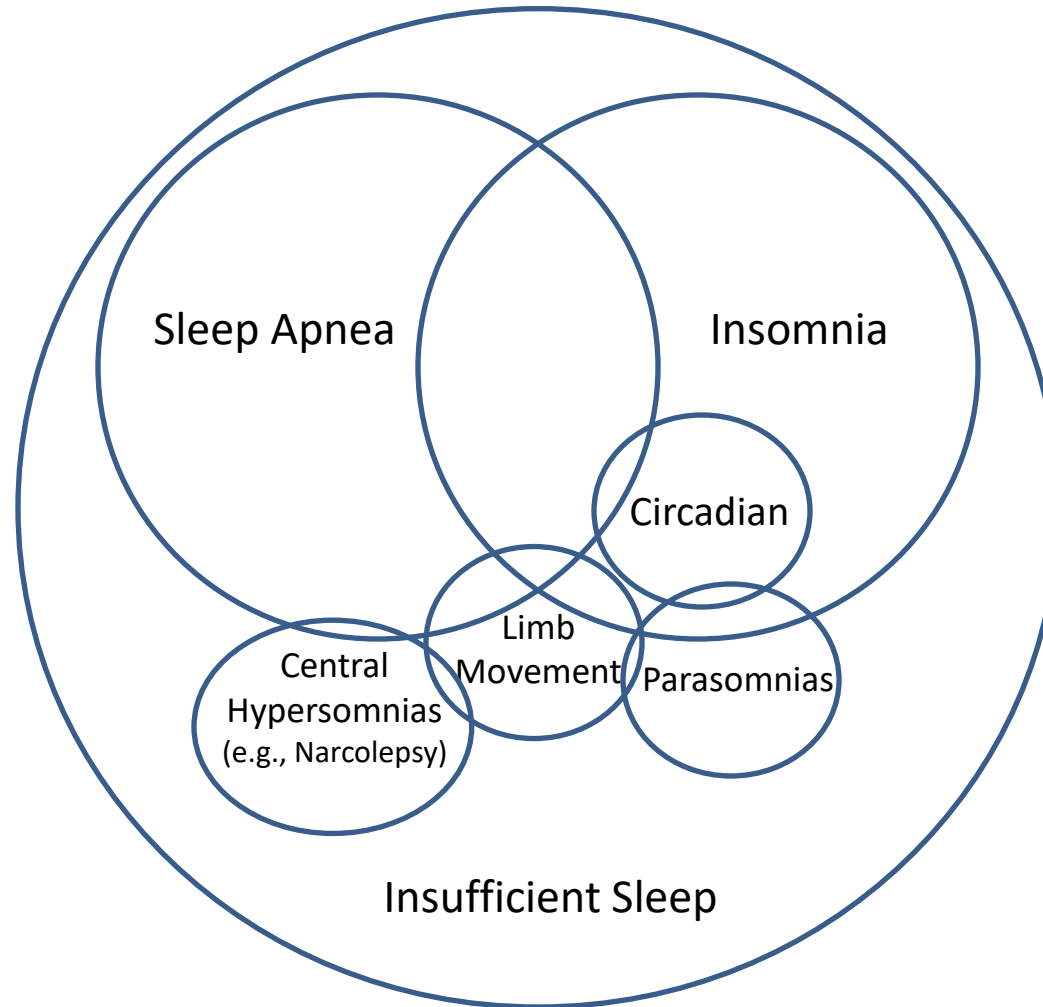
Sleep Fragmentation

- Sleep Apnea
- Limb movement d/o
- Pain
- Noise
- Insomnia

High Central Drive

- Narcolepsy / Idiopathic
- Post-traumatic / TBI
- Sedatives / Pain meds
- Chronic insomnia

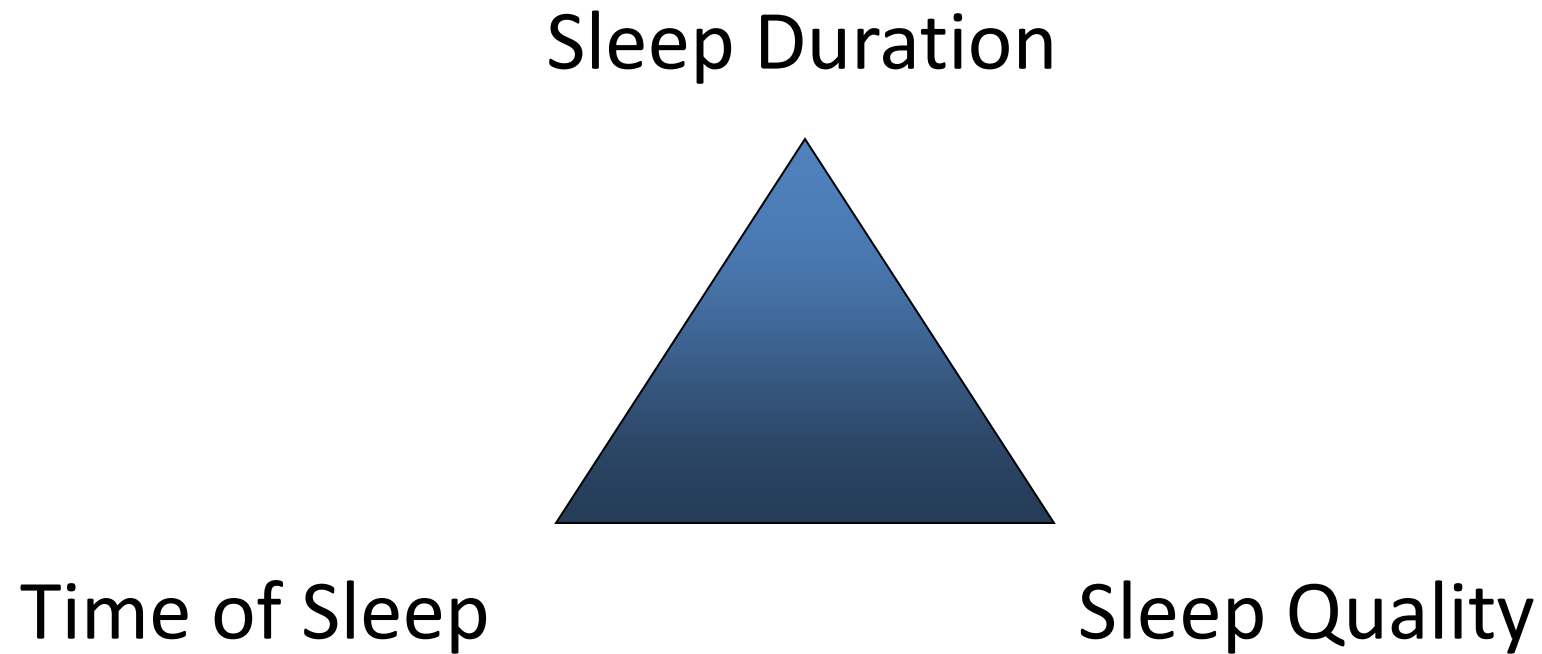
Common sleep disorders often overlap



Personalized Sleep Apnea Medicine will bring the next era and challenge current practices

- **Predict**
 - Disease with multivariable instruments / genetics (OMIC)
 - Benefit from specific therapy
 - Response to therapy for symptom / complication
- **Prevent**
 - Primary prevention during childhood
 - Secondary prevention in asymptomatic OSA patients
- **Personalize** diagnosis and treatment
 - Identify subgroups / phenotypes based on sx, pathophys, molecular signatures
 - Move away from AHI-based approach
 - Extract more data from diagnostic studies and therapies
- Patient engagement to **Participate** in care and research
 - Patient-centered outcomes based on end-user
 - Coordinated care management

Cornerstones of Good Sleep



Questions?

