Beyond the Pearls: Intense Sleep Medicine Board Review

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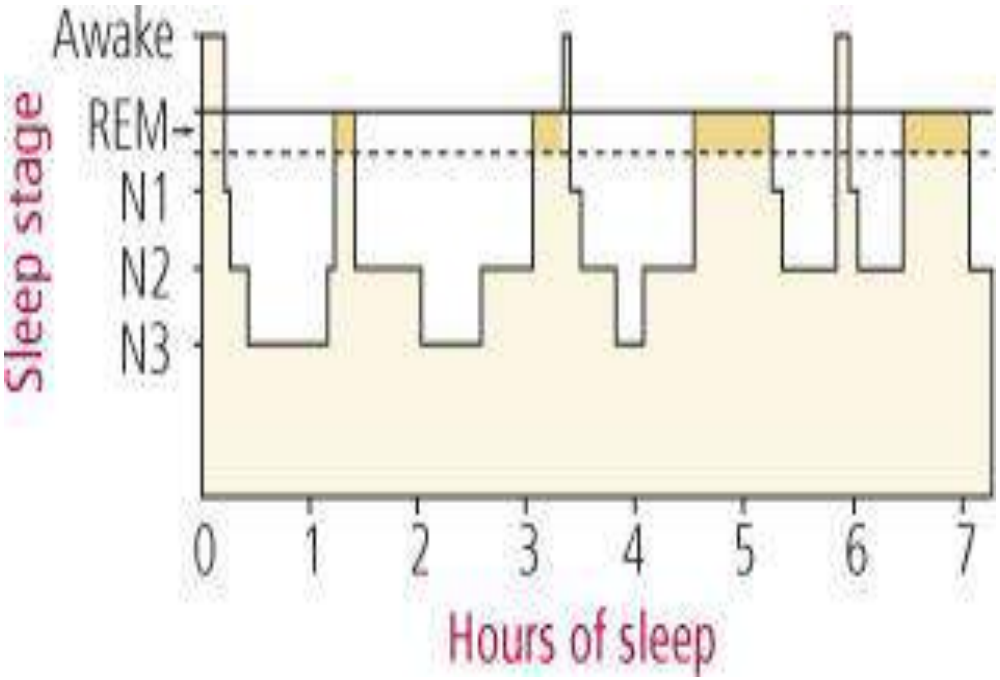
Outline

- Basic sleep physiology
- Sleep disordered breathing
- Insomnia
- Hypersomnia
- Circadian rhythm disorders
- Parasomnias
- Sleep related movement disorders

Normal Sleep and Sleep Stages

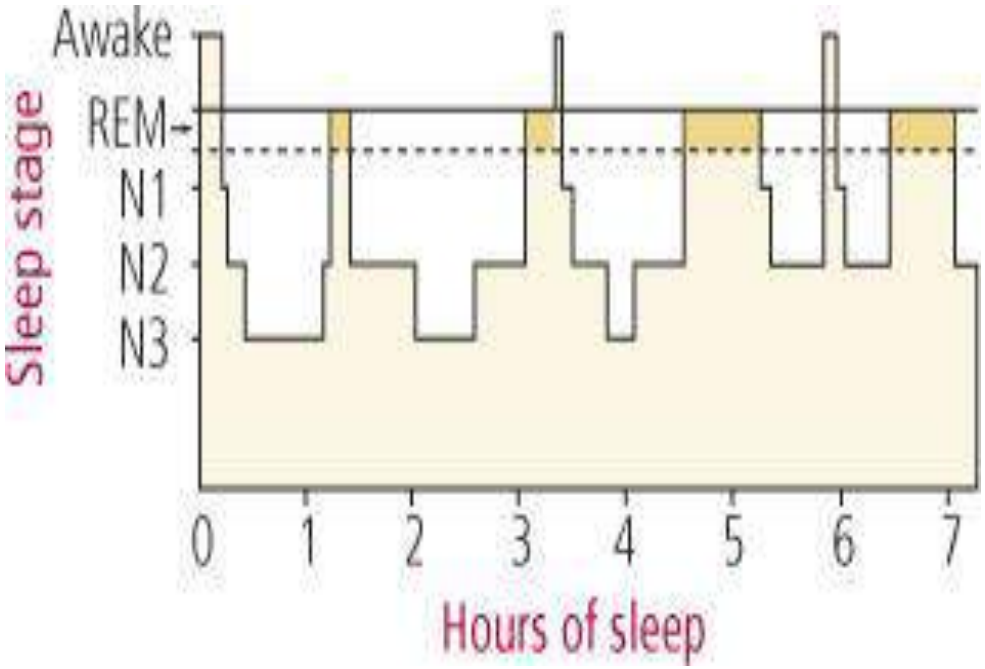
Normal Sleep in Adults

- Normal sleep is divided into **NREM** and **REM**
- NREM is further divided into progressively deeper stages:
  - Stage **N1**
  - Stage **N2**
  - Stage **N3**
- As NREM stages progress, stronger stimuli are required to awaken meaning a high arousal threshold
  - “Sleep cycle” phone app
  - **Sleep inertia**



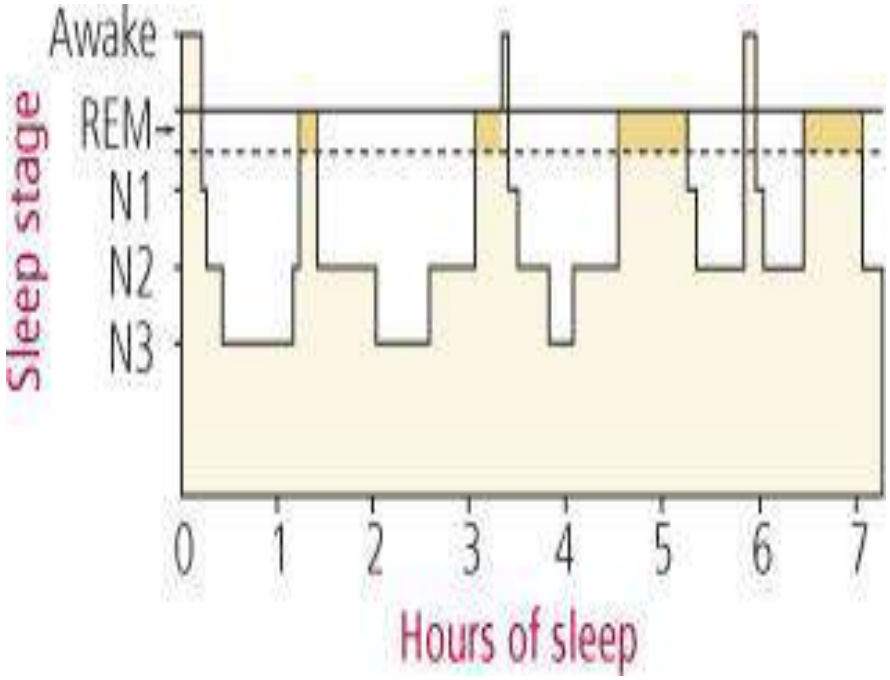
Normal Sleep in Adults

- **Wake** usually transitions into light **NREM** sleep via the posterior hypothalamus
  - Exception: narcolepsy and newborns



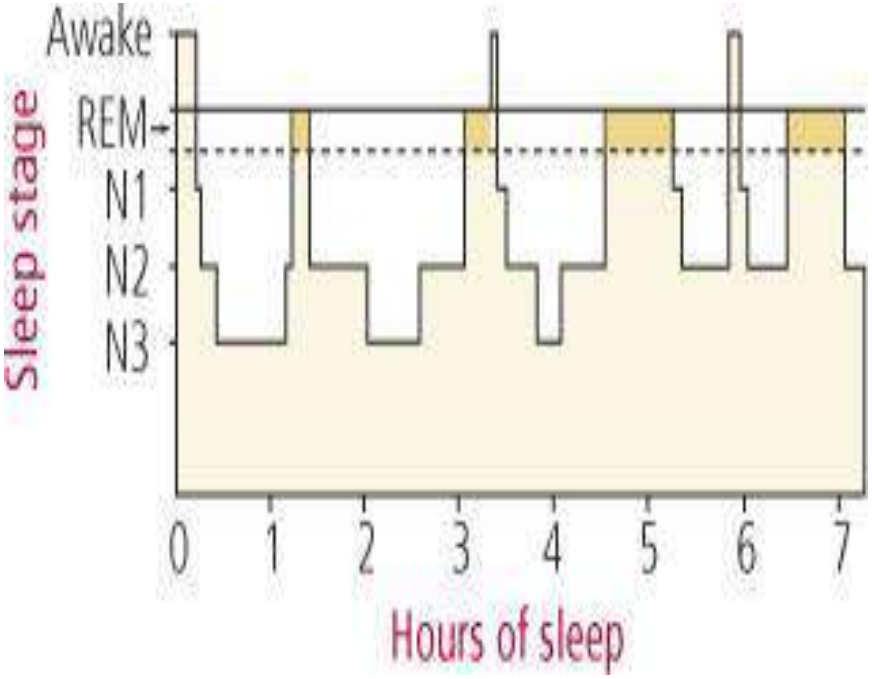
Normal Sleep in Adults

- **REM** sleep follows NREM sleep and occurs **4-5 times** during an 8 hour sleep period
- The first REM period may be less than **10 min**, while the last may exceed **60 min**
- NREM-REM cycle varies in length from **70-120 min**



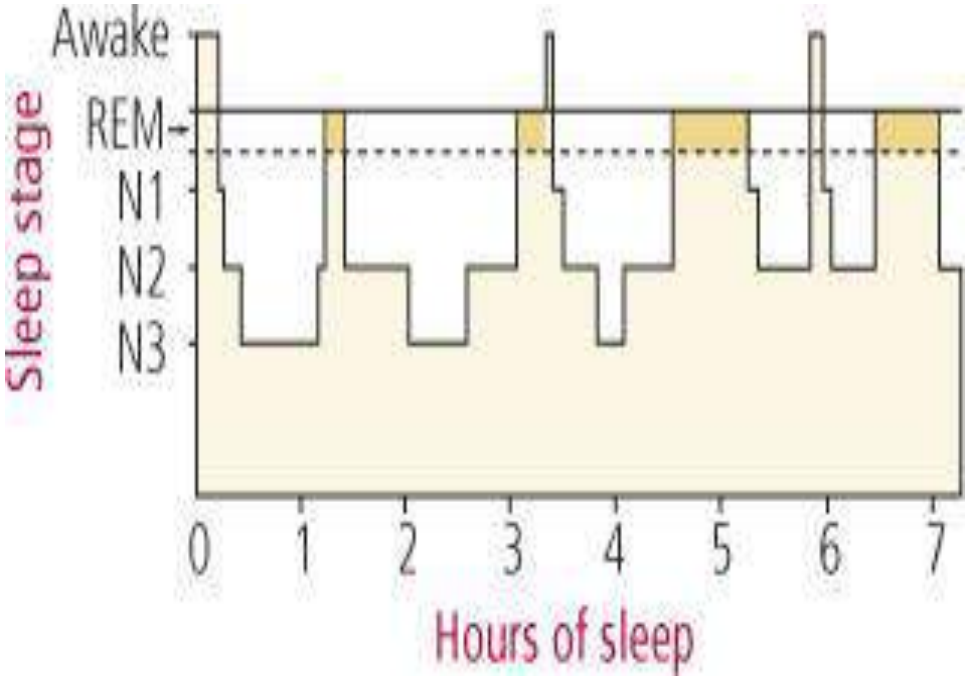
Normal Sleep in Adults

- REM sleep has tonic and phasic components
  - **Phasic REM:**
    - Sympathetically driven
    - Rapid eye movements
    - Muscle twitches
    - Respiratory variability
  - **Tonic REM:**
    - Parasympathetically driven
    - No eye movements

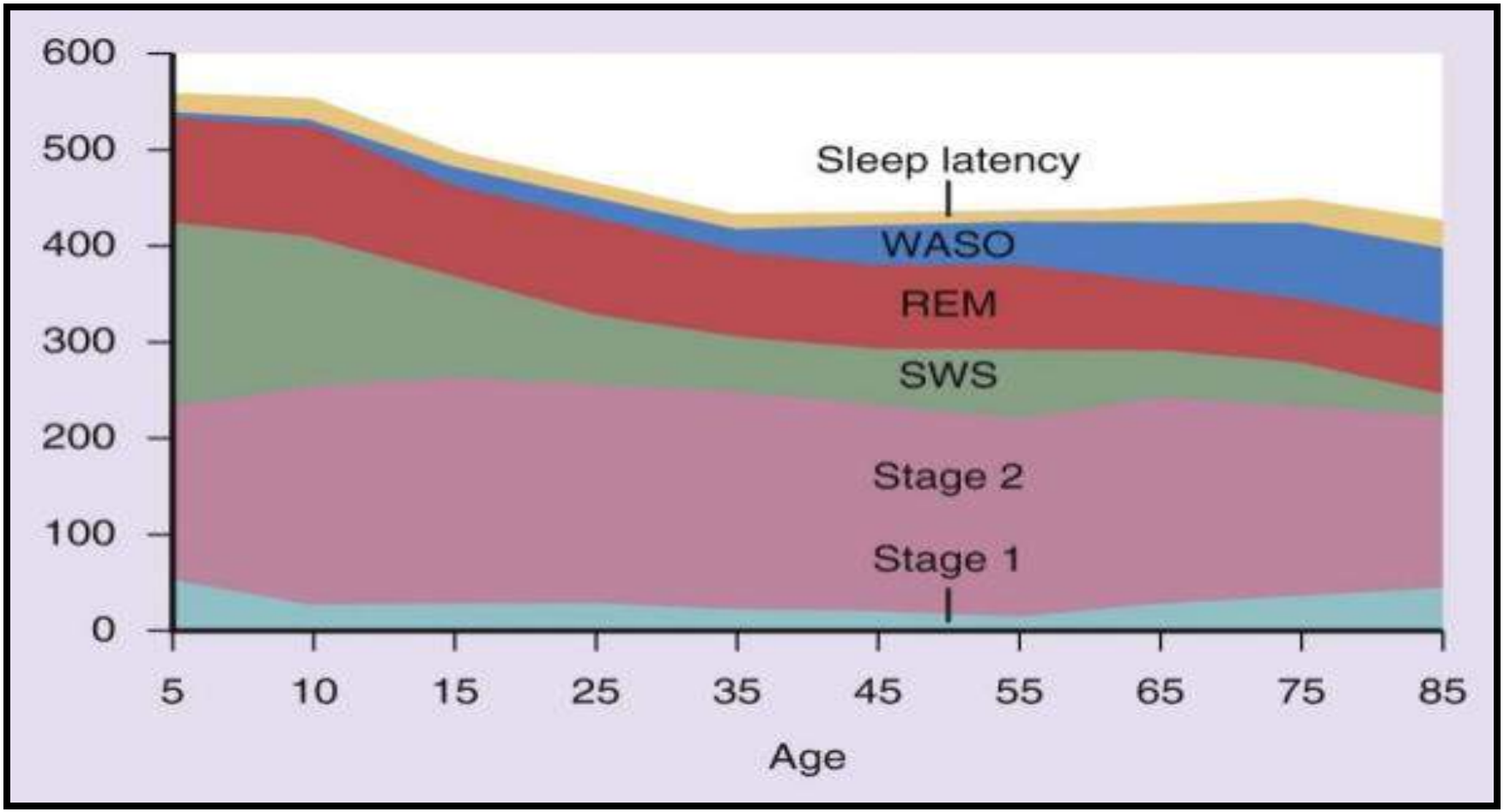


Normal Sleep in Adults

- **N3** sleep is mainly at the beginning night, whereas **REM** sleep predominates in the last third of the night
- **NREM parasomnias** typically occur in the first third of the night during N3 sleep
- **REM parasomnias** typically occurs in the last half of the night



Changes in sleep with age

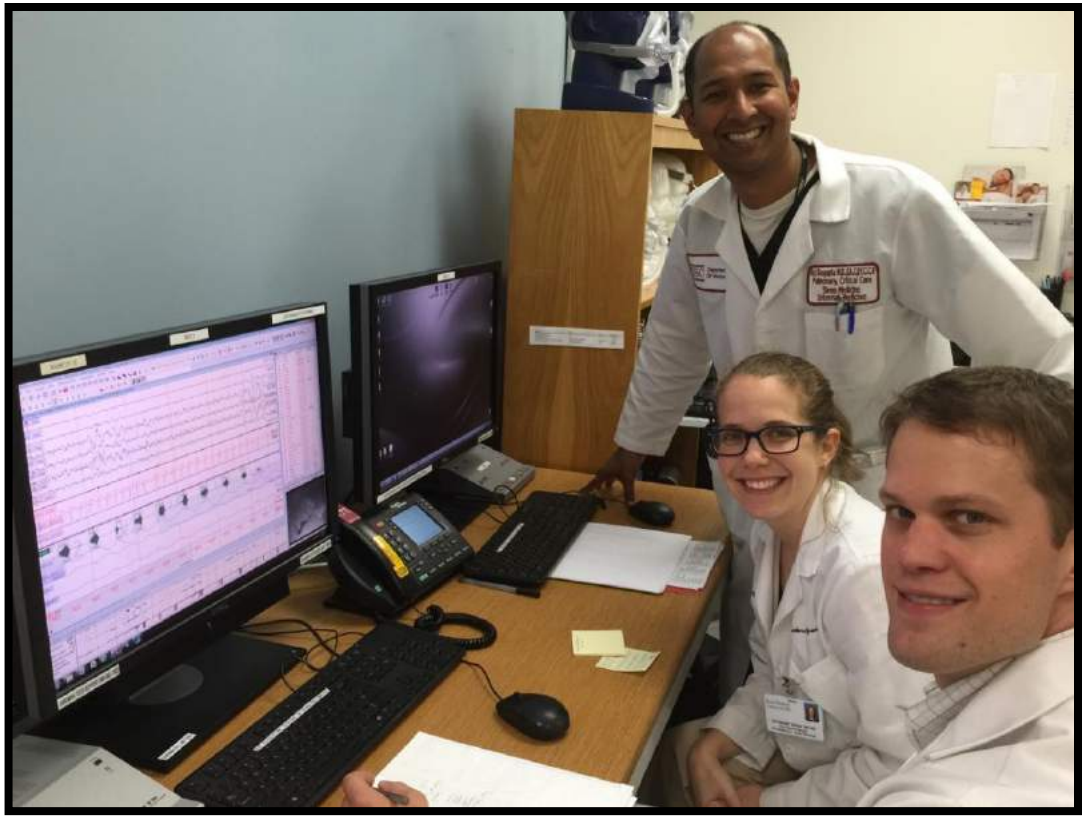


Normal WASO is 5-10% in adults

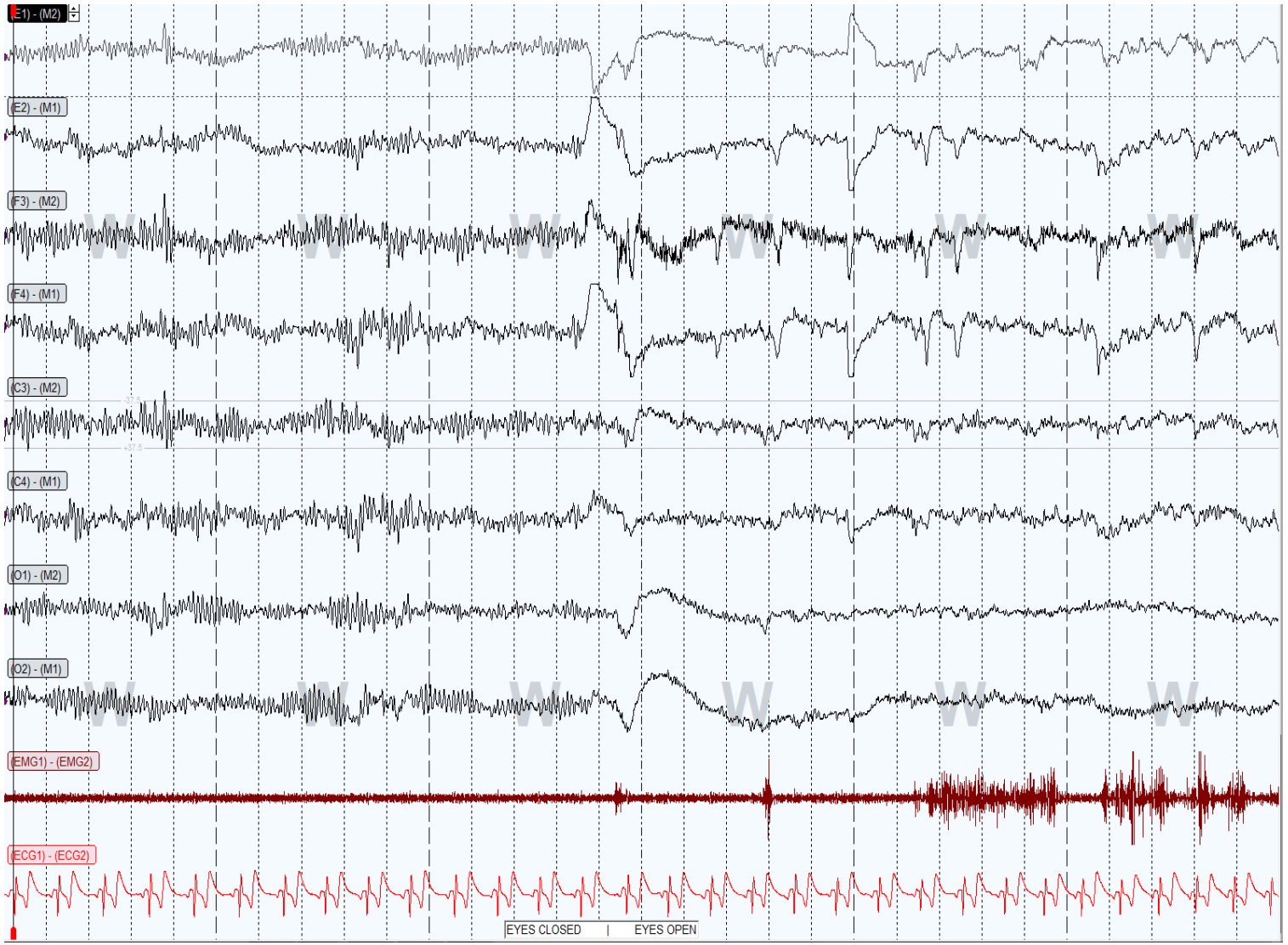
Sleep Physiology: NREM vs. REM

Physiological Process	NREM (versus wake)	REM
Heart rate **Blood pressure**	Decreases	Increases and varies v NREM
Respiratory Rate	Decreases	Increases and varies v NREM
Respiratory Parameters	Minute vent decreases Apnea threshold increases	Increases and varies from NREM; may show brief pauses; cough suppressed
Muscle tone **Airway resistance**	Similar	Absent Increases and varies
Autonomic Nervous System	Stability Increased vagal tone	Instability Vagal and sympathetic surges

Sleep Staging



Awake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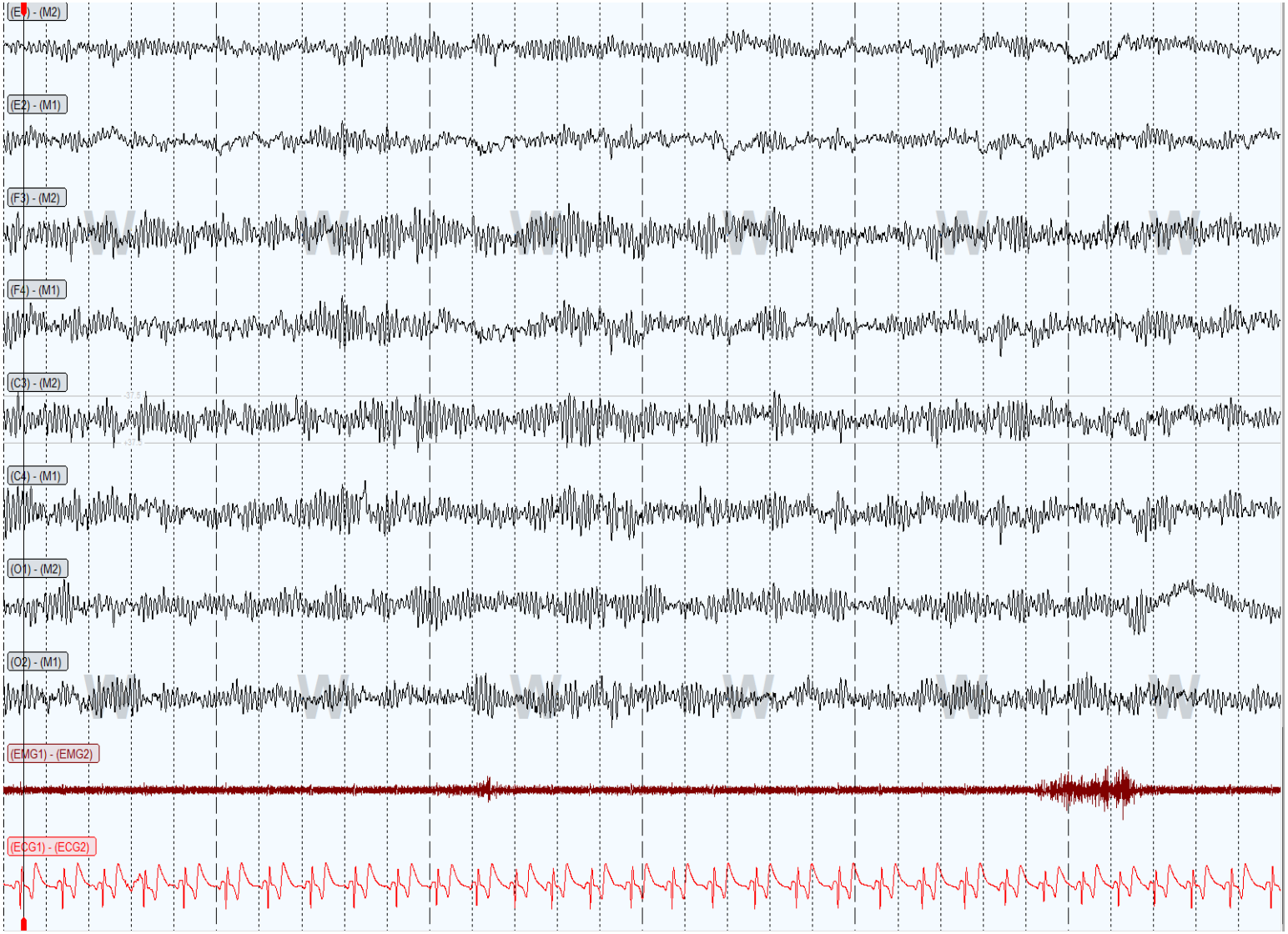
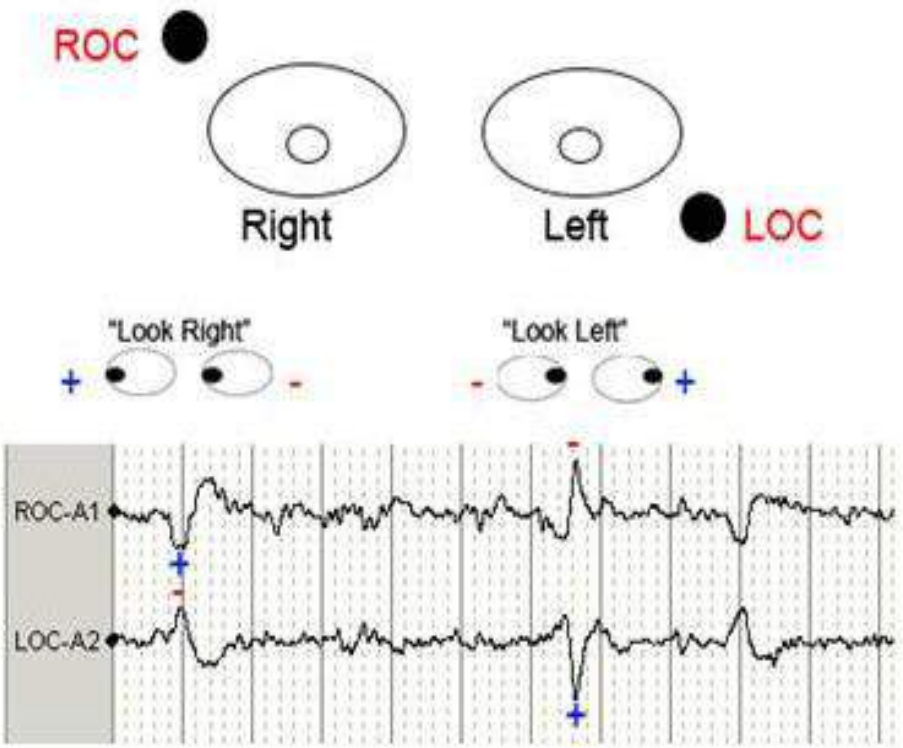
(F3) - (M2)
(F4) - (M1)
(C3) - (M2)
(C4) - (M1)
(O1) - (M2)
(O2) - (M1)
(EMG1) - (EMG2)
(ECG1) - (ECG2)
EYES CLOSED | EYES OPEN

Awake Eyes Closed



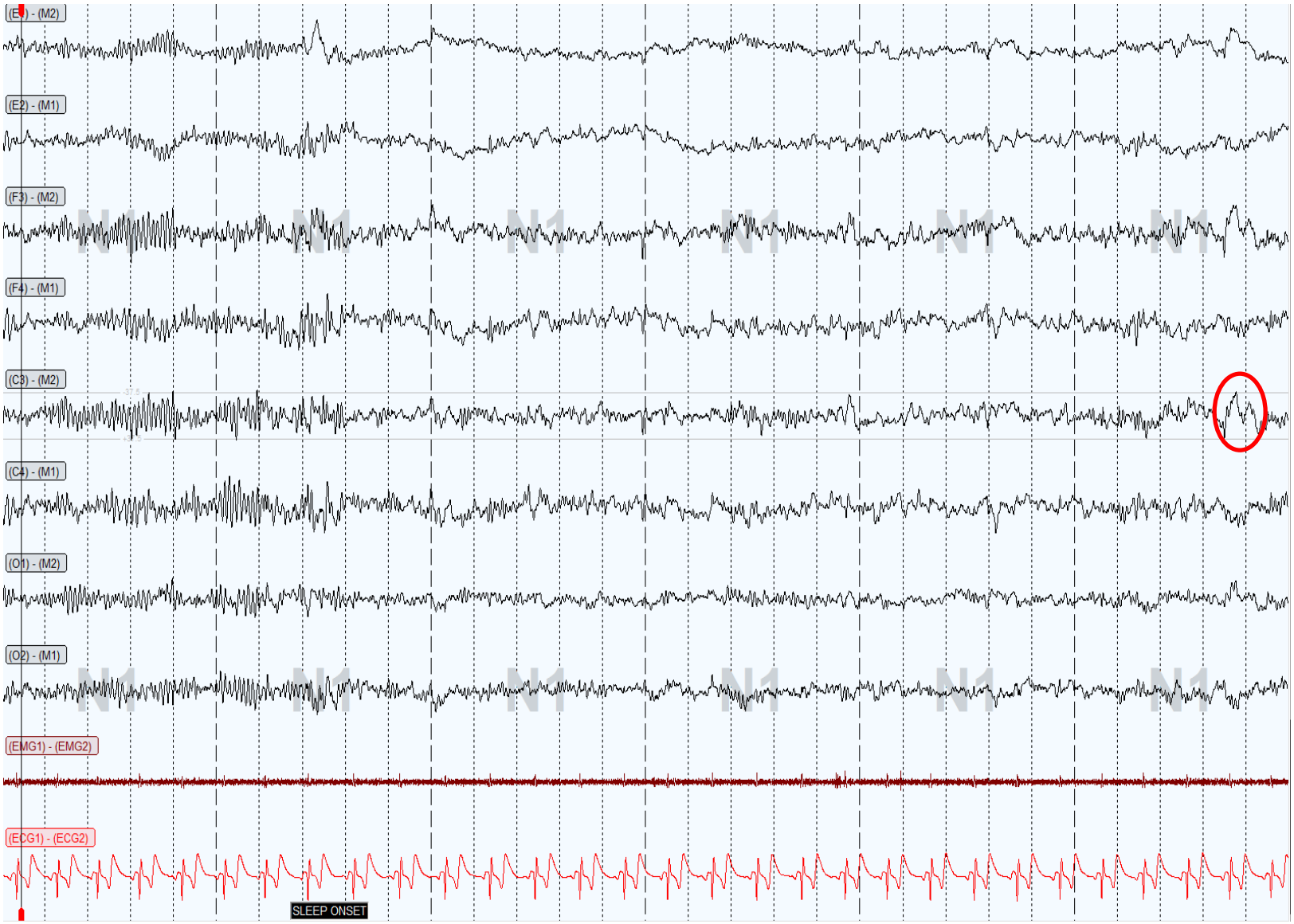
Awake Eyes Closed

- **EOG**: Slow rolling eye movements
- **EEG**: Over 50% of epoch is alpha activity usually 8-13 cycles per second best seen in the occipital region
- **Sub-mental EMG**: Relatively high tone



- EOG: Electro-oculogram ROC: Right outer canthus LOC: Left outer canthus
- Canthus: Either corner of the eye where the upper and lower eyelids meet

Stage N1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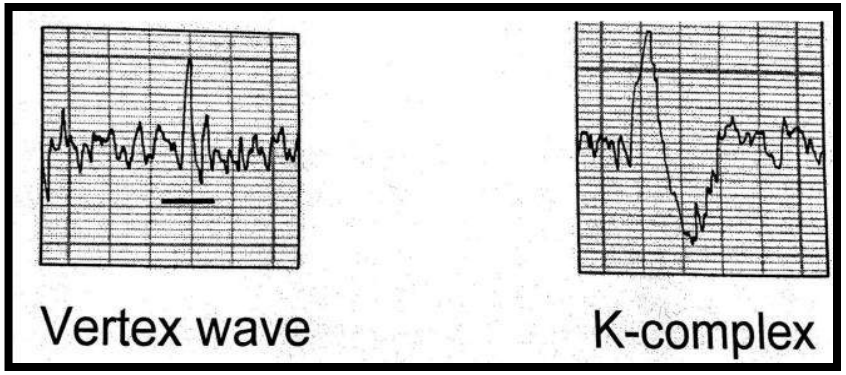
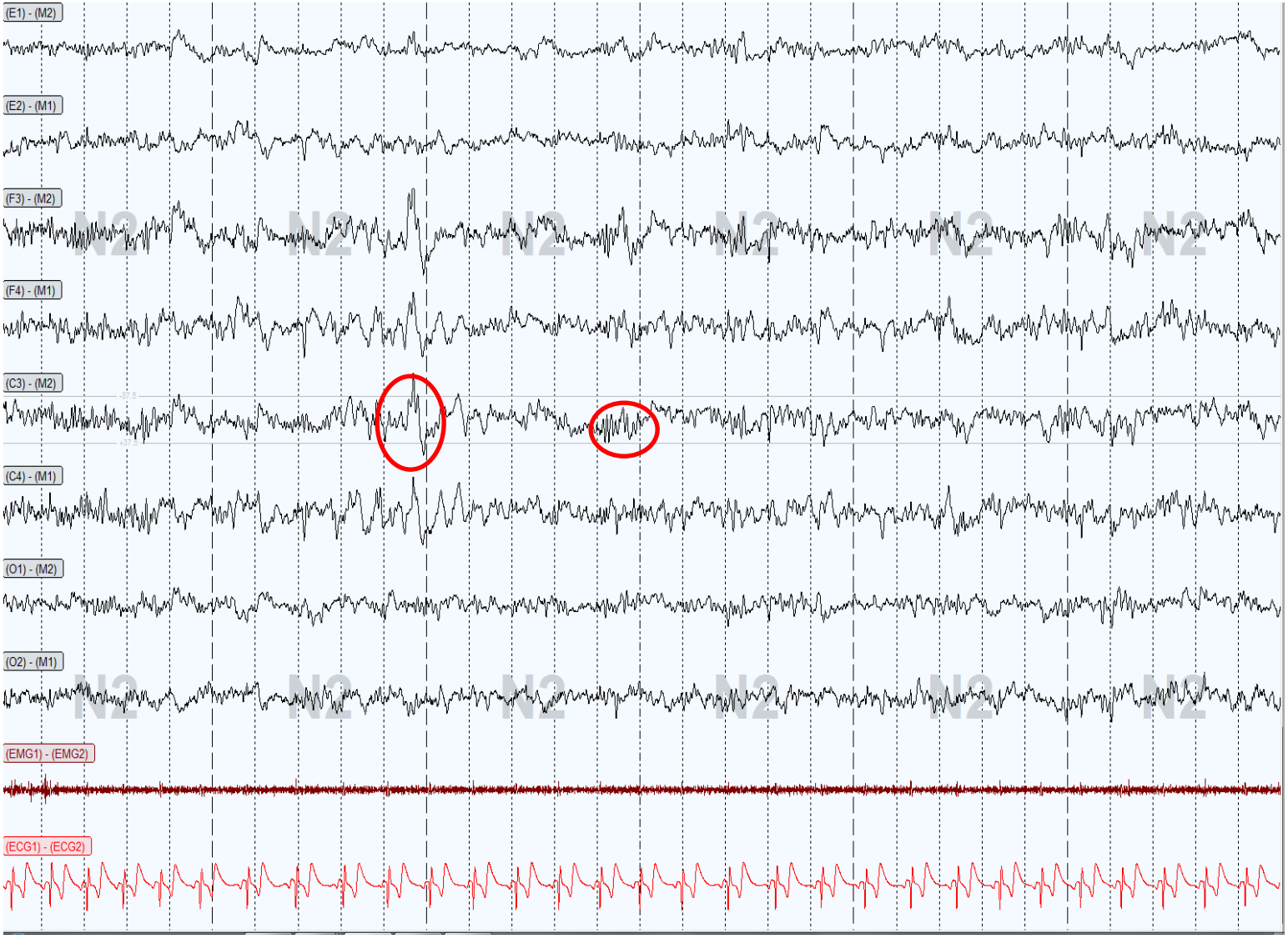
(EMG1) - (EMG2)
(ECG1) - (ECG2)
N1
SLEEP ONSET

Stage N1

- About **5-10%** of the night
- Alpha waves are replace by low amplitude mixed frequency (**LAMF**) frequency of 3-7 cycles per second
- More than 50% of the epoch is **theta** frequency of 3-7 cycles per second
- **Vertex sharp waves**
  - Sharply contoured
  - Negative deflection
  - Duration ≤0.5 seconds
  - Central leads
- Slow rolling eye movements
- High sub-mental muscle tone



Stage N2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(O2) - (M1)
(EMG1) - (EMG2)
(ECG1) - (ECG2)
N2

Stage N2

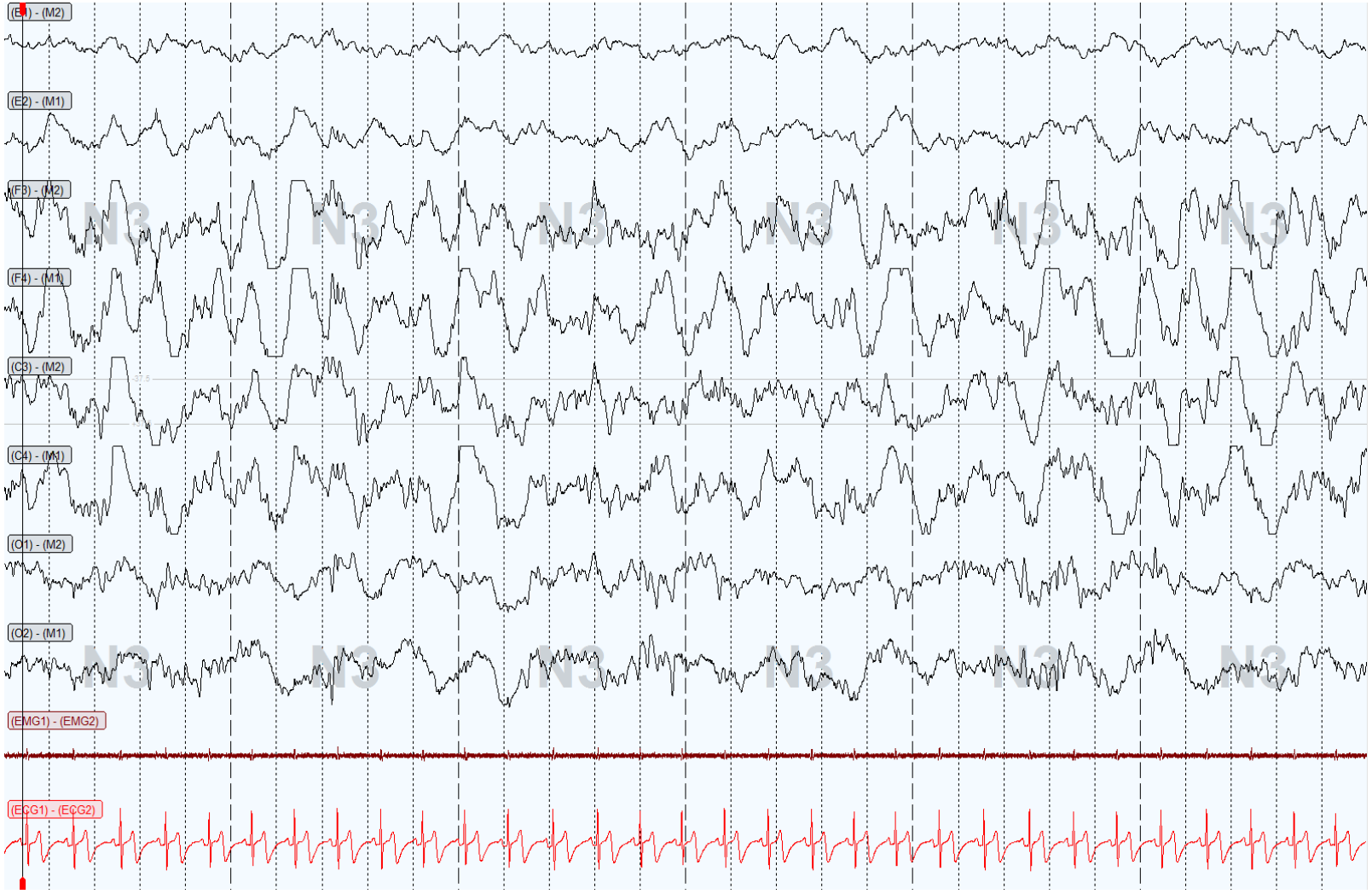
Sleep Spindles

- Generated in the **thalamus**
- Characteristic of Stage N2 sleep
- Seen best over the **central** or **frontal** regions
- Usually at **12 cycles** per second
- Pseudo-spindles may be associated with **benzodiazepine** use

K-Complexes

- Response to external stimuli such as sounds
  - "Knock" complexes
- Brief negative high voltage peak then **slower positive complex**
- Has duration criteria ($\geq$0.5 sec) but no amplitude criteria
- Seen best in frontal leads

Stage N3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(O1) - (M2)
(O2) - (M1)
(EMG1) - (EMG2)
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N3
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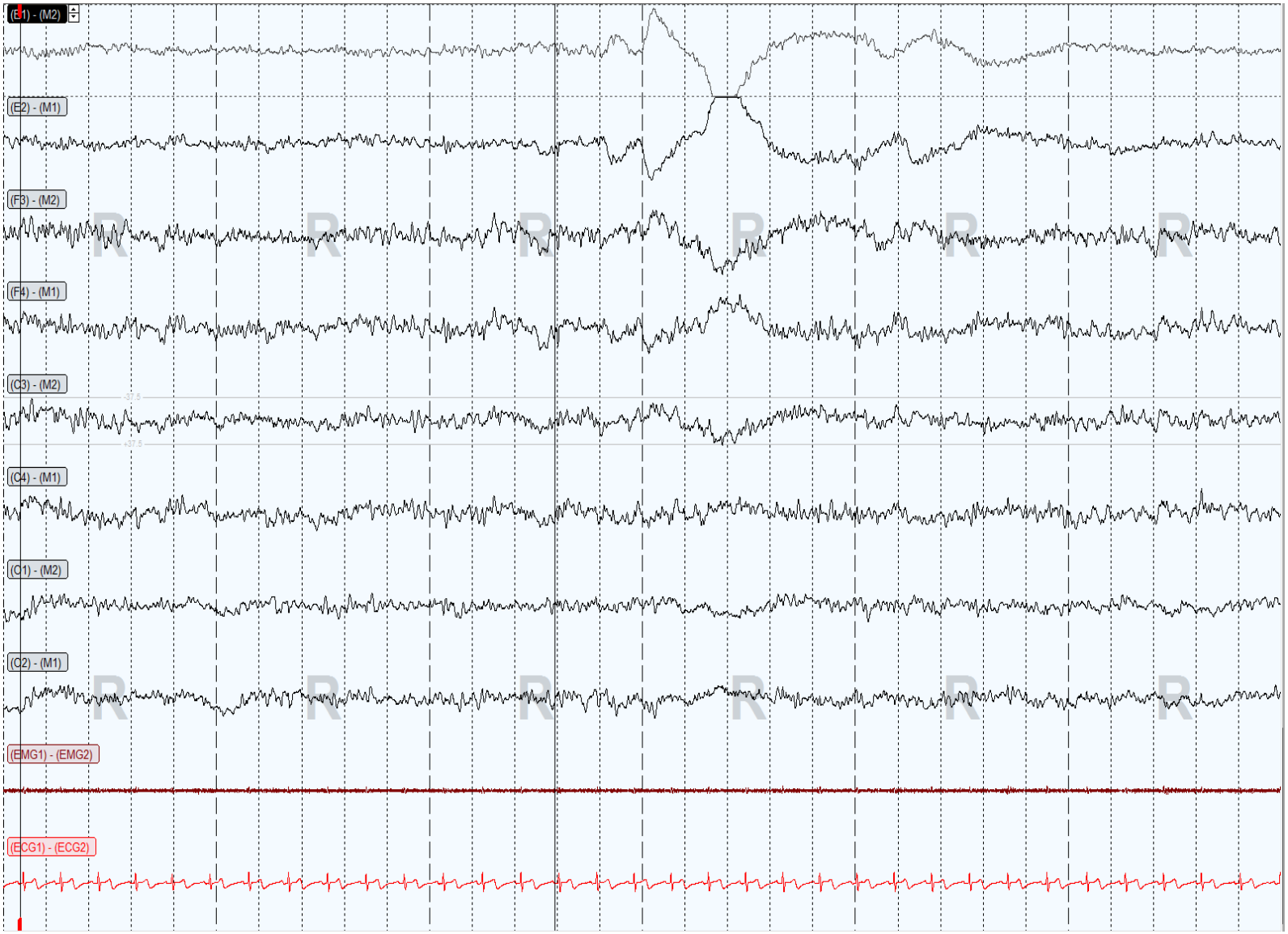
Stage N3

- Associated with learning and memory
- Decreases with age
- First stage to **rebound** after period of sleep deprivation
- **Benzodiazepines, ETOH, opioids** suppress SWS
- GHB (**Zyrem**) and **lithium** increases SWS

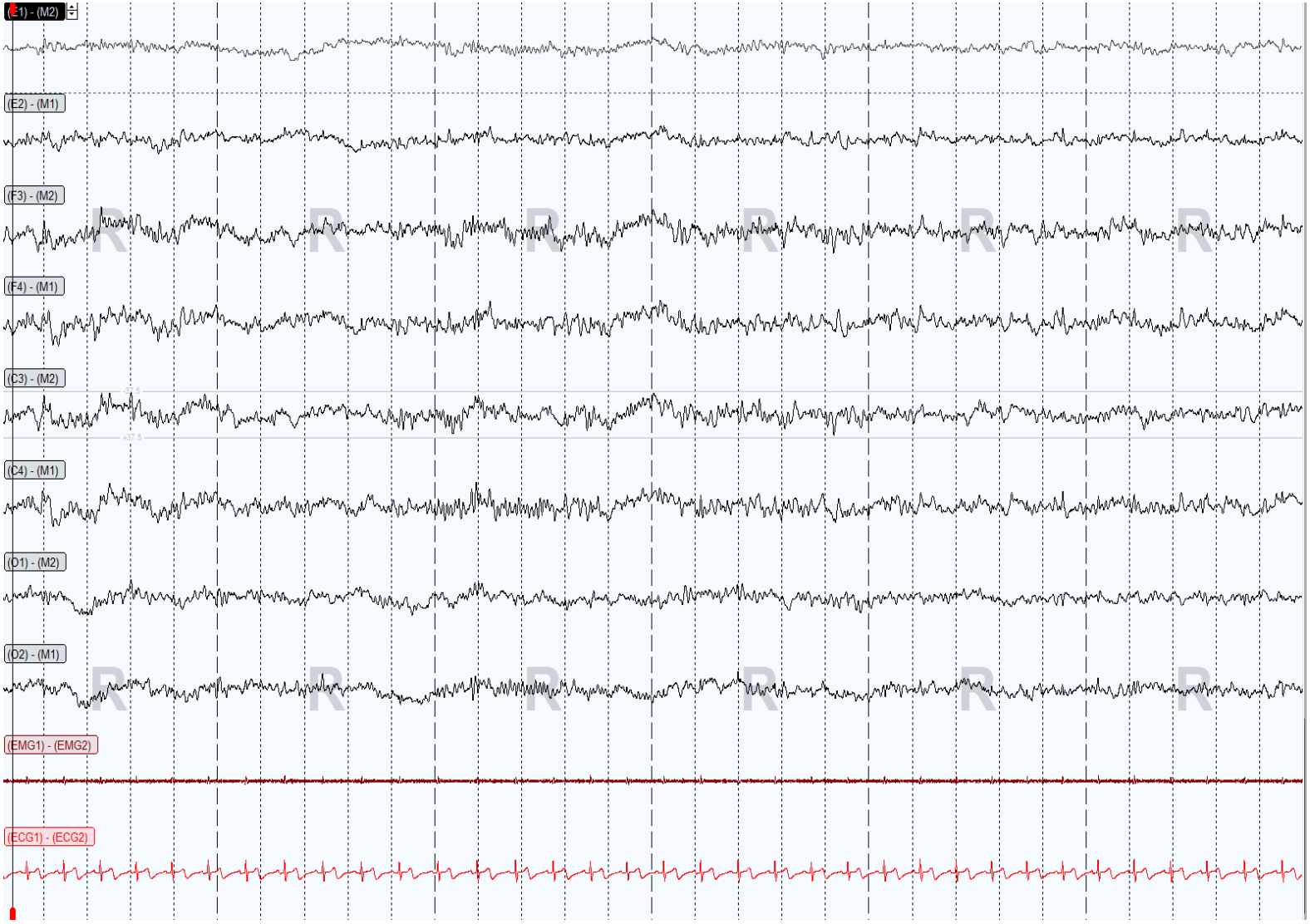
- **20%** of an epoch is delta waves
- Delta waves
  - Occur at frequency of 0.5-2 cycles per second
  - Occurs in clusters
  - **Amplitude** > 75 mHz

Normal EEG and EOG filters are: 0.3 to 35 Hertz to capture delta and beta waves

Stage Phasic REM

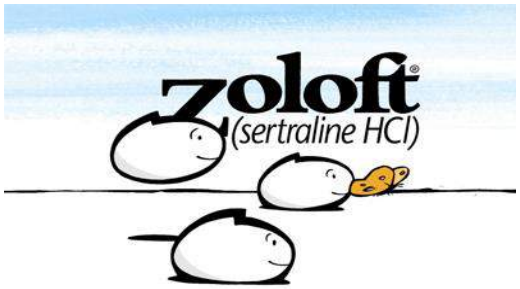


Stage Tonic REM



Stage REM

- **20-25%** of total sleep
- Characterized by:
  - Decreased sub-mental EMG activity
  - Rapid out of phase eye movements
  - **Saw toothed** waves (not require for scoring
- Respiratory, HR & BP increased compared to NREM and has **variability**
- Worsening of OSA
  - Young women with REM-OSA
- Anti-depressants such as MAOIs, TCA, SSRI & SNRI suppress REM
  - SSRI and SNRI **prevent atonia** in REM



REM density: defined as the number of eye movements per each 30-second epoch of REM sleep

Neuroscience of Sleep for the Boards

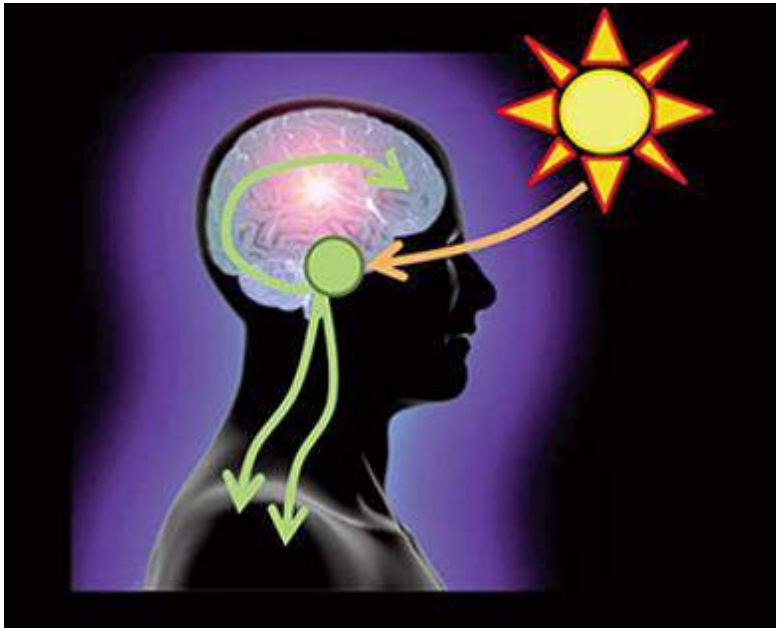
Sleep Overview

- Sleep is characterized by a dissociation of the CNS from the external environment
- Sleep is also **rapidly reversible**, which distinguishes it from coma
- Sleep is generated and maintained by CNS networks
  - Localized in **specific areas** of the brain
  - Using **specific neurotransmitters**
  - Hypothalamus for sleep and brain stem for wake

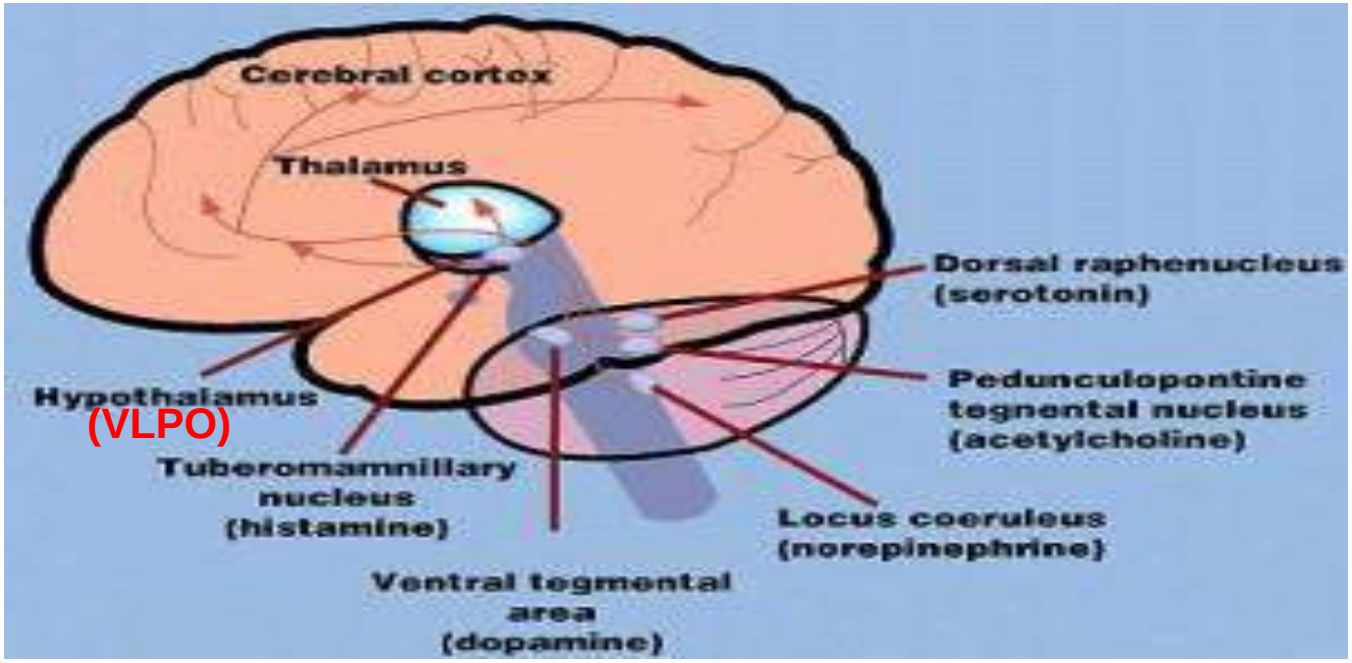
Sleep Overview

- Sleep is governed by 2 interacting processes:
  - **Homeostatic drive** (process S)
    - Regulated by recent duration of wakefulness
    - Adenosine
  - **Circadian drive** (process C)
    - Cycles during a 24hour period (Tau) +/-
    - External environmental stimuli (Zeitgebers) influence this drive
    - Suprachiasmatic nucleus (**SCN**) serves as the pacemaker for the circadian rhythms
      - Transmits to the pineal gland for the release of melatonin

- In a simplistic sense
  - The summation of both drives at any given point determines the individual's **propensity toward sleep**



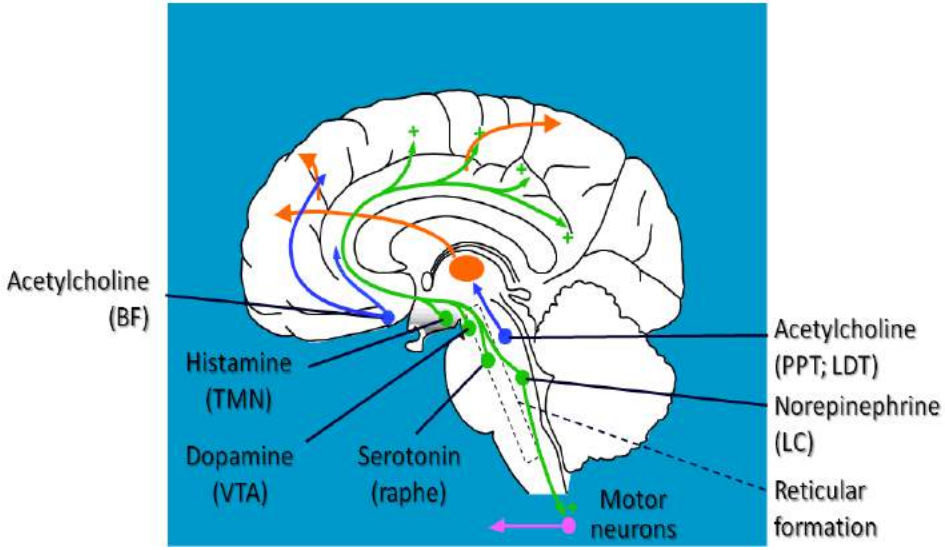
Neuroscience of Sleep



Sleep = Hypothalamus vs. Wake = Brainstem

Systems Generating Wakefulness: Reticular Activating System

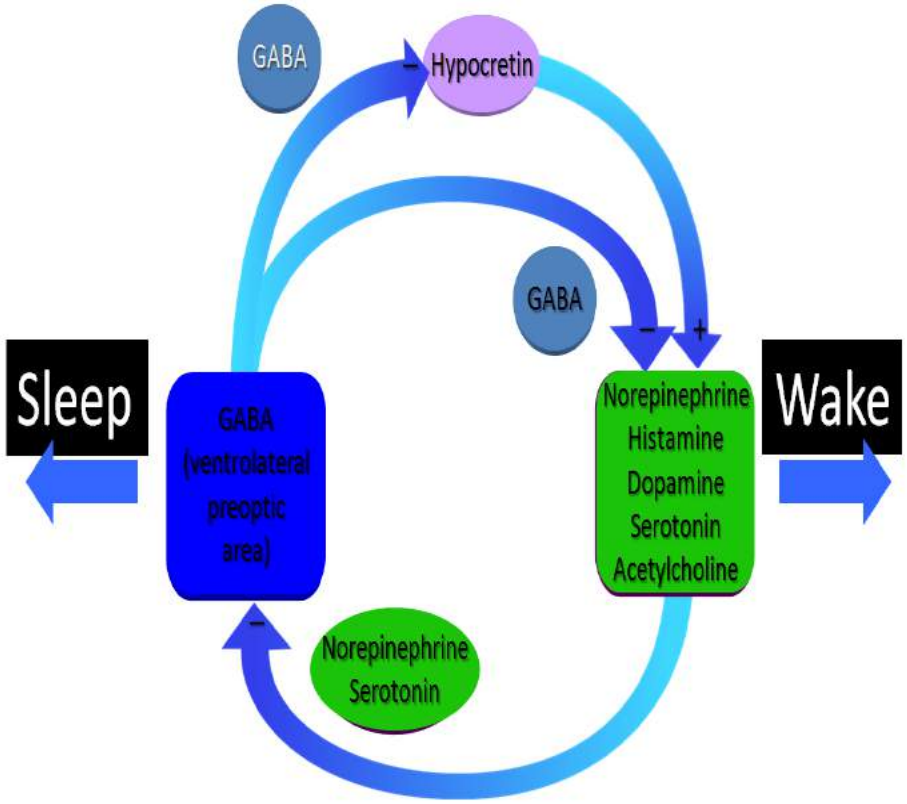
- Responsible for regulating arousal and sleep-wake transitions
- The **RAS** is composed of several neuronal circuits connecting the brainstem to the cortex



- Areas traditionally included in the **RAS**:
  - **Basal forebrain**: Acetylcholine
  - **Lateral hypothalamus**: Hypocretin
  - **Locus ceruleus**: Norepinephrine
  - **Tuberomammillary nucleus**: Histamine
  - **Ventral tegmental area & periductal grey matter**: Dopamine
  - **Dorsal nucleus of Raphe**: Serotonin

Systems Generating NREM Sleep

- **Hypothalamus**: GABA and Galanin
  - **Ventrolateral preoptic nucleus (VLPO)** is a group of neurons in the hypothamlamus
    - Primarily active during NREM, and inhibit other neurons that are involved in wakefulness
    - Release the inhibitory neurotransmitters Galanin and GABA to inhibit wakefulness
- **Basal forebrain**: GABA and adenosine
- **Thalamus**: Generation of sleep spindles

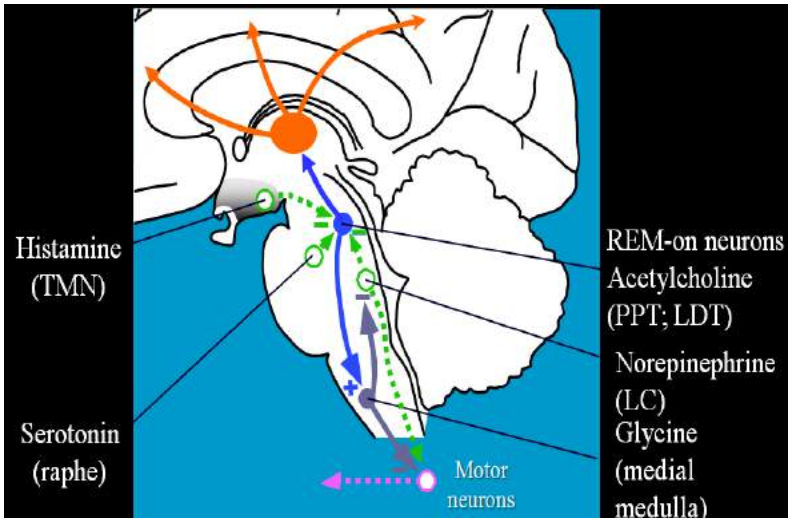


Sleep/Wake Switch (The "Flip-Flop" Switch)

REM On and Off Neurons

REM "on" cells

- Cholinergic neurons (acetylcholine) in the:
  1. LDT (lateral dorsotegmental)
  2. PPT (pedunculopontine)



REM "off" cells

- Neurons in the:
  1. Dorsal raphe (serotonin)
  2. Locus coeruleus (norepinephrine)
  3. Ventral tegmental area (dopamine)
  4. Tuberomammillary nucleus (histamine)

Summary of Important Sleep-Wake Neurotransmitters

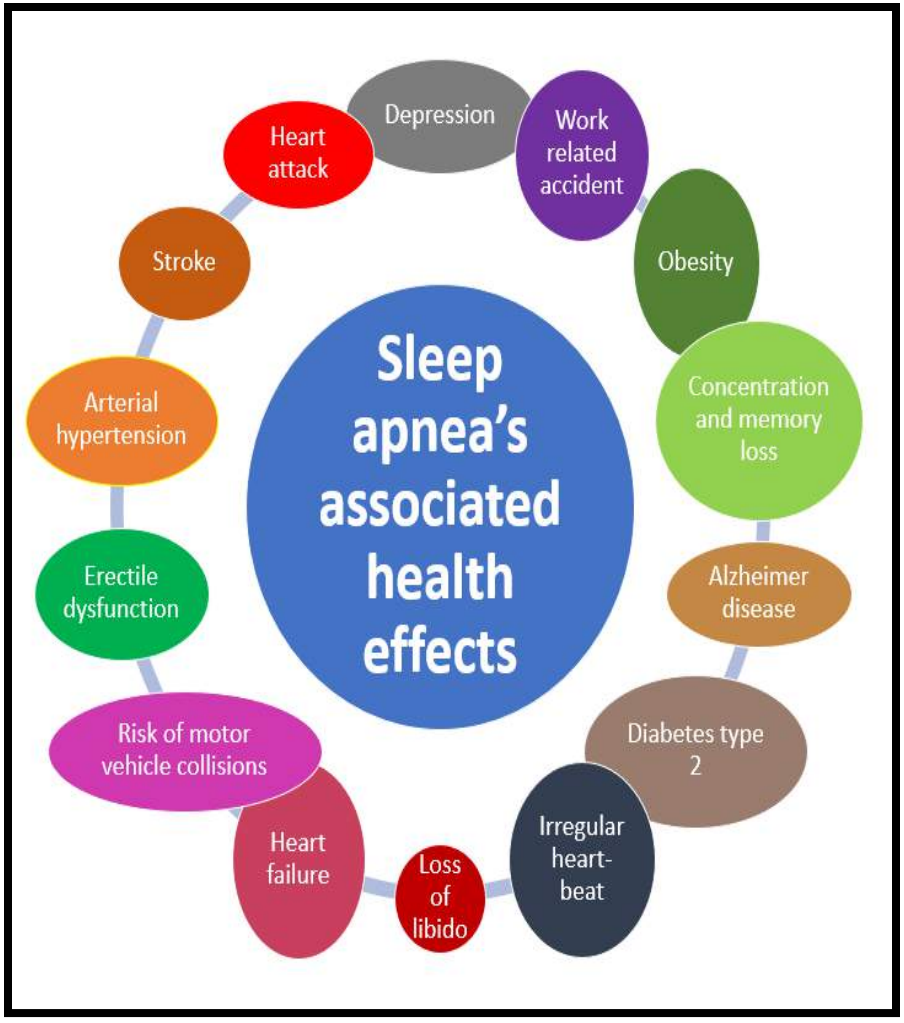
	Wakefulness	NREM	REM
Acetylcholine	Increased	0	Increased
Monoamines	Increased	Reduced	0
Orexin / Hypocretin	Increased	Reduced	Reduced
GABA / Galanin	0	Increased	Reduced

Summary of Important Sleep-Wake Neurotransmitters

- **Glutamate**:
  - Main CNS excitatory neurotransmitter
- **Gamma-aminobutyric acid (GABA)**:
  - Main CNS inhibitory neurotransmitter
- **Glycine**:
  - Main inhibitory neurotransmitter in the spinal cord
  - Responsible for REM sleep-related muscle atonia-hypotonia
- **Acetylcholine**:
  - Main REM neurotransmitter
- **Adenosine**:
  - Responsible for the homeostatic sleep drive
  - Builds up during the day
  - Inhibited by caffeine
- **Hypocretin / Orexin**:
  - Dysfunction is responsible for narcolepsy

Obstructive Sleep Apnea

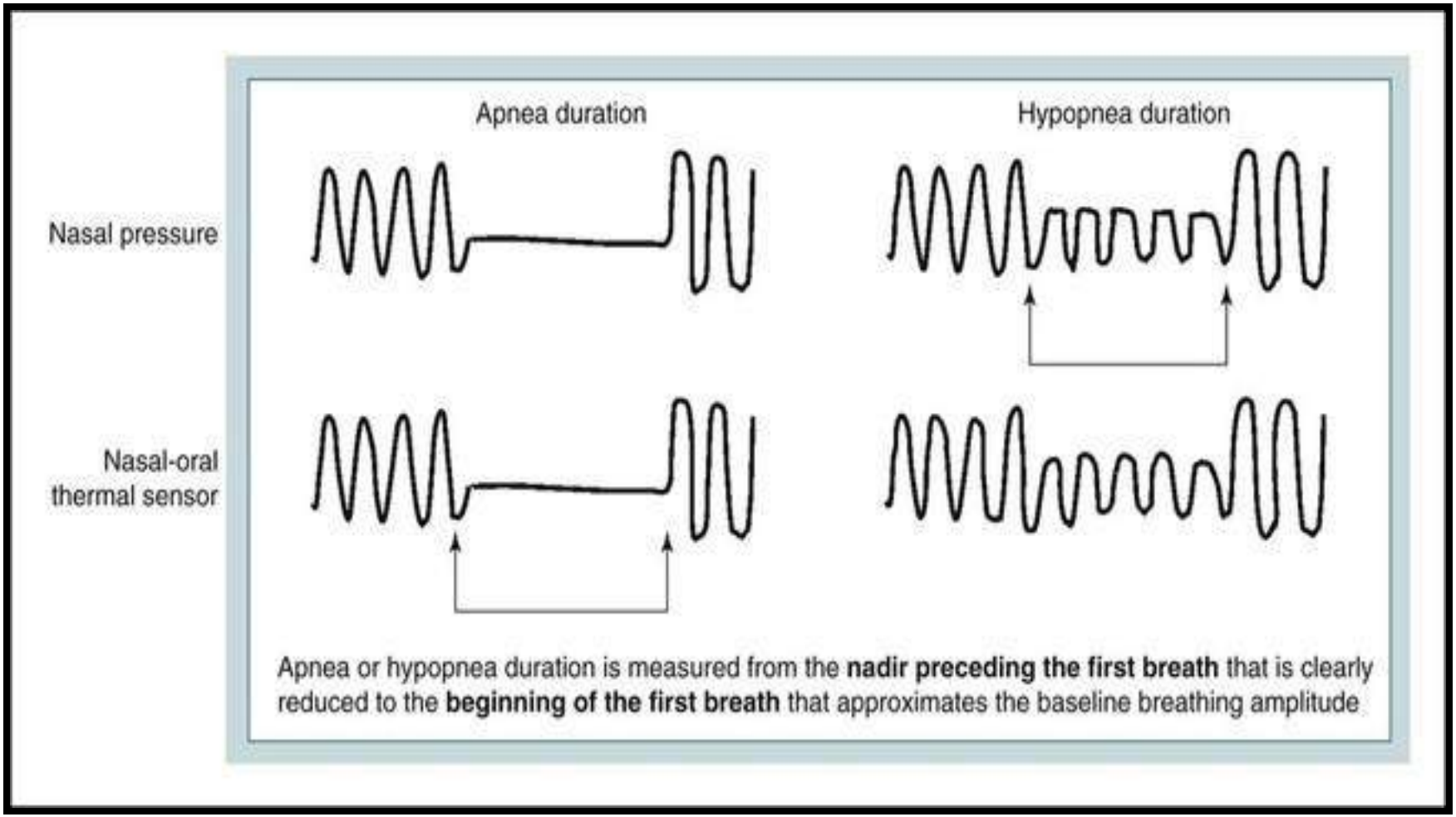
Sleep Apnea: Health Crisis



Beyond the Pearls: Question

- With regard to the American Academy of Sleep Medicine (AASM) scoring guidelines, which of the following statements regarding scoring of hypopneas is true?
  A. The preferred flow signal for scoring hypopnea is the thermistor signal
  B. The recommended rule for scoring hypopneas requires at least a 4% oxygen desaturation
  C. Arousals are required for scoring hypopneas by the recommended hypopnea definition
  D. The duration of the 30% drop in signal excursions is $\geq$ 10 seconds

Answer: D


Apnea duration
Hypopnea duration
Nasal pressure
Nasal-oral thermal sensor
Apnea or hypopnea duration is measured from the **nadir preceding the first breath** that is clearly reduced to the **beginning of the first breath** that approximates the baseline breathing amplitude

Beyond the Pearls: Question

- 67 year old man with snoring and witnessed apneas undergoes an evaluation for sleep apnea. He has a level 3 home sleep apnea test (HSAT) performed. Which of the following is the correct calculation for the respiratory event index (RDI)
  A. Apnea + hypopneas / total sleep time
  B. Apneas + hypopneas + respiratory effort related arousals (RERAs) / total sleep time
  C. Apneas + hypopneas / total recording time
  D. Apneas + hypopneas + RERAs / total recording time

Answer: C

Beyond the Pearls: Question

- Which of the following is true regarding clinical risk factors for OSA?
  - A. Women are more likely to present with snoring and witnessed apneas than daytime fatigue and mood disturbances
  - B. Obesity is associated with anterior-posterior collapse of the upper airway
  - C. There is less association of sleep symptoms among older adults compared to middle-aged adults
  - D. There is a stronger association between BMI and OSA among Asian patients compared to patients in western countries
  - E. Longer thyromental distance increases risk for OSA

Answer: C

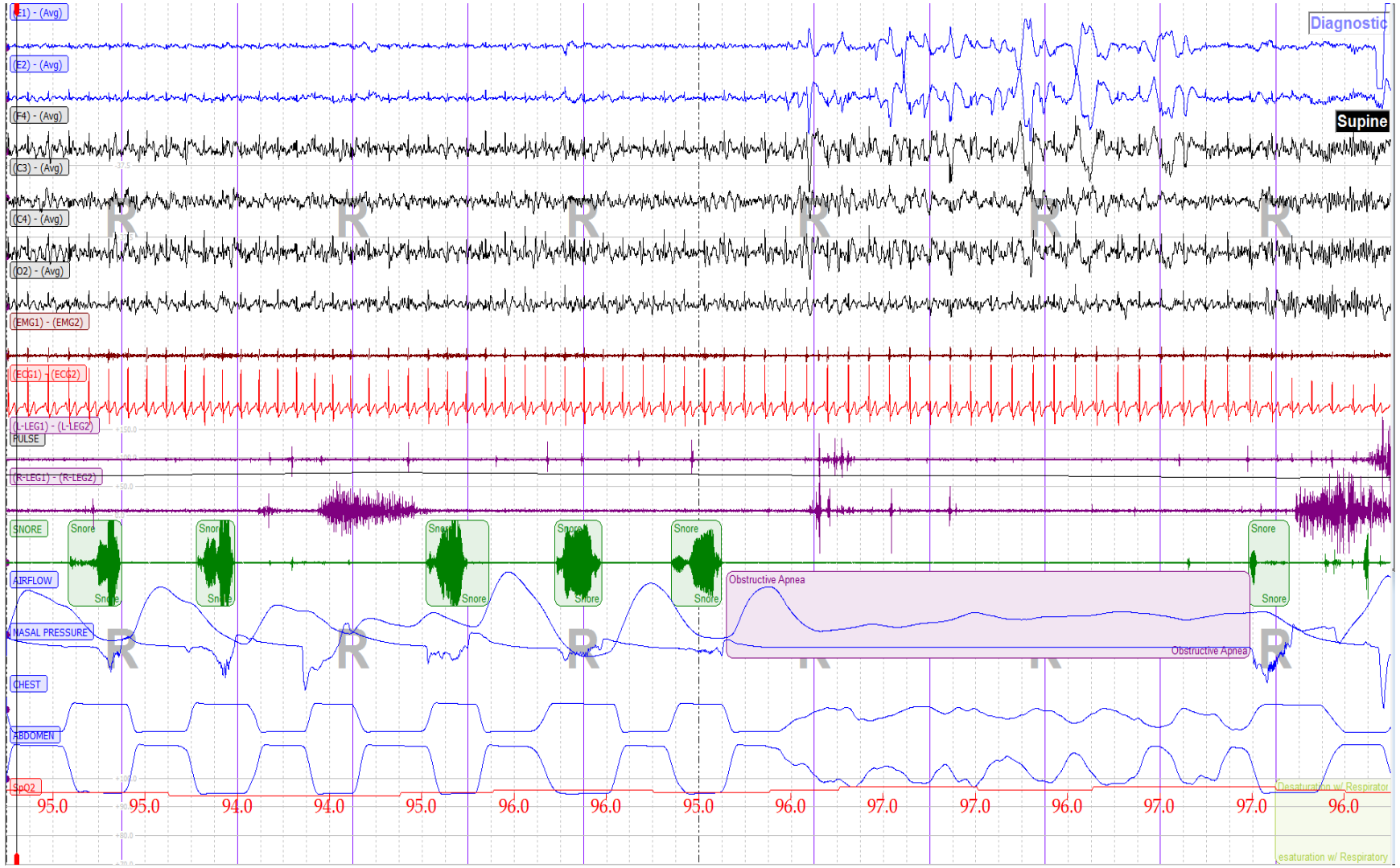
Sleep Apnea: Scoring

- Obstructive apnea criteria:
  - Cessation of airflow > 90% in the thermal sensor and 10 seconds duration, oxygen desaturation is NOT part of the definition
- Obstructive hypopnea has 2 main criteria:
  - 1A scoring (AASM):
    - Cessation of airflow > 30%, 3% decrease in oxygenation from baseline or arousal and lasting 10 seconds
  - 1B scoring (Medicare):
    - Cessation of airflow > 30%, 4% decrease in oxygenation from baseline and lasting 10 seconds
- RERA (Respiratory effort related arousals)
  - Last for 10 seconds, the event is not an apnea or hypopnea

Sleep Apnea: Diagnosis

- **Previously the best initial test**
  - Overnight pulse oximetry desaturation study
    - Good to evaluate hypoxemia in patient's using PAP
- **Gold standard confirmation test**
  - Polysomnography (sleep study)
    - ECG, EEG, EMG, Oximeter, Tidal CO2 recorder
    - Split study
    - Differentiates obstructive and central sleep apnea
      - Presence or absence of inspiratory effort during the apneic episodes
    - The frequency of hypoxic apneic episodes determines the severity of the disease
      - Normal <5/hr
      - Mild 5-15/hr
      - Moderate 15-30/hr
      - Severe >30/hr

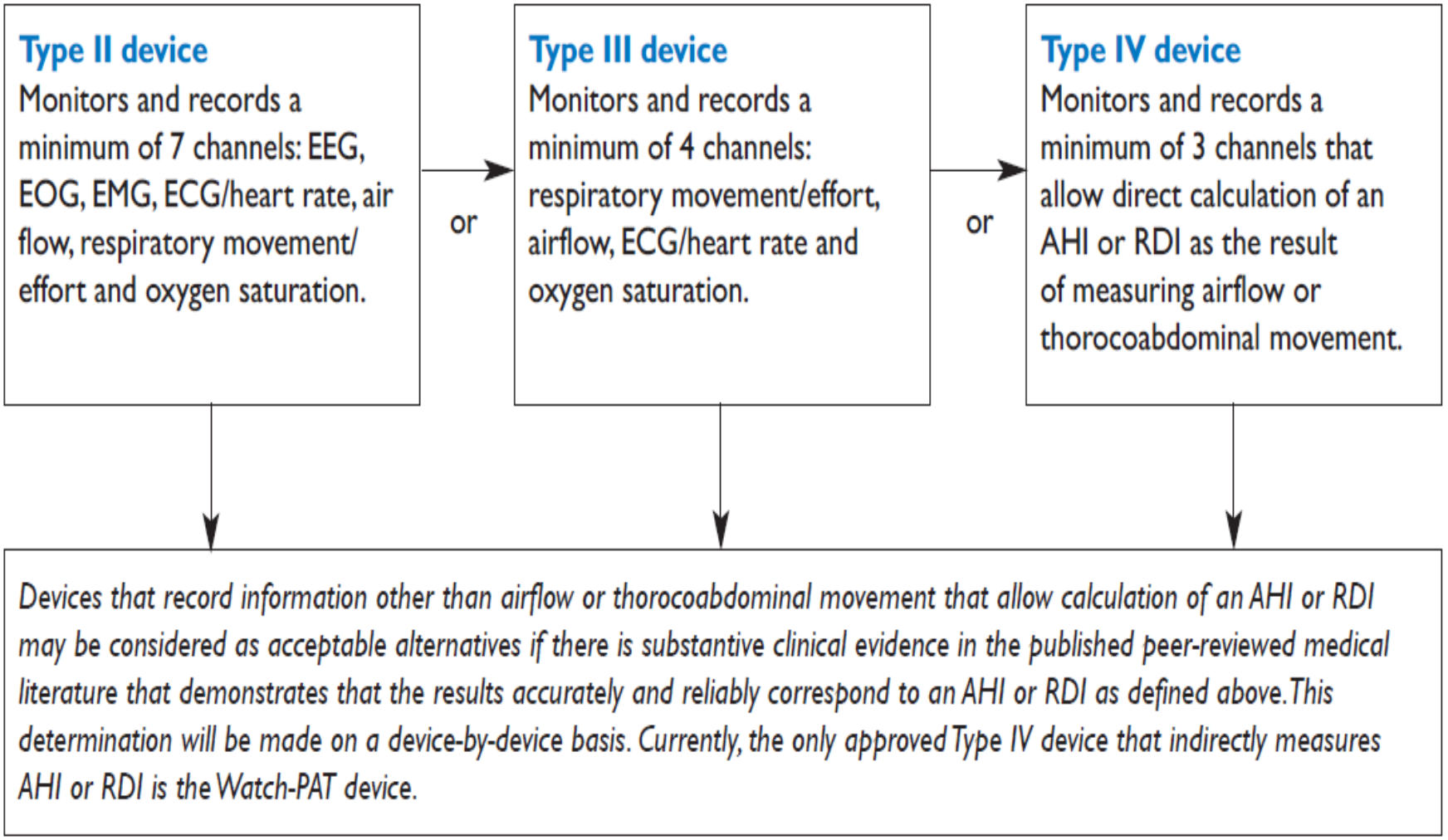
Type I Sleep Test



Benefits of Home Sleep Studies

- Familiar surroundings (reducing **first night effect**)
- Advantageous to the home-bound, elderly, or those with chronic illness, who require:
  - Specialized care such as a nurse or family member spending the night
  - Expensive transportation costs
- For those with trouble arranging time out of their schedules to spend the night in-lab
- Fraction of the cost of an in-lab sleep study

Types of Devices

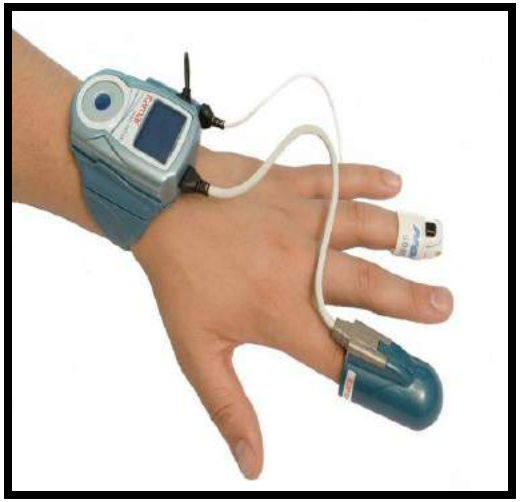


What we use at the USC Sleep Center: Apnea Link Air ResMed

- Type III home sleep testing device
- Capable of recording up to 5 channels of information:
  1. Respiratory effort
  2. Pulse
  3. Oxygen saturation
  4. Nasal flow
  5. Snoring

Watch PAT

- Portable device that measures peripheral arterial vasoconstriction and via mathematical algorithm connects this vasoconstriction with apneic episodes



WatchPAT™ ONE

First and Only Disposable HSAT

Beyond the Pearls: Question

- 60 year old moderately **obese** man is referred to the sleep clinic for long-standing snoring and **excessive daytime sleepiness** with no significant cardiovascular or respiratory comorbidity. The patient averages 7 to 8 hours of "unrefreshing" sleep per night with associated morning headaches and **witnessed apneas**. His Epworth Sleepiness Scale score is 16. His collar size is **17 in** and he is observed to have small mandibular size. A home sleep apnea test shows the following results:

- Total recording time: 480 min
- Obstructive apneas: 13
- Hypopneas: 21
- Apnea-hypopnea index: **4.1/h**
- Mean oxygen saturation: 91%
- Low SaO_2: 81%
- <90% oxygen saturation: 15 min
- Which is the best recommendation, based on this study?
  A. Repeat the home sleep apnea testing
  B. Attended in lab polysomnography
  C. Empiric auto-titrating PAP therapy
  D. Supplemental oxygen during sleep

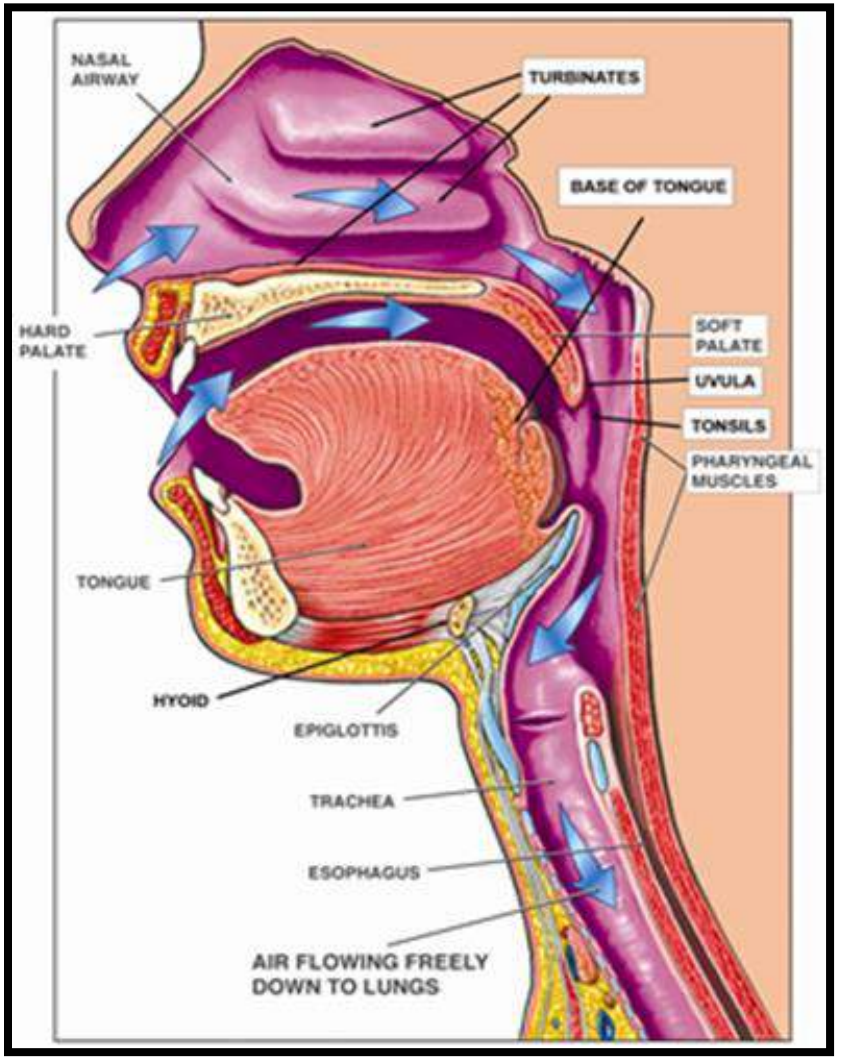
Answer: B

- Portable or home sleep apnea testing does **not directly** measure total sleep time
- Many devices calculate the AHI based on total recording time and some devices use a surrogate measurement of sleep time (actigraphy or other measures of motion detection) to calculate the AHI
- Devices that calculate the AHI based on total recording time may underestimate the severity of the patient's OSA, especially for patients whose sleep efficiency is reduced on the night of home testing
- Home sleep apnea tests can also **underestimate** the severity of the patient's sleep-disordered breathing, based on **technical problems** that may have occurred during the unattended study, so it is imperative that the interpreting physician reviews the raw data to assure that the study results are based on valid and reliable waveforms

Physiology of Classic Obstructive Sleep Apnea Patient

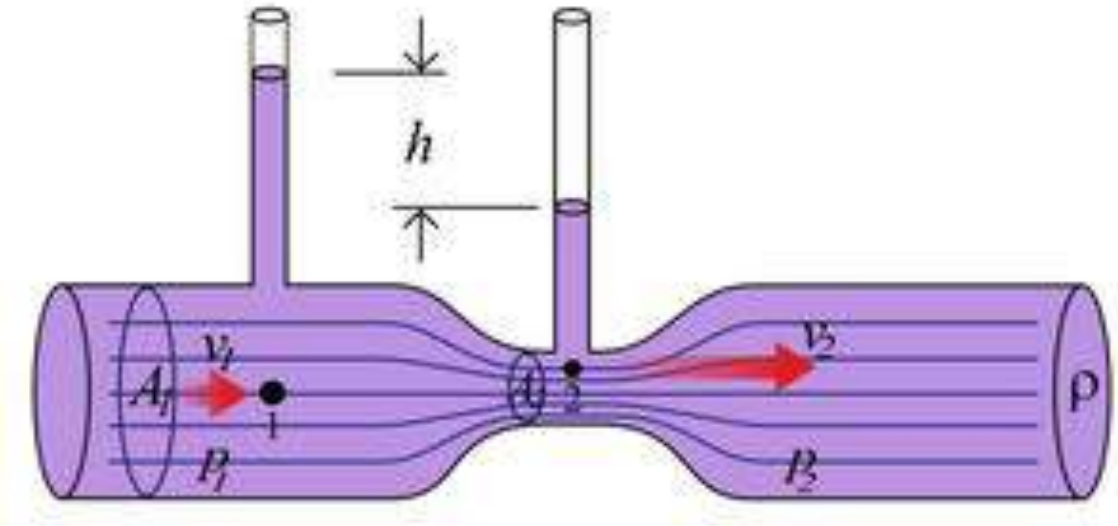
Upper Airway Collapsibility Pathophysiology

- The patency of the airway is dependent on the interaction of forces that:
  1. Collapse the lumen
  2. Open the lumen
- OSA is the clinical manifestation that occurs when these forces are skewed towards the collapse of the airway lumen
  - Two principles of fluid/air flow
    1. Bernoulli principle
    2. Venturi effect



Venturi Effect

- When air/fluid passes through the narrowest section of a tube it moves faster
- Greater the speed of the air the **less pressure** exerted

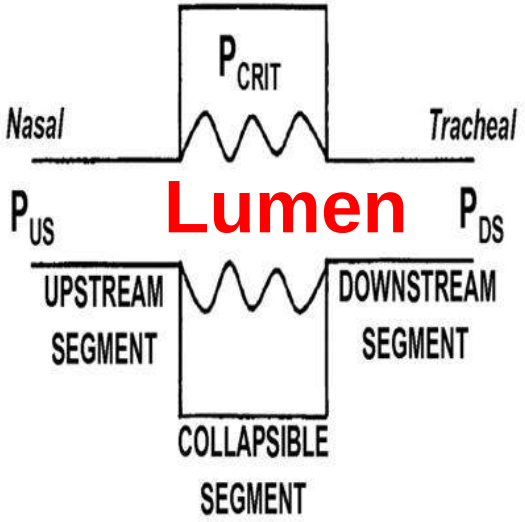


Bernoulli Principle

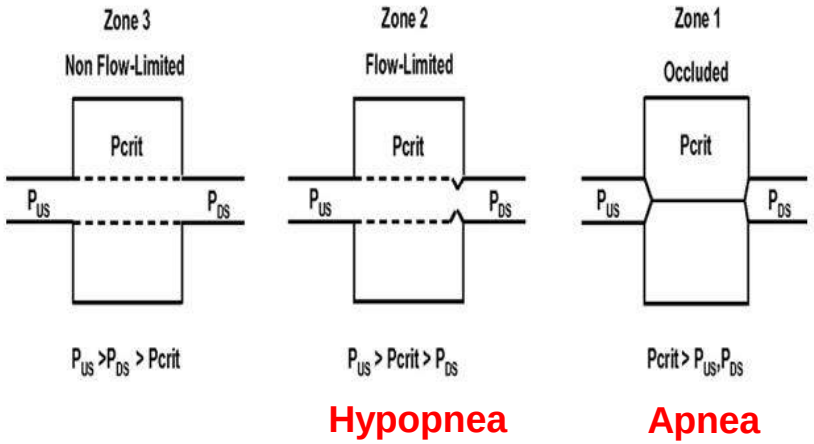
1. As the velocity of a fluid/air increases, the pressure exerted by that fluid decreases
2. A partial vacuum exists at the outer edges of a column of moving fluid/air
   - As airflow speed increases, the partial vacuum pressure increases
     - This principle is illustrated by a drinking straw: if too much negative pressure is generated within the straw, it collapses

Upper Airway Collapsibility Starling Resistor Model

- Reductions in **intraluminal pressures** cause the pharynx to flow-limit or occlude when upstream and downstream pressures fall below P_{crit}



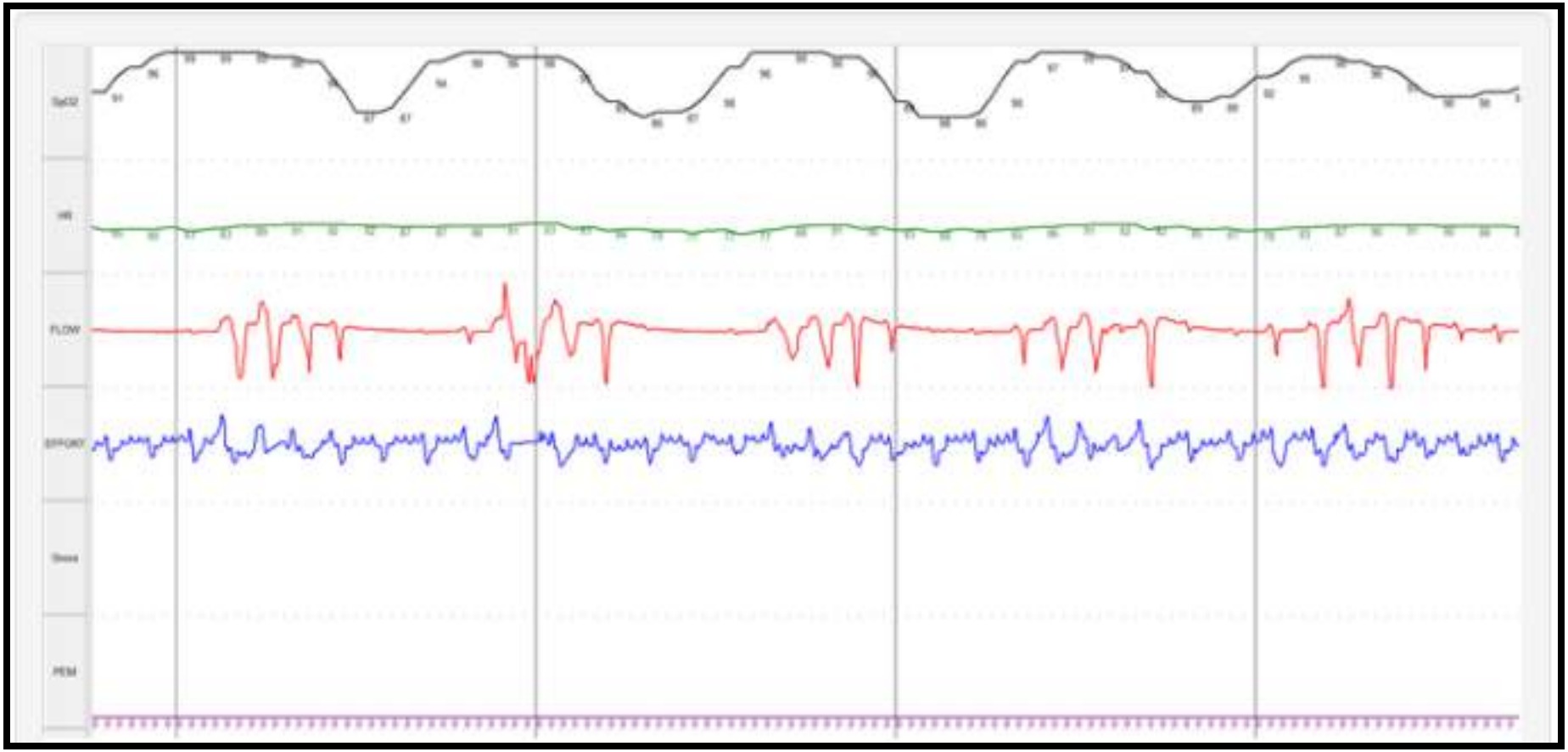
- Obstructive sleep apnea ensues whenever P_{crit} exceeds pressures upstream and downstream to the collapsible site (P_{us}, $P_{ds} < P_{crit}$)



Treatment

Beyond the Pearls: Question

- 54 year old man has a **home sleep apnea test** because of snoring, obesity, and sleepiness. Assuming that the 2-minute, compressed epoch below is representative of the entire study



Beyond the Pearls: Question

- Which of the following is the most appropriate next step?
  A. In-lab split-night study
  B. Multiple sleep latency testing
  C. Auto titrating CPAP
  D. Reassurance that nothing further needs to be done

Answer: C

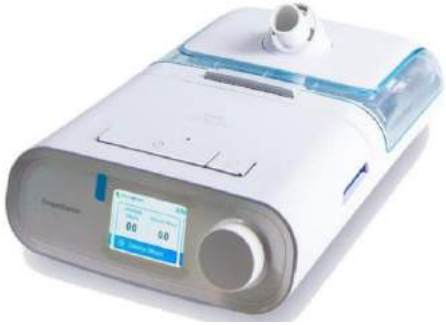
- The tracing from the home sleep study shows rhythmic apneas, each of which is accompanied by persistent movement in the Effort channel, as well as by oxygen desaturations.
- This is clearly significant OSA. Further, the patient has a classic history for OSA, including sleepiness and hypertension. At this point, it is most appropriate to begin treatment, especially since this patient is symptomatic
- There is no need for a formal CPAP titration, as auto CPAP has the same short-term outcomes as does in-laboratory titrated CPAP for uncomplicated OSA without unnecessary additional cost and delay

Sleep Apnea Treatment

- OSA (lifestyle modifications)
  - Weight loss
  - Avoiding
    - Alcohol
    - Sedatives
    - Hypnotics
  - Avoid the supine position

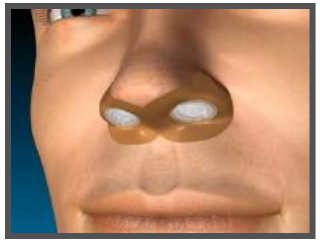
Mainstay Therapy of OSA

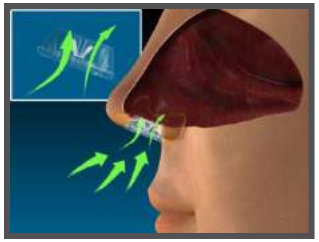
- **PAP ventilation**
  - **CPAP**
    - Continuous positive airway pressure
  - **BiPAP**
    - Bi-level positive airway pressure
  - **ASV**
    - Adaptive servo ventilation
  - **AVAPS**
    - Average volume assured pressure support

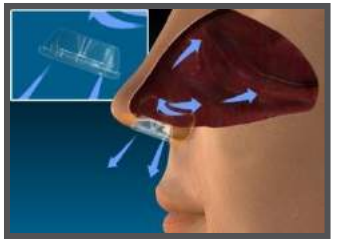


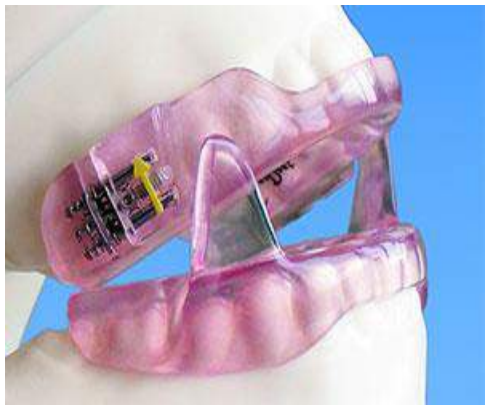
Unfortunately not everyone tolerates PAP therapy

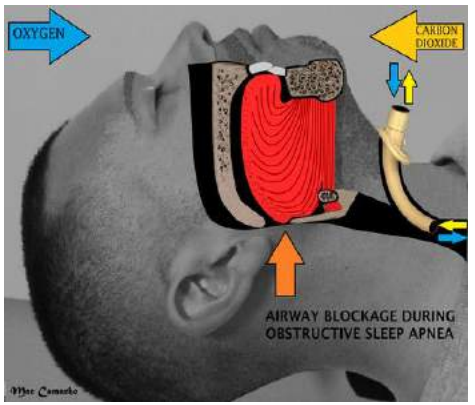
- **Oral appliance**
  - Mandibular advancement
- **Surgery**
  - UPPP
  - “Inspire”
  - Tracheostomy
- **“Provent”**
  - Discontinued June 2020

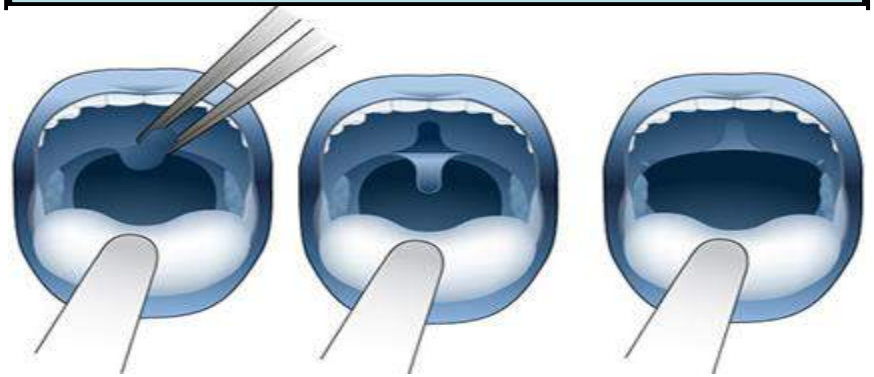




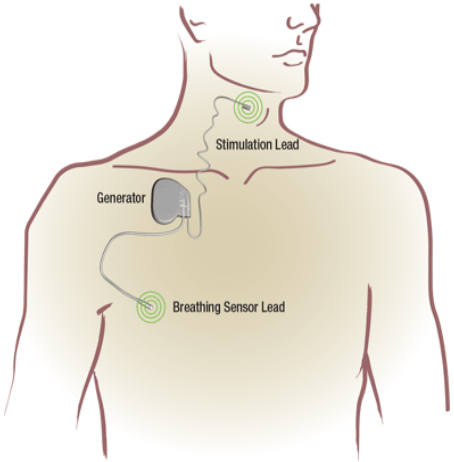








Uvulopalatopharyngoplasty



Neuromuscular Evaluation For Possible Surgery

Invasive VS. **Non-Invasive**

- MRI
- CT

Awake

- Muller's maneuver

Sleep

D.I.S.E and V.O.T.E

Velum (soft palate)
- UPPP

Oropharyngeal lateral walls
- Tonsillectomy

Tongue Base
- Inspire & see AP collapse only

Epiglottis
- Epiglottectomy

Beyond the Pearls: Question

- An oral appliance would be most appropriate for use in which of the following conditions
  - A. Obesity hypoventilation syndrome
  - B. Mild to moderate OSA
  - C. Central sleep apnea
  - D. Severe OSA

Answer: B

- OA are traditionally indicated for use in patients with mild to moderate OSA who:
  - Prefer OA to CPAP
  - Do not respond to CPAP
  - Not candidates for CPAP
  - Fail treatment attempts with CPAP
  - Fail treatment with behavioral measures such as weight loss or positional therapy

Are severe OSA that respond but how do you identify that phenotypes . J Sleep Res. 2013 Jun;22(3):348-55. doi: 10.1111/jsr.12008. Epub 2012 Dec 4. **Sleep endoscopy** with simulation bite for prediction of oral appliance treatment outcome.

Beyond the Pearls: Question

- Which of the following measures have been shown to enhance PAP adherence?
  - A. Bi-level positive airway pressure
  - B. CPAP with expiratory pressure relief technology
  - C. Ramping mechanism
  - D. Use of heated humidification
  - E. Use of a nasal mask interface compared to oronasal mask interface
  - F. Behavioral, supportive & educational interventions
  - G. E & F

Answer: G

Nasal Pillows Mask

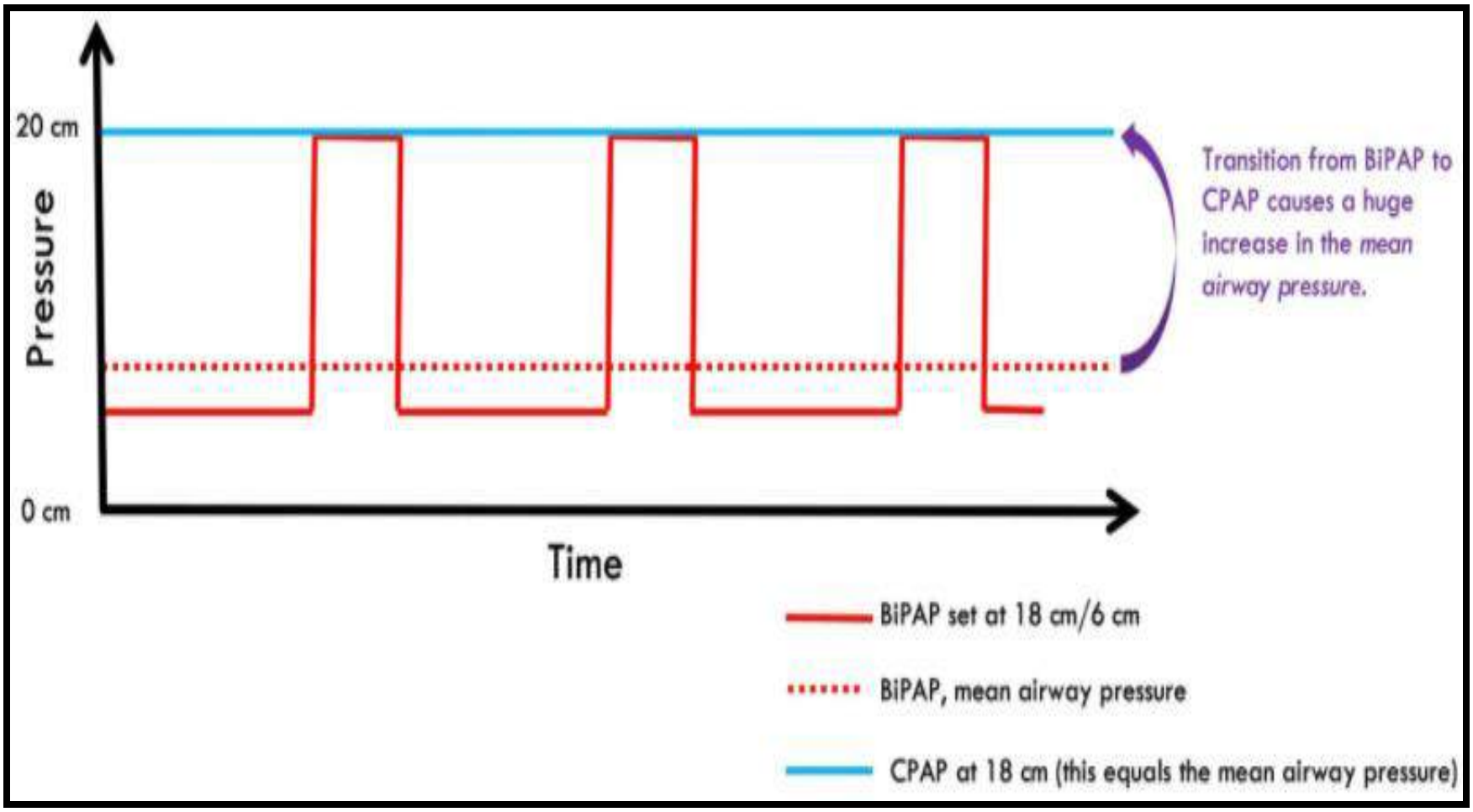
Nasal Mask

Full-Face Mask

Beyond the Pearls: Question

- Which of the following is a benefit of APAP (auto-PAP) over CPAP?
  A. Greater reduction in AHI
  B. Less negative impact on sleep architecture
  C. Higher SaO2 levels
  D. Lower mean airway pressures

Answer: D


20 cm
Pressure
0 cm
Time
Transition from BiPAP to CPAP causes a huge increase in the mean airway pressure.
BiPAP set at 18 cm/6 cm
BiPAP, mean airway pressure
CPAP at 18 cm (this equals the mean airway pressure)

Bottom Line: CPAP and OSA

Bottom Line: CPAP Adherence

- Early CPAP adherence establishes long-term usage pattern
- No difference of CPAP adherence in mild OSA in comparison to moderate-severe OSA
- **Adherence: Behavioral, Supportive and Educational**
  - Behavioral interventions: improvement of 1.2 hours/night
    - Ex. CBT
  - Supportive interventions: improvement of 0.7 hours/night
    - Ex. Automated phone calls, inquires via computer
  - Educational intervention: improvement of 0.6 hours/night
    - Ex. Written material, watching a video

Bottom Line: CPAP Adherence

- **Adherence: Interface type**
  - No difference in mean adherence between intra-nasal compared with nasal interfaces
  - Improvement in adherence with nasal over oronasal interface
- **Adherence: Hypnotics**
  - Eszopiclone 3mg x 14 days improved adherence, both nights used and hours per night after 6 months
- **Adherence: Heated humidifier**
  - No improvement in PAP adherence
  - Heated humidification with PAP devices should be considered to reduce side effects of therapy

Bottom Line: CPAP Impact on Clinical Outcomes

- Optimal usage level differs depending on the outcome in question
- CPAP on Hypertension
  - Meta-analysis AASM 2019 showed a reduction in 24 hour mean BP of -2.6 mmHg
  - BP lowering is greater in those with EDS and refractory HTN
- In non-sleepy OSA patients the effect of CPAP prescription remains unclear

AASM: “refractory” is worse than “resistant” HTN

Bottom Line: CPAP Impact on Clinical Outcomes

- In non-sleepy adults with moderate to severe OSA, CPAP does not prevent primary or secondary CV events as used in RCTs with compliance < 4 hours
- In the cardiovascular inpatient population (ex. CHF, arrhythmias and MI) with OSA, CPAP initiation and compliance may decrease readmission rates
- Limited and conflicting data regarding mild OSA and CV outcomes
- Other outcomes:
  - CPAP is not associated with weight loss
  - CPAP is associated with reduction of motor vehicle accidents
  - Inconsistent results regarding DM, hyperlipidemia and metabolic syndrome

Bottom Line: CPAP Guidelines for OSA (Strong Recommendations)

- **To treat OSA in adults:**
  - Use PAP to treat OSA with excessive daytime sleepiness
  - Use either CPAP or APAP for initiation and ongoing treatment
  - Implement educational interventions with PAP initiation
  - Use PAP to treat sleep-related quality of life or comorbid hypertension
  - Implement behavioral or telemonitoring-guided interventions during initial period of PAP therapy

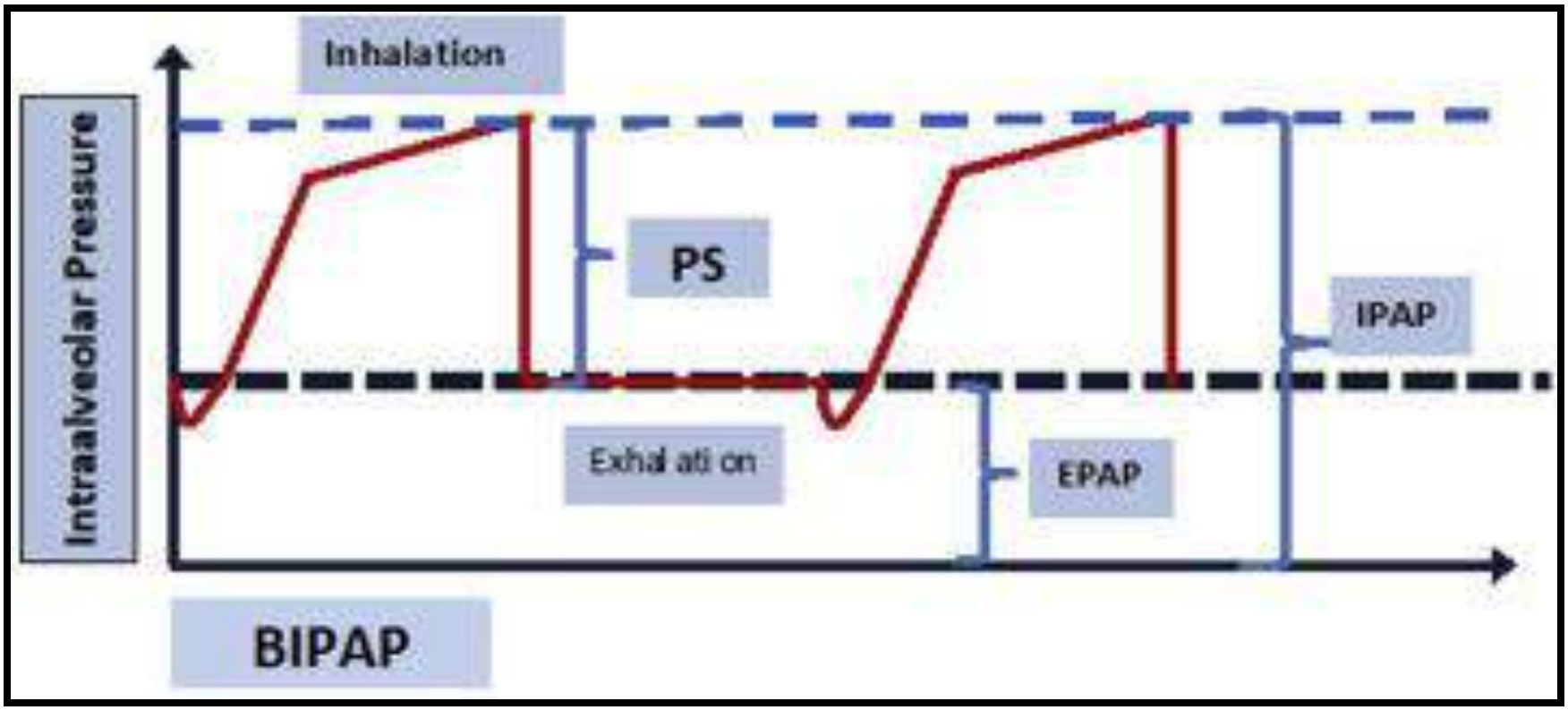
Bilevel Devices:
BPAP +/- ST
AVAP
ASV

Beyond the Pearls: Question

- 72-year-old man with hypercapnic COPD has started using BPAP in spontaneous/timed mode during sleep. He reports feeling as if his device is breathing for him before he is ready to breathe in. He also reports more frequent awakenings during sleep since starting his use of the device.

- Which of the following changes to the patient's BPAP settings would be most likely to improve his dyssynchrony?
  - A. Increase the inspiratory time
  - B. Lengthen the rise time
  - C. Increase the cycle sensitivity
  - D. Increase the trigger sensitivity

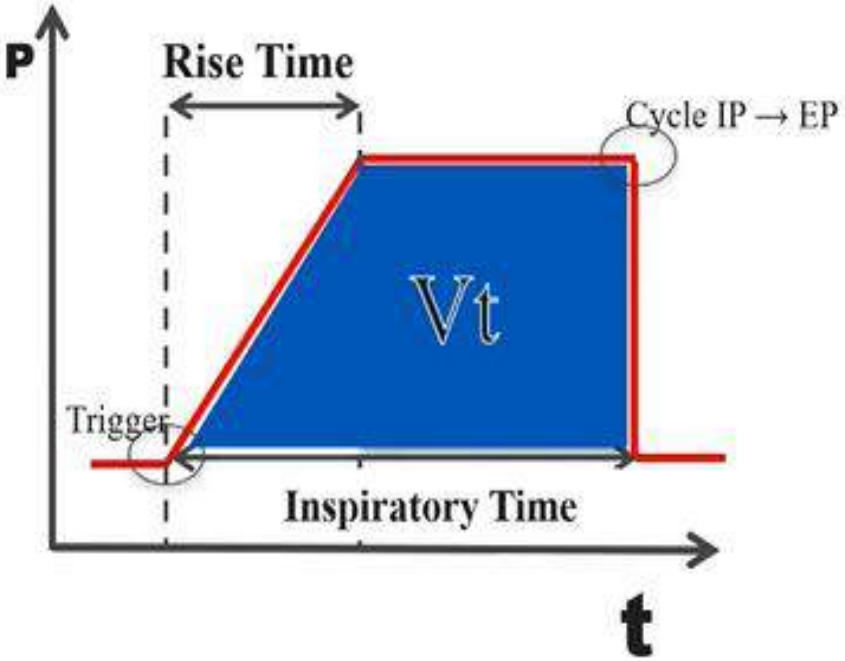
Answer: C



Ventilator Dyssynchrony

Bilevel: BPAP

Bilevel PAP (BPAP): Wave Form



Trigger sensitivity: inspiratory flow set above which EPAP -> IPAP

Rise Time: time it takes the device to transition from EPAP to IPAP

Inspiratory Time: time the device spends in IPAP

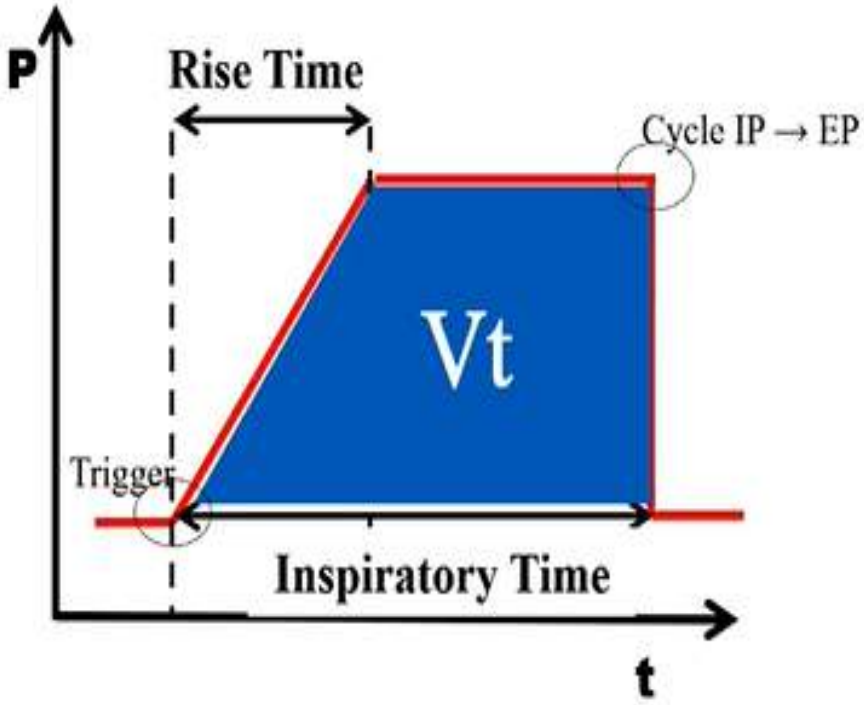
Cycle sensitivity: inspiratory flow set below which IPAP -> EPAP

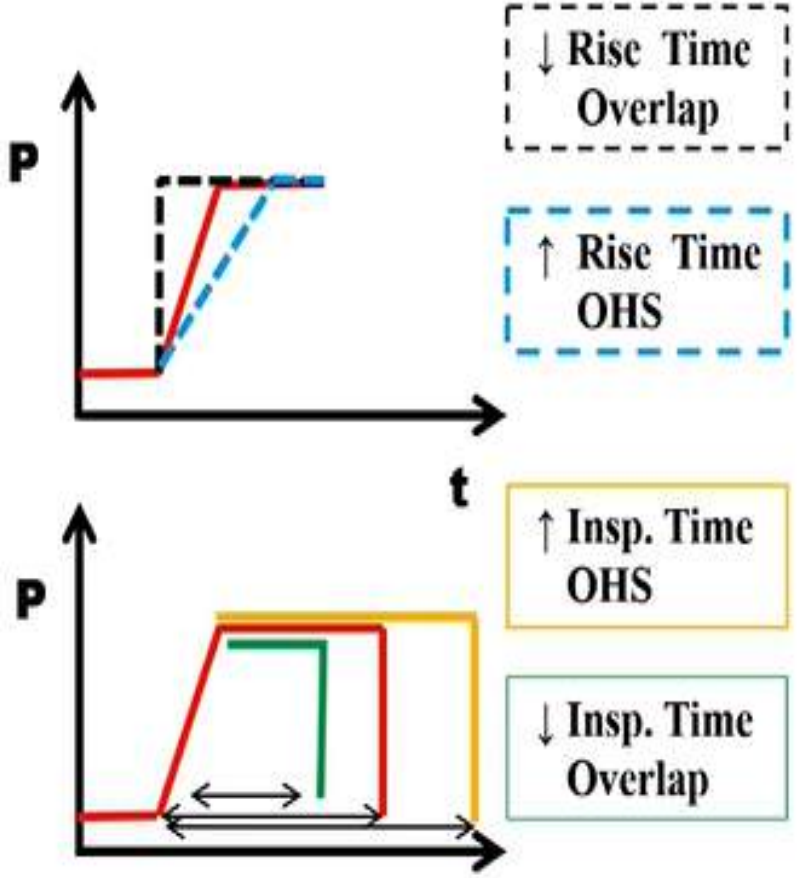
Tidal volume

To have synchrony you need to adjust 4 main things: Trigger, Rise Time, Inspiratory Time & Cycle Sensitivity

Bilevel: BPAP

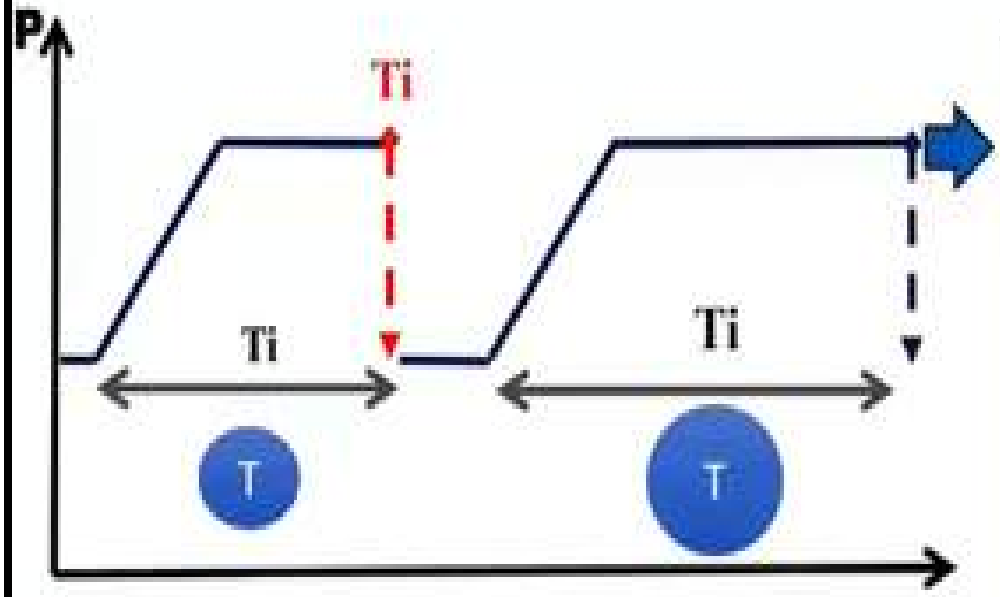
Bilevel PAP (BPAP) ST: Rise Time – Insp. Time

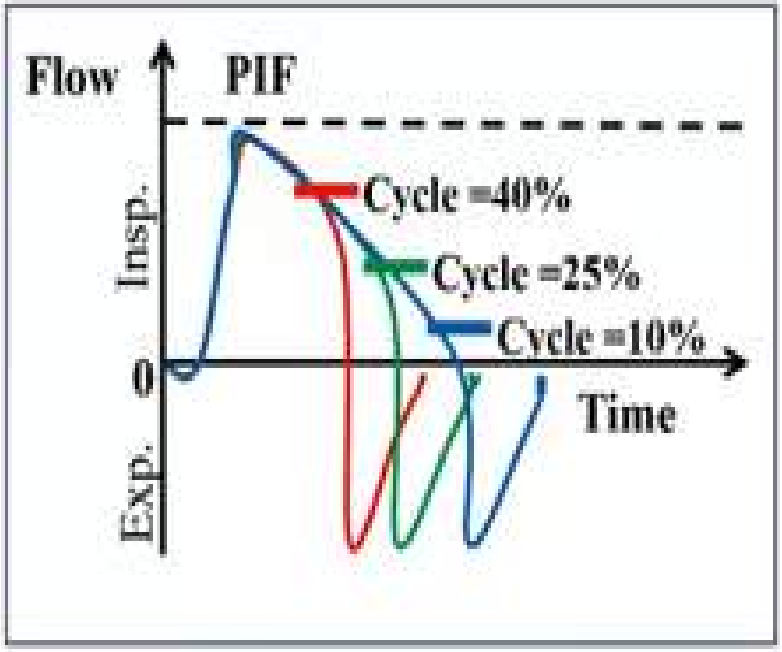




Bilevel: BPAP

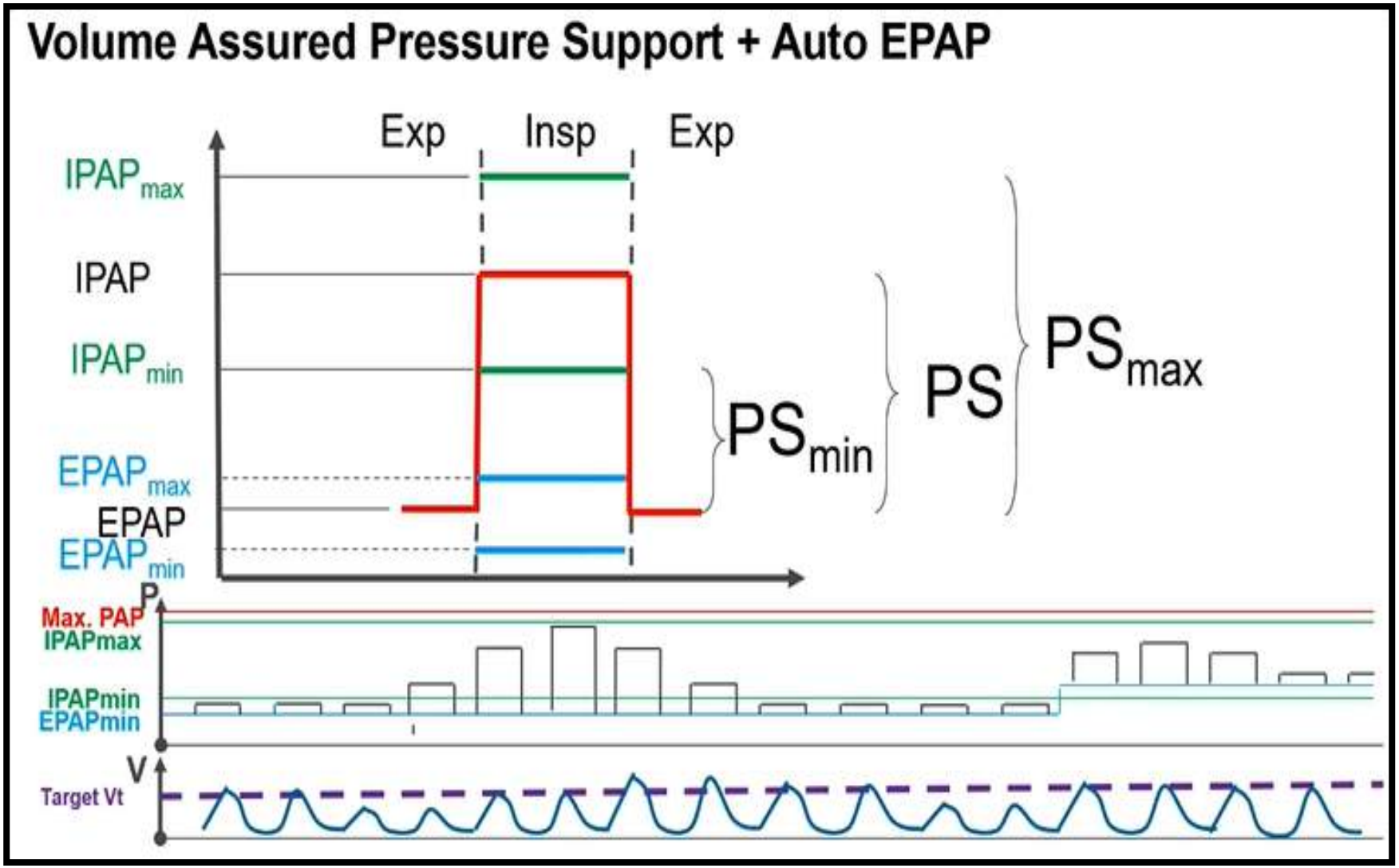
Cycling in BPAP-ST: Inspiratory Time (Ti) vs. Flow



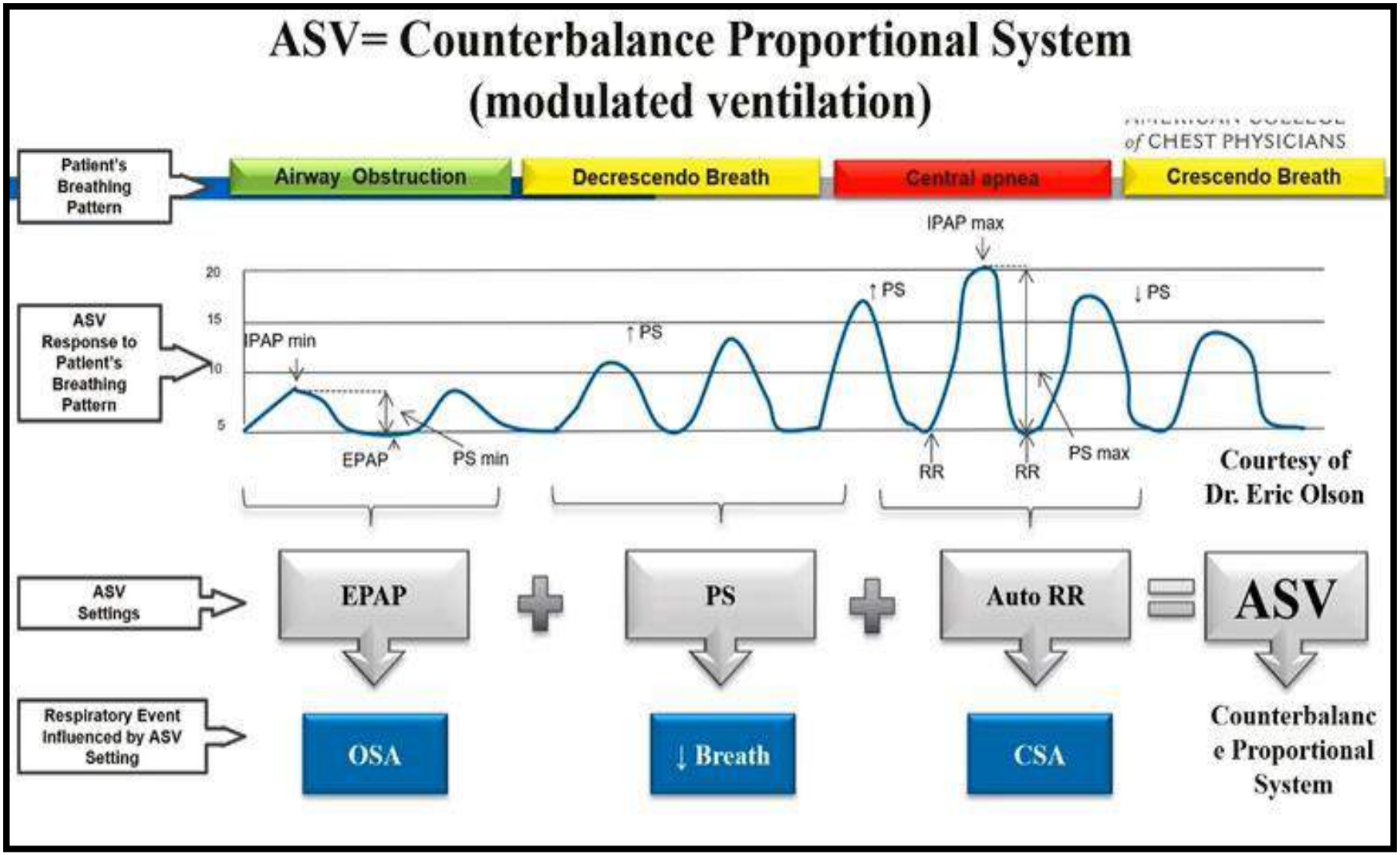


The lower is the % of peak flow , the later the inhalation will terminate

Bilevel: AVAPS



Bilevel: ASV


ASV= Counterbalance Proportional System
(modulated ventilation)
of CHEST PHYSICIANS
Patient's Breathing Pattern
Airway Obstruction
Decrescendo Breath
Central apnea
Crescendo Breath
ASV Response to Patient's Breathing Pattern
IPAP max
IPAP min
↑ PS
↑ PS
↓ PS
EPAP
PS min
RR
RR
PS max
Courtesy of Dr. Eric Olson
ASV Settings
EPAP
PS
Auto RR
ASV
Respiratory Event Influenced by ASV Setting
OSA
↓ Breath
CSA
Counterbalance Proportional System

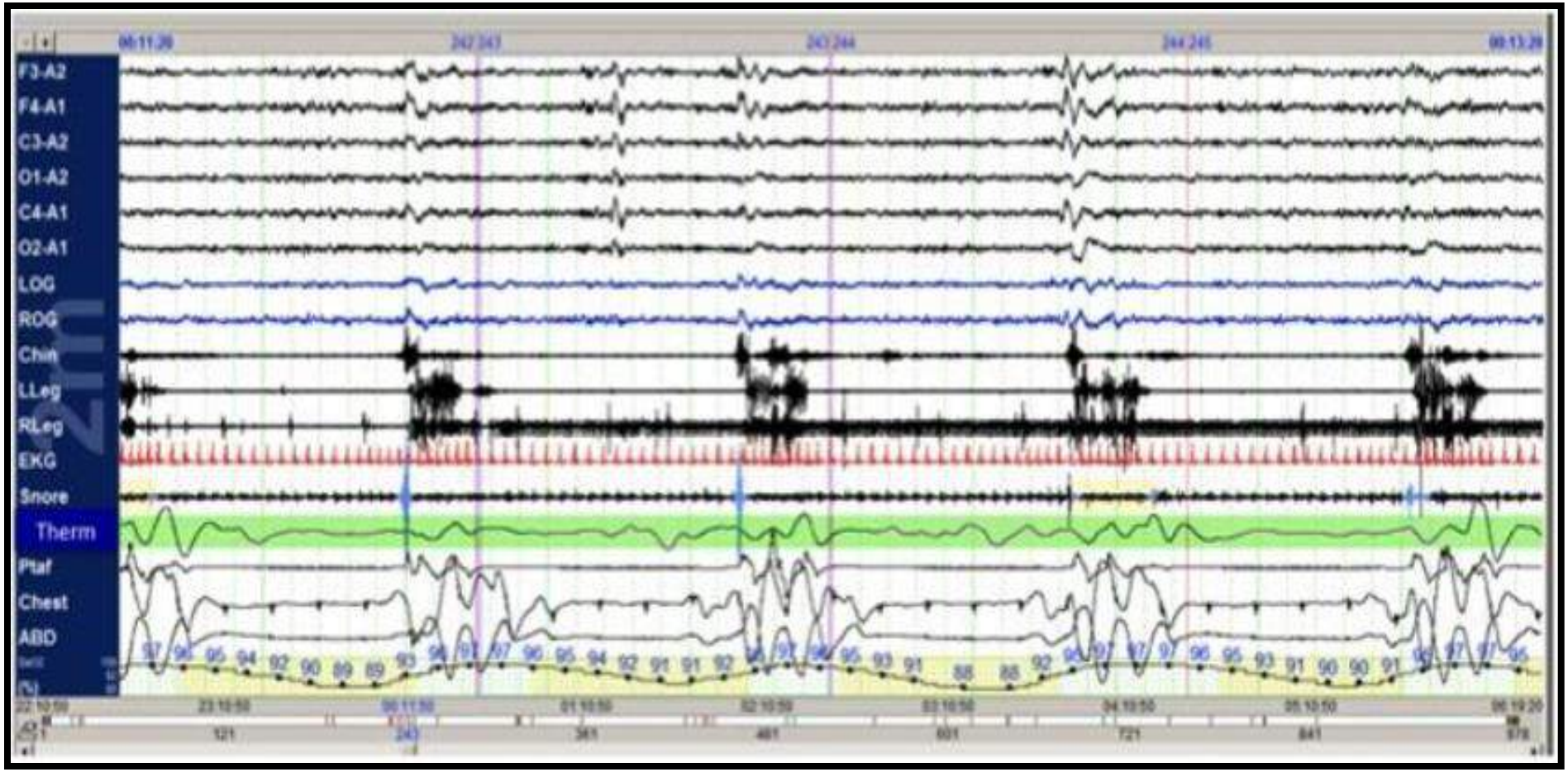
Central Sleep Apnea

Beyond the Pearls: Question

- 36 year old man without significant PMH is referred for symptoms of fragmented sleep, **sleep maintenance insomnia**, and daytime sleepiness (ESS 13). His wife has observed that the patient has apneas throughout the night but denies snoring. The patient's sleep disruption and observed sleep-disordered breathing occur more during the **first half** of the night and improve as the night progresses. Symptoms are **not positional** and are not associated with awakenings related to shortness of breath. He denies any cardiac disease, chest pain, other chronic pain syndromes, restless legs syndrome symptoms, or depression and has no history of stroke or other neurologic disease. He also denies dyspnea on exertion or lower-extremity edema.
- Meds and allergies: None
- Social history: Lives in a Midwestern city (altitude 1,000 ft/300 m) and is a nonsmoker
- Physical exam: BMI 24, vital signs and physical WNL
- Tests and labs: Normal spirometry, echocardiogram, ECG, and urine toxicology screen
- ABG on RA: ph 7.45, PCO_2 35 mm Hg, PO_2 100 mm Hg, HCO_3 24 mmol/L
- A split-night polysomnography was performed and characteristic sleep-disordered breathing findings from the baseline and CPAP titration portions of the study, respectively, are shown on the next 2 slides

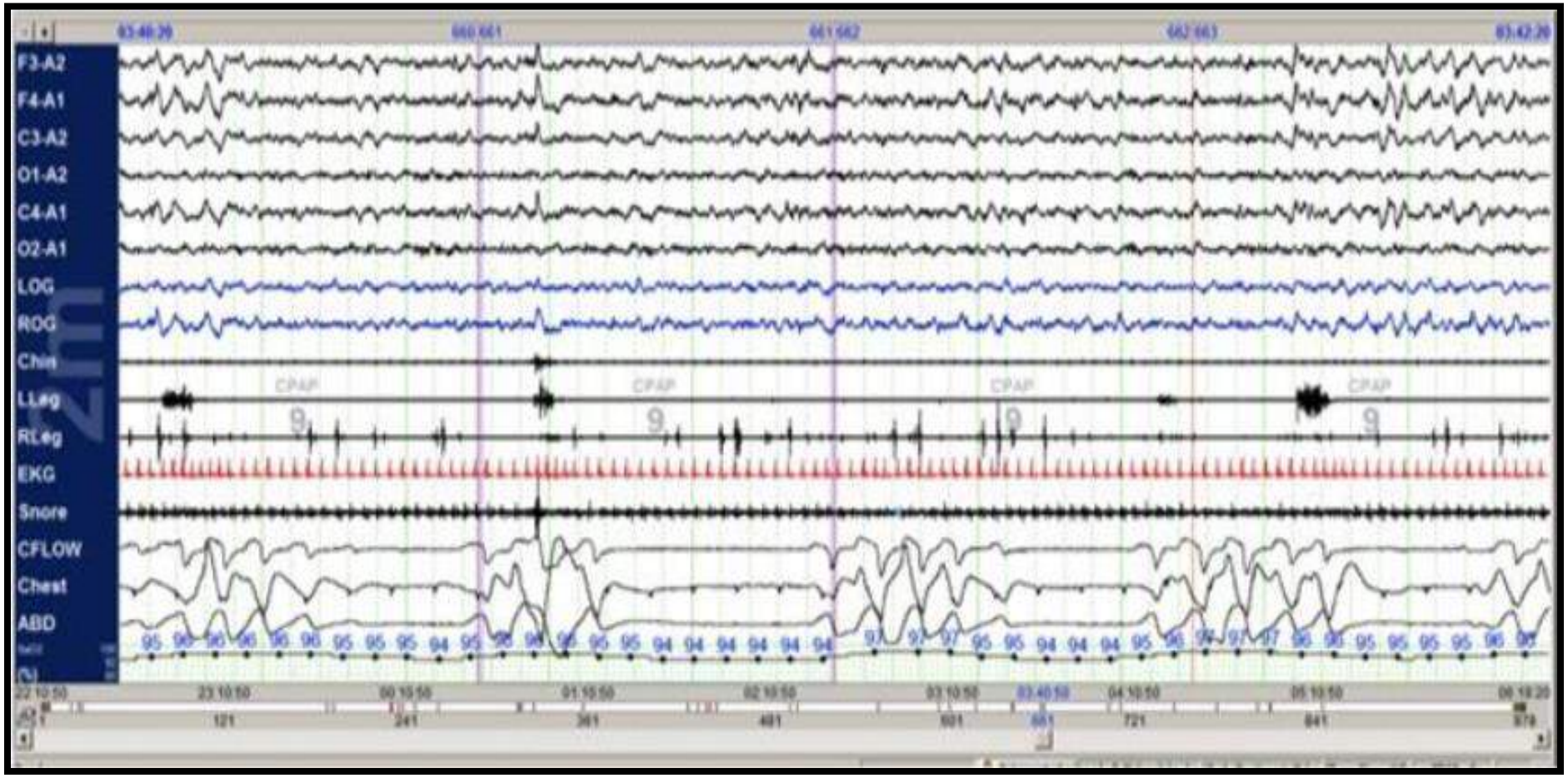
Beyond the Pearls: Question

A split-night polysomnography was performed. The results shown below is a 2 minute from the patient's N2 sleep



Beyond the Pearls: Question

A split-night polysomnography was performed. The results shown below is a 2 minute from the patient's N2 sleep during CPAP titration



Beyond the Pearls: Question

PSG Parameters	Baseline	CPAP Titration
Total sleep time (min)	180	240
Total AHI	50	32
NREM AHI	60	40
REM AHI	0	0
Obstructive apnea index	5	0
Central apnea index	40	25
Hypopnea index	5	5
Oxygen nadir (%)	85	89
Periodic limb movement index	0	0

AHI = apnea-hypopnea index; PSG = polysomnography.

Beyond the Pearls: Question

- Which one of the following is the most likely diagnosis?
  A. Central sleep apnea (CSA) caused by high-altitude periodic breathing
  B. CSA with Cheyne-Stokes respiration
  C. Primary CSA
  D. Treatment-emergent CSA

Answer: C

- Primary, or idiopathic, CSA is a rare disorder of unknown prevalence or etiology. Patients typically present with sleep fragmentation, sleep-onset or maintenance insomnia, snoring, witnessed apneas, and/or daytime sleepiness
- PSG findings are characterized by recurrent central apneas and/or hypopneas, which make up more than 50% of the sleep-disordered breathing events
- This disorder is a **diagnosis of exclusion**, as other disorders (congestive heart failure, CNS disease, sleep-related hypoventilation) and factors that predispose to CSA (narcotics, high altitude) need to be ruled out prior to confirming this diagnosis.
- Most patients with primary CSA demonstrate central events predominantly in **N1 and N2 sleep with resolution in REM sleep**. This sleep-stage pattern is similar to other CSA syndromes and is likely related to a reduced chemo-responsiveness to CO_2 and O_2 in REM sleep

Question for the G.O.A.T

- **47 year old** corporate executive without significant PMH has just undergone a complete physical and has been found to be in excellent health is referred for PSG based upon complaints of fatigue and witnessed apneas during sleep. He takes no regular medications. A summary of the results of the **first portion** of the PSG are shown
- A trial of **CPAP** between 5-15 cm of H2O during the latter half of the night is unsuccessful at improving the shown abnormalities

- TRT: 195 minutes
- TST: 178 minutes

- N1: 24%
- N2: 74%
- N3: 2%
- REM: 0%

- AHI 38.6
- Obstructive apnea index: 3.7 / hr
- Central apnea index: 25.8 / hr
- Hypopnea index 9.1 / hr
- Nadir O2 saturation 79%
- PLM Index 0.8 / hr

Question for the G.O.A.T

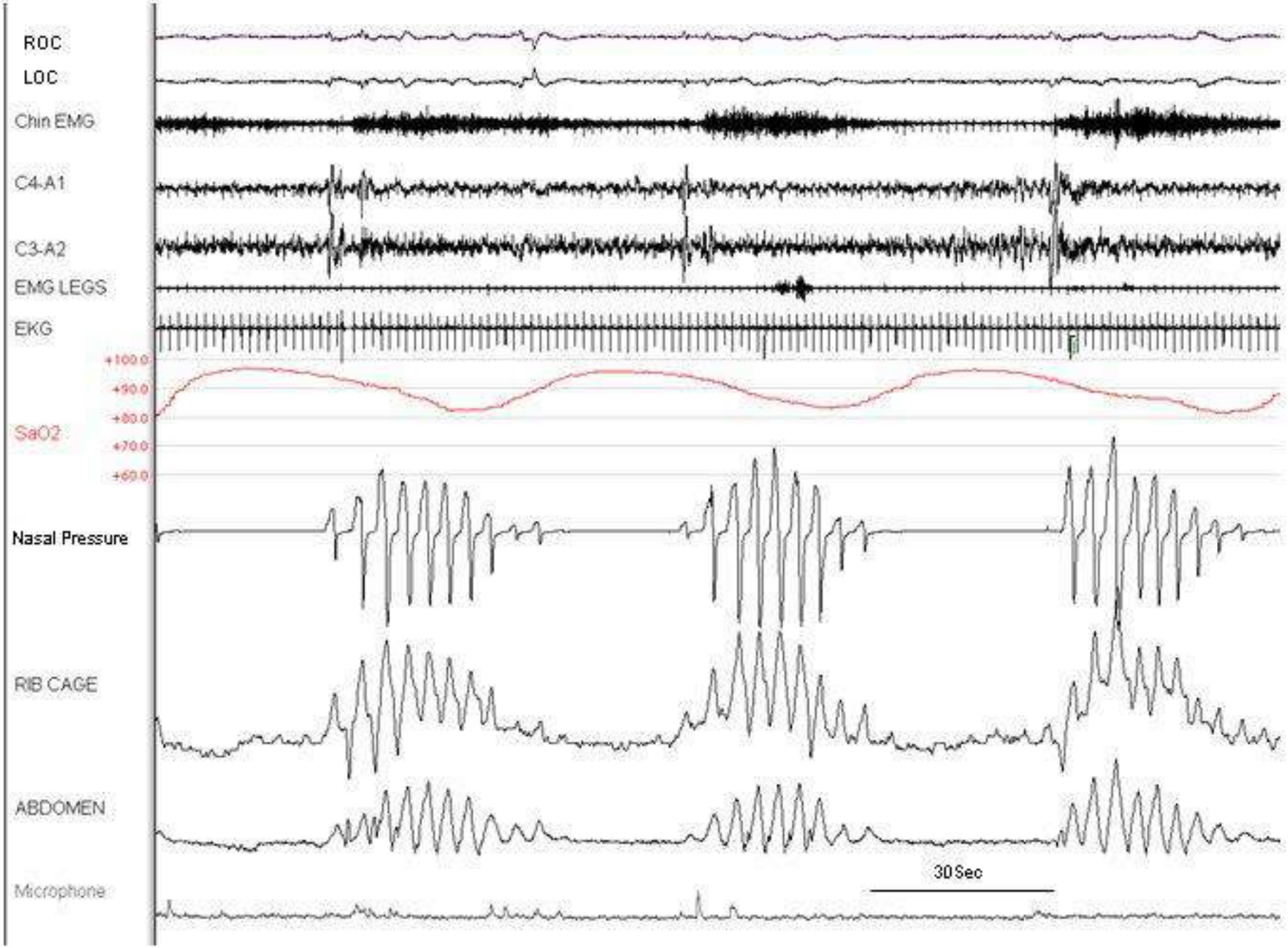
- Which of the following is true with regard to this patient's most likely diagnosis?
  - A. The disorder is likely to worsen during REM sleep
  - B. Bilevel pressure, spontaneous mode, is an effective therapy
  - C. The use of low dose hypnotics is likely to exacerbate disease
  - D. The addition of supplemental oxygen during sleep may decrease the frequency of events

Answer: D

- The PSG findings are diagnostic for central sleep apnea (CSA); this can be a primary or secondary condition.
  - **Secondary**: Cheyne-Stokes, high altitude, opioids, NM
  - **Primary**: In the absence of the above
- Supplemental O2 during sleep is indicated for patients with **hyperventilation**-related CSA who have hypoxemia during sleep. It can be used along with positive airway pressure therapy and is also indicated for patients who **do not tolerate or fail** positive airway pressure therapy
  - Supplemental oxygen during sleep not only mitigates hypoxemia during sleep, but it may also reduce the AHI
  - The mechanism by which supplemental oxygen during sleep improves CSA is unknown
- Sedative-hypnotics have be evaluated for **primary CSA** and have been shown to reduce severity.
  - No formal recommendation for use of this therapy

Question: Part 1

- 65 year old obese male presents for evaluation of daytime fatigue and loud snoring. He reports difficulties in maintaining sleep during the night, with the need to urinate on awakening. History of **DM** and **HTN**. On review of systems, he reports symptoms of **orthopnea**
- On exam, **S3** is heard on heart auscultation he has **lower extremity edema** and a normal neurologic examination
- In lab PSG in perform


ROC
LOC
Chin EMG
C4-A1
C3-A2
EMG LEGS
EKG
+100.0
+90.0
+80.0
SaO2
+70.0
+60.0
Nasal Pressure
RIB CAGE
ABDOMEN
30 Sec
Microphone

Question: Part 1

- Based on the PSG tracing, which of the following tests would be most appropriate to perform next

  A. MRI of the brain

  B. Echocardiogram

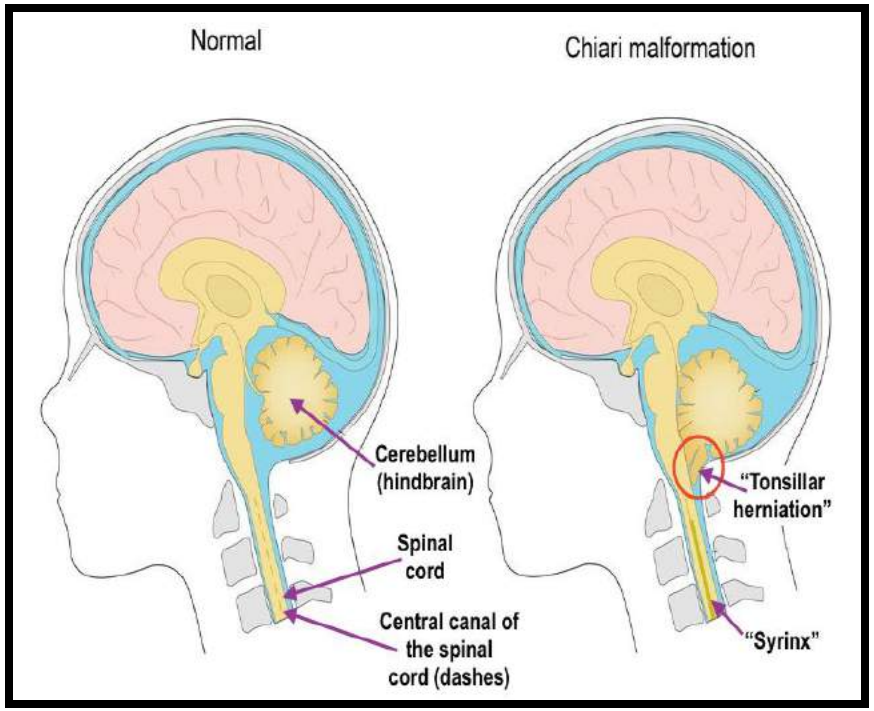
  C. ASV titration

  D. Tilt table test

  E. Cardiac catheterization

Answer: B

- ASV controversy
- Treating the underlying cause of CSA, in this case the CHF, would be the most appropriate
- Cardiac catheterization would confirm a potential etiology of the CHF, but would not be the most immediate test to request
- MRI to look for Arnold Chiari Type 1 malformation. Treatment is base of skull surgery.



Question: Part 2

- Based on the previous PSG tracing shown, which statement is **most correct** regarding this patient with congestive heart failure

A. Oxygen therapy will improve long-term survival

B. The patient has an increased risk of mortality

C. The patient has decreased chemoreceptor responsiveness

D. The patient has an increased PaC02 during wakefulness

Answer: B

- Patients with CHF have:
  1) Increased chemoreceptor responsiveness (also know as high loop gain)
  2) Increased circulatory times
  3) Decreased oxygen stores
- Patients with CHF and CSR have increased mortality compared to CHF without CSR
- The cycle length for CSR is > 40 seconds compared to primary CSA the cycle length is < 40 seconds

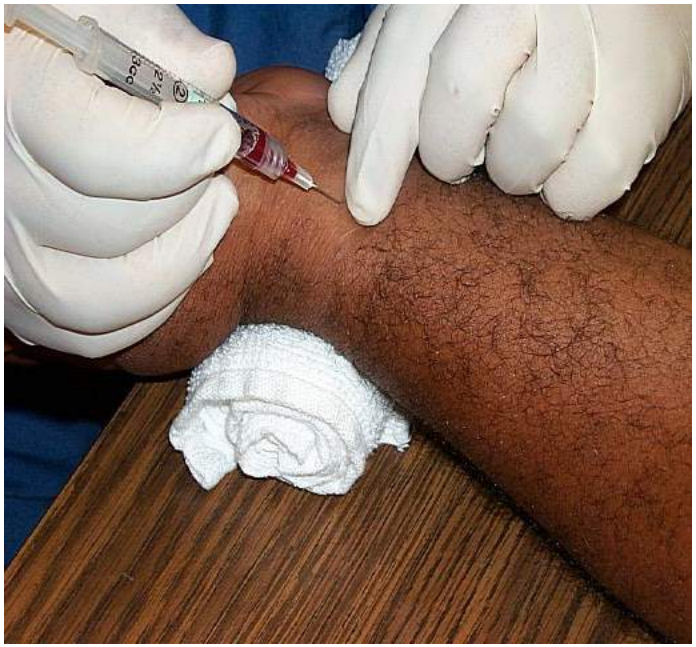
Central Sleep Apnea Classification: Hypercapnic

- High **sleep** and **waking** PaCO2
- **Decreased** ventilatory response to hypercapnia
- Causes:
  - **Neuromuscular disorders**
    - ALS, Myasthenia Gravis, Gillian Barre, Muscular Dystrophy
  - **Chronic opioid use**
    - Mu receptors in the “Pre-Botzinger” complex which is a neural network responsible for inspiration during respiratory activity in in the brainstem
    - Ataxic or Biot’s respiration during NREM sleep
    - Two important risk factors are:
      1. Morphine equivalent dose > 200mg/day and dose dependent
      2. Low or normal BMI
    - CPAP may reduce AHI but frequently ineffective. Therefore ASV or BiPAP-ST (especially if hypoventilation)

ALS Association
Fighting Lou Gehrig's Disease

Central Sleep Apnea Classification: Non-hypercapnic

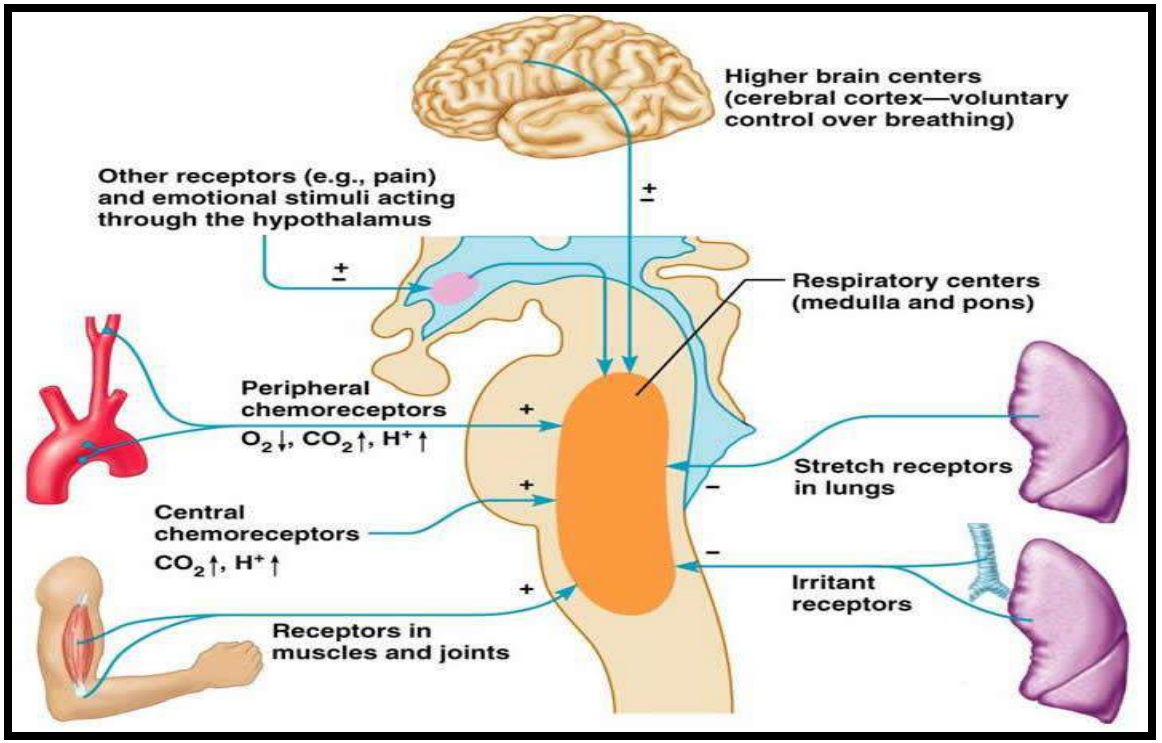
- Normal or **low** waking PaCO2
- **Increased** ventilator response to hypercapnia
- Causes:
  - Primary or Idiopathic CSA
  - Sleep-onset CSA
  - Cheyne Stokes Respiration
  - High altitude periodic breathing
  - Treatment emergent central sleep apnea

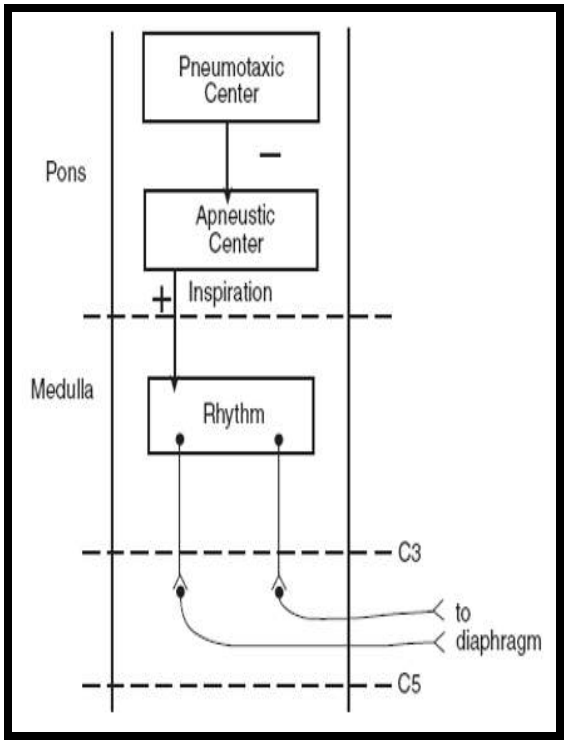


Beyond the Pearls: Question

- What is the physiology behind CPAP induced central sleep apnea?
  A. High loop gain
  B. Hering-Breuer reflex
  C. CPAP maladaptation causing increased arousals resulting in sleep onset centrals
  D. All of the above

Answer: D



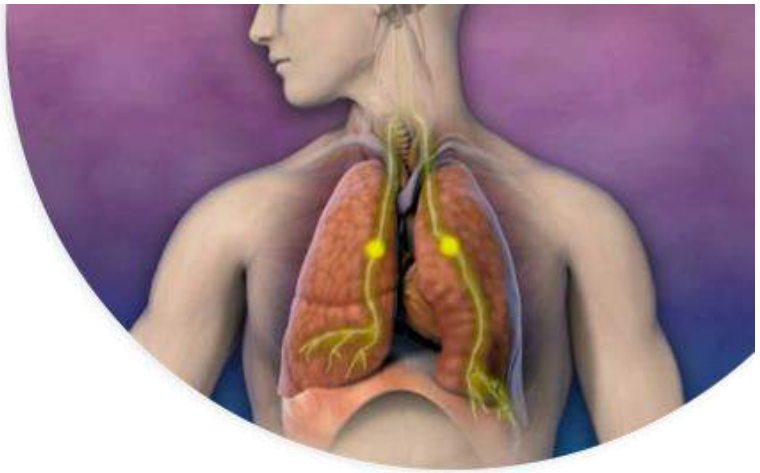


- 5-15% of patient with OSA will develop treatment-emergent CSA
- 85% of treatment-emergent CSA will eventually resolve with CPAP therapy
- Consider a trial of ASV if persistent CSA on CPAP
- Treatment emergent CSA can occur from dental devices and ENT surgery for OSA

CSA Treatment

- Not standardized
- Treat underlying cause
- NIPPV
  - CPAP +/- oxygen
  - BiPAP with backup rate
  - ASV (not for CHF)
- Nocturnal oxygen vs CO2
- Phrenic nerve stimulation (PNS)
- Medications
  - Acetazolimide (high altitude)
  - Medroxyprogesterone

Respicardia®
Respiratory Rhythm Management™



ORIGINAL ARTICLE

Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure

Martin R. Cowie, M.D., Holger Woehrle, M.D., Karl Wegscheider, Ph.D., Christiane Angermann, M.D., Marie-Pia d'Ortho, M.D., Ph.D., Erland Erdmann, M.D., Patrick Levy, M.D., Ph.D., Anita K. Simonds, M.D., Virend K. Somers, M.D., Ph.D., Faiez Zannad, M.D., Ph.D., and Helmut Teschler, M.D.

Hypoventilation Syndromes

- **Congenital Central Alveolar Hypoventilation Syndrome (Ondine's curse)**
  - Failure of autonomic control of breathing
  - Diminished responsiveness to O2 and CO2
  - Onset in infancy but can **occur later in life** and at times trigger in adults after anesthesia
  - Clinically have a normal respiratory rate with very low tidal volumes
  - Diagnosis requires identification of mutations in **PHOX2B gene**

Clinical Pearl: Outside of infancy, CSA with or without hypoventilation is very unusual and requires further evaluation

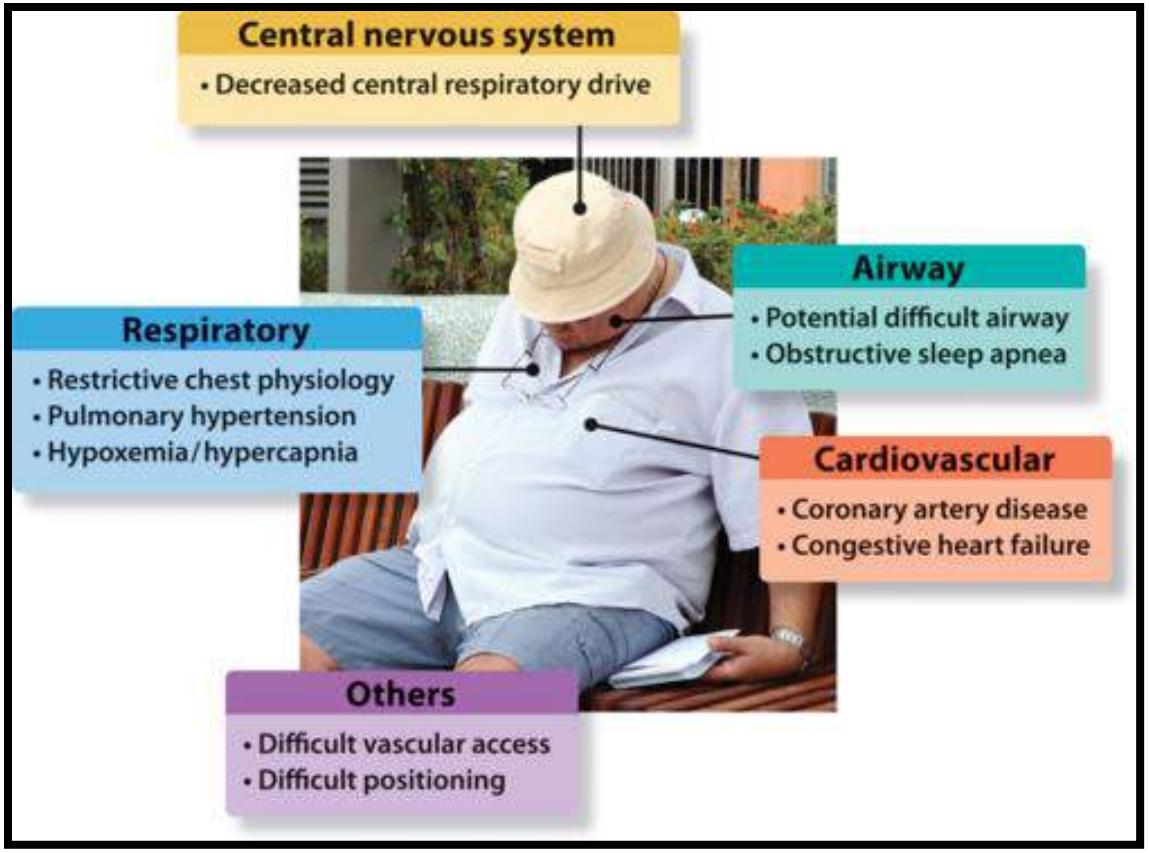
OHS and Hypercapnia

Beyond the Pearls: Question

- 63 year old man with a BMI 43 visits an outpatient sleep clinic with symptoms of daytime sleepiness and loud snoring that have developed over the last few years. He has not had any hospitalizations in the past year. His ESS score is 11. Exam reveals that his neck circumference is 43 cm and he has trace bilateral pedal edema. He has normal muscle strength.
- Sleep testing demonstrated an AHI of 65 (95% obstructive events and 5% central apneas) with a mean SpO_2 of 89%. Spirometry demonstrated an FEV_1/FVC 80%, FEV1 85% & FVC 82%. ABG testing showed a pH of 7.40, a $PaCO_2$ 51, PaO_2 60 and an HCO_3 30

- What PAP modality should be recommended for initial management?
  A. CPAP
  B. Adaptive servoventilation (ASV)
  C. BPAP in spontaneous/timed mode (ST)
  D. Volume-assured pressure support (VAPS)

Answer: A



Obesity Hypoventilation Syndrome ATS Guidelines

Obesity Hypoventilation Syndrome

AMERICAN THORACIC SOCIETY DOCUMENTS

Evaluation and Management of Obesity Hypoventilation Syndrome
An Official American Thoracic Society Clinical Practice Guideline

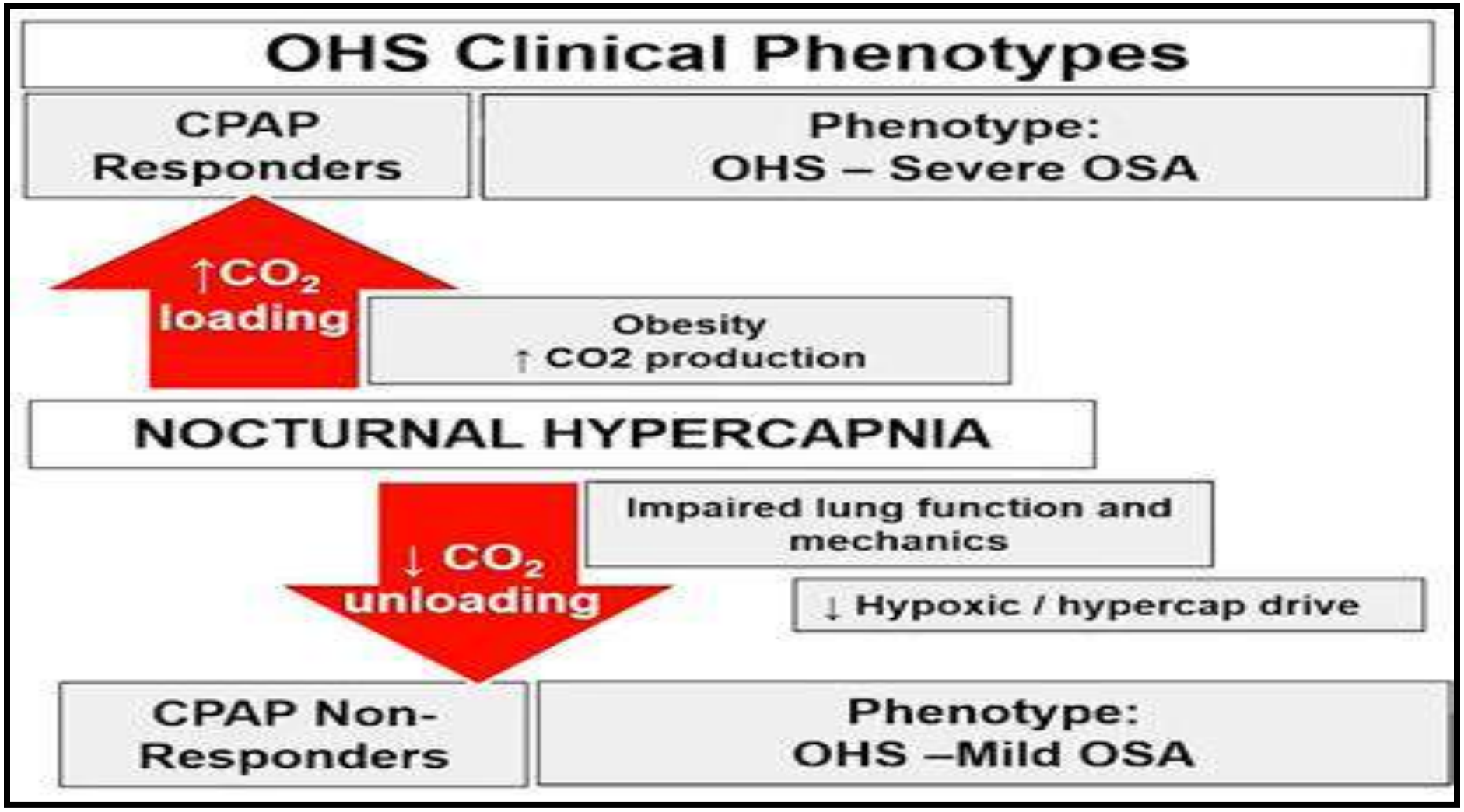
Babak Mokhlesi, Juan Fernando Masa, Jan L. Brozek, Indira Gurubhagavatula, Patrick B. Murphy, Amanda J. Piper, Aiman Tulaimat, Majid Afshar, Jay S. Balachandran, Raed A. Dweik, Ronald R. Grunstein, Nicholas Hart, Roop Kaw, Geraldo Lorenzi-Filho, Sushmita Pamidi, Bhakti K. Patel, Susheel P. Patil, Jean Louis Pépin, Israa Soghier, Maximiliano Tamae Kakazu, and Mihaela Teodorescu; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

2019

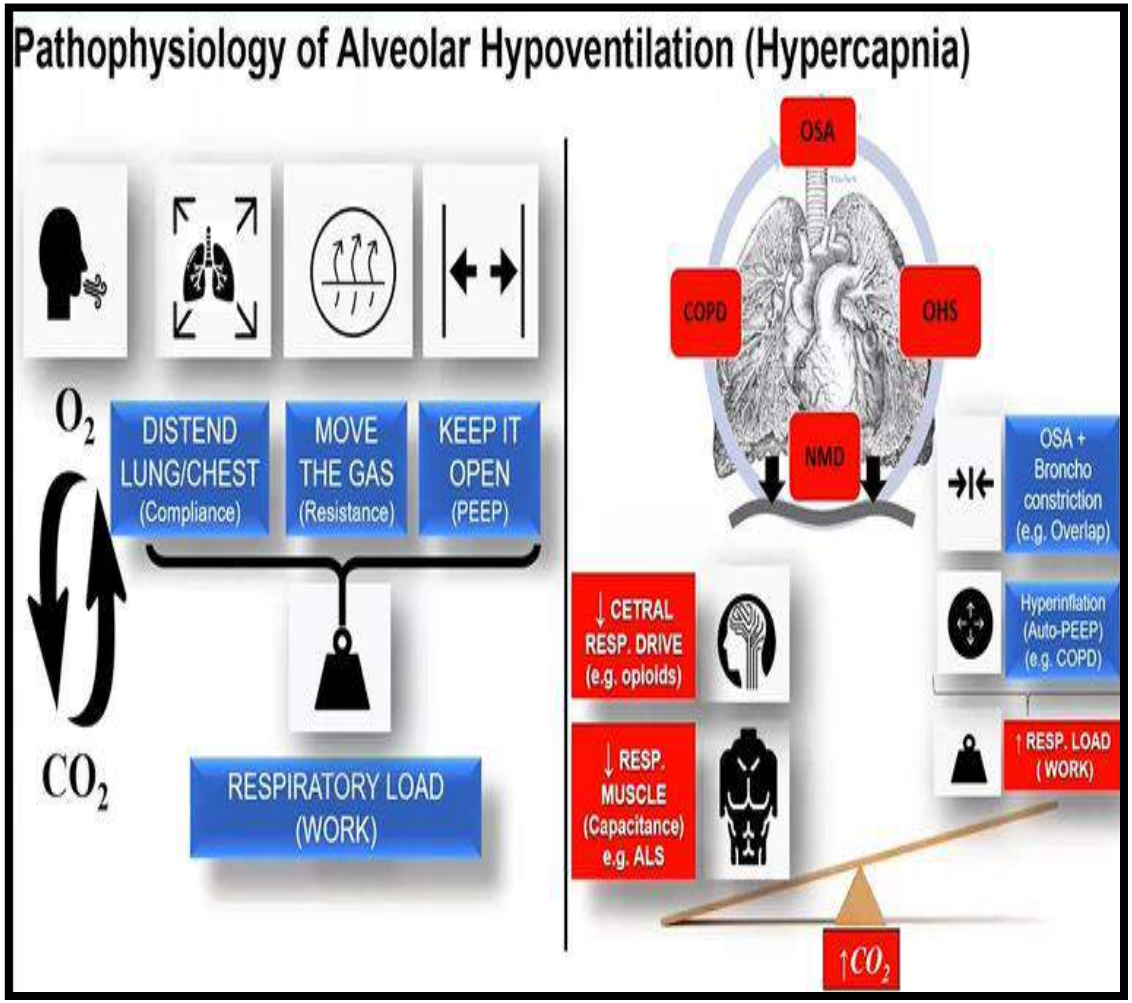
- **Practice guideline** (ATS) all recommendations are conditional, very low level of certainty in the evidence

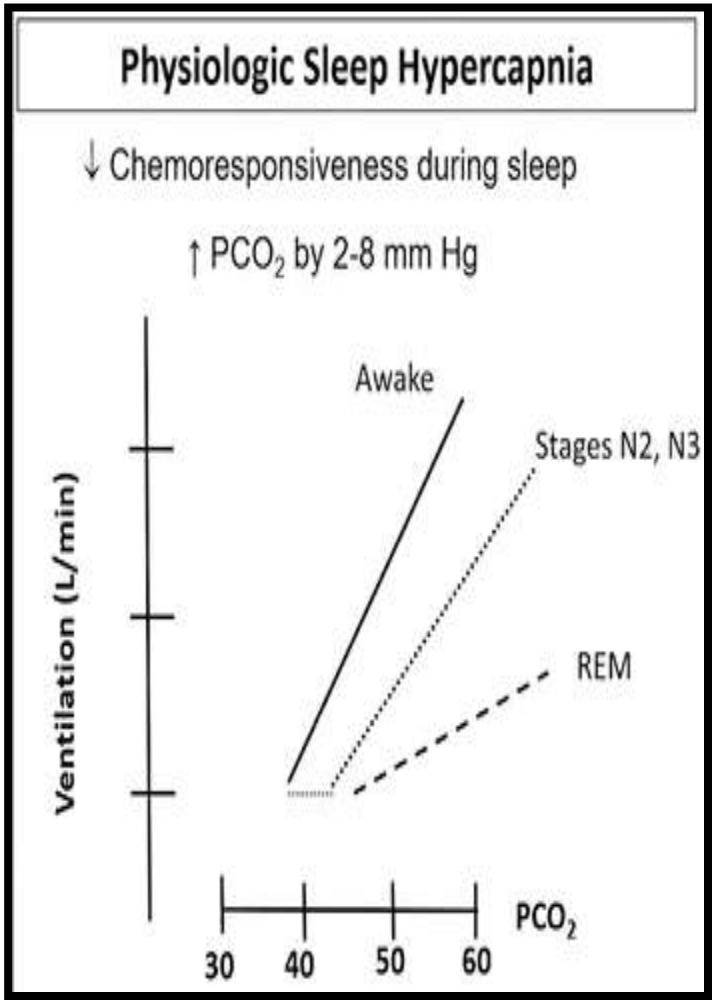
- **Testing** $PaCO_2$ and serum bicarb based on pretest probability of OHS:
  - High probability, measure $PaCO_2$
  - Low to intermediate probability (< 20%), measure serum $PaCO_2$
    - Bicarbonate <27 mmol/L has a high negative predictive value
    - Bicarbonate ≥ 27 mmol/L requires $PaCO_2$ for diagnosis confirmation
- **Therapy**
  - PAP therapy:
    - Ambulatory, stable OHS-severe OSA (AHI ≥ 30/h): CPAP (first line therapy) *
    - Hospitalized with respiratory failure and suspected OHS: NIV (outpatient work up /PAP titration in 3 months)
  - Weight-loss intervention:
    - Weight loss intervention 25-30% of actual body weight (if failure, evaluate for bariatric surg.)

Obesity Hypoventilation Syndrome: Clinical Phenotypes



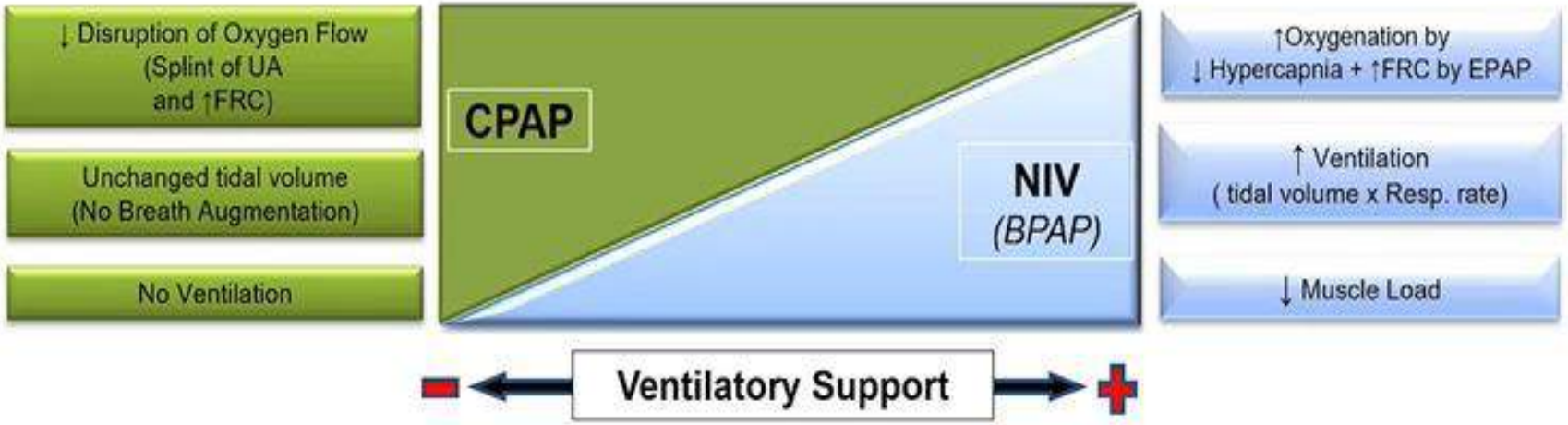
Obesity Hypoventilation Syndrome: Physiology of Hypercapnia





Obesity Hypoventilation Syndrome: CPAP VS. BiLevel

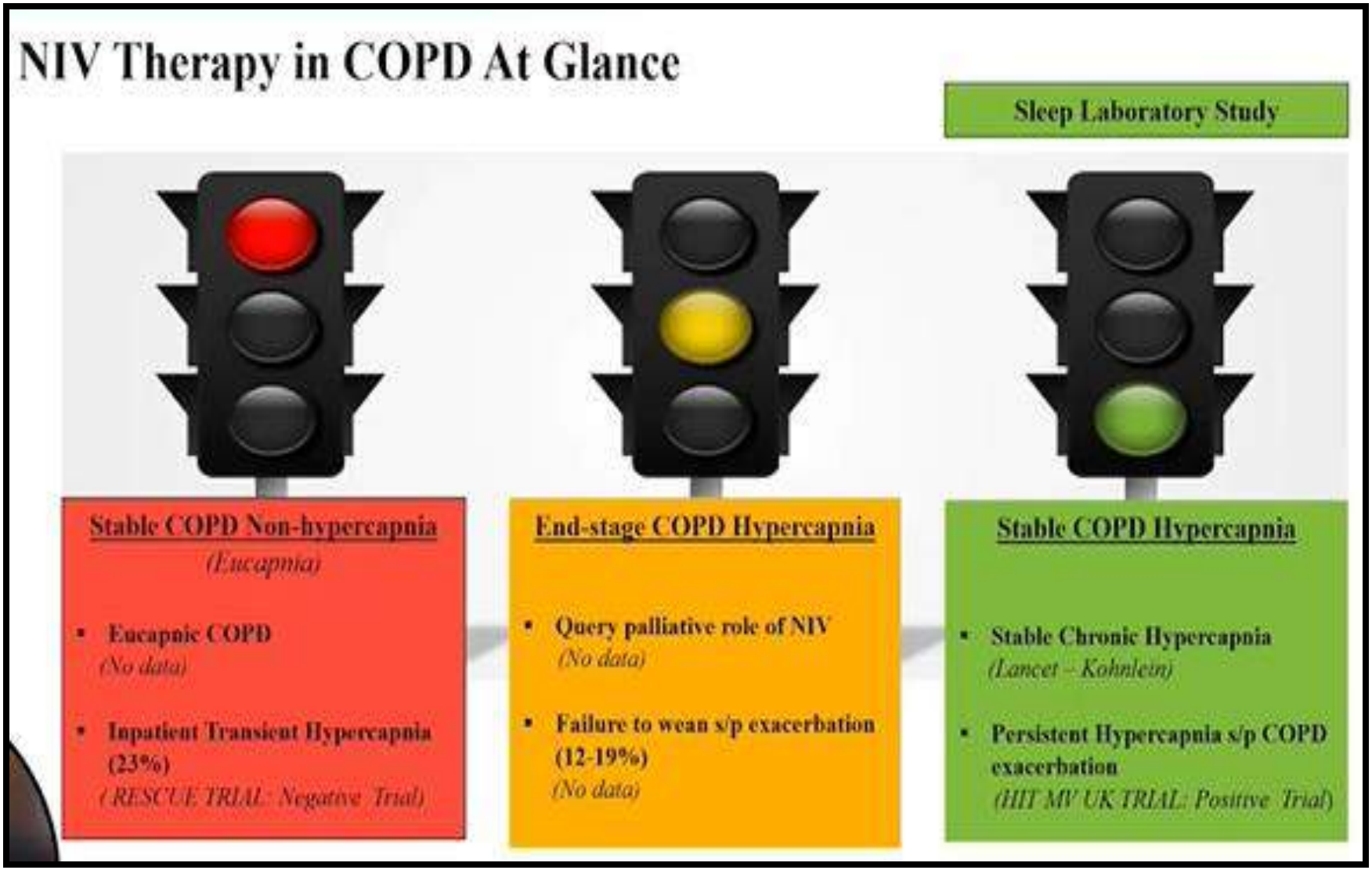
Ventilatory Support: CPAP vs. Non-invasive Ventilation in Hypercapnia



Non-invasive Positive Airway Pressure (PAP) Therapy for Hypercapnia

Non-invasive Ventilation (NIV) *(Bilevel Positive Airway Pressure Modes)*	• Bilevel PAP devices without back-up rate (BPAP-S
	• Bilevel PAP devices with back-up rate BPAP-ST)
	• Volume Assured Pressure Support (VAPS)

Beyond the Pearls: NIPPV for COPD



Beyond the Pearls: NIPPV on Discharge for COPD Exacerbation

Hi-PPV After Exacerbation - Readmission/Death

JAMA

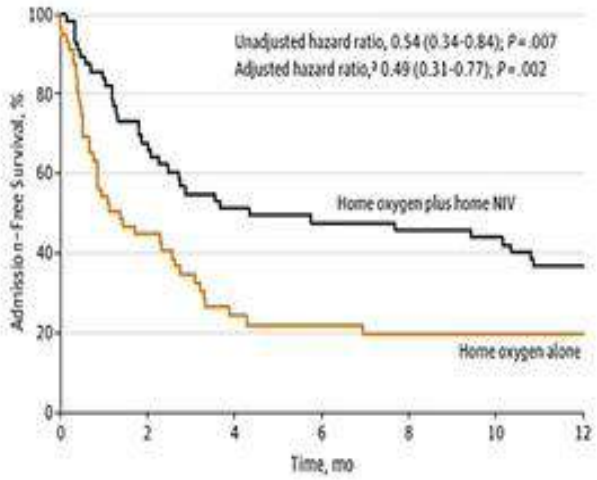
CHEST

Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation
A Randomized Clinical Trial

Patrick B. Murphy, PhD; Sunita Rehal, MSc; Gill Arbane, BSc (Hons); Stephen Bourke, PhD; Peter M. A. Calverley, PhD; Angela M. Crook, PhD; Lee Dowson, MD; Nicholas Duffy, MD; G. John Gibson, MD; Philip D. Hughes, MD; John R. Hurst, PhD; Keir E. Lewis, MD; Rahul Mukherjee, MD; Annabel Nickol, PhD; Nicholas Oscroft, MD; Maxime Patout, MD; Justin Pepperell, MD; Ian Smith, MD; John R. Stradling, PhD; Jadwiga A. Wedzicha, PhD; Michael I. Polkey, PhD; Mark W. Elliott, MD; Nicholas Hart, PhD

June 2017

Figure 2. Kaplan-Meier Survival Plot of Time to Readmission or Death From Randomization to the End of Trial Follow-up at 1 Year



No. at risk

Home oxygen plus home NIV	57	37	28	26	25	24	16
Home oxygen alone	59	23	11	10	8	8	6

The **12-month risk of readmission or death** was 63.4% in the home oxygen plus home Hi-PPV group vs 80.4% in the home oxygen alone group

Absolute risk reduction of 17.0%
(95% CI, 0.1%-34.0%)

NNT: 6

Insomnia

Beyond the Pearls: Question

- 48 year old woman with a **6 to 8 year history** of problems **going** to sleep and **staying** asleep. She does not remember having sleeping difficulty when her children were young but has gradually experienced increasing problems with sleep
- These problems intensified during her **husband's recent hospitalization** and emergency cardiac surgery, and **she now dreads bedtime**. She is concerned about her sleeping problems and fears that sleep loss is **causing her to be irritable** with her husband and also affecting her immune system
- Because she is so concerned about getting enough sleep, she **gets in bed about 8:30 pm** and cannot fall asleep until 11:30 pm or midnight. She then awakens about 2:30 am and then sleeps off and on until about 7:30 am. Sometimes she **naps** in the afternoon to make up for sleep lost at night.

Beyond the Pearls: Question

- She snores slightly but does not have witnessed apneas or uncomfortable leg sensations. She had hypertension, a history of depression, and obesity (**BMI 31**). She currently takes **no medications**. Her physical examination is normal
- Which of the following statements is true about this patient's sleep problem?

A. They are strongly contributing to her elevated blood pressure

B. They will improve as she enters menopause

C. They are likely perpetuated by her behavior and beliefs

D. Depression and antidepressant medications do not affect the underlying disorder

Answer: C

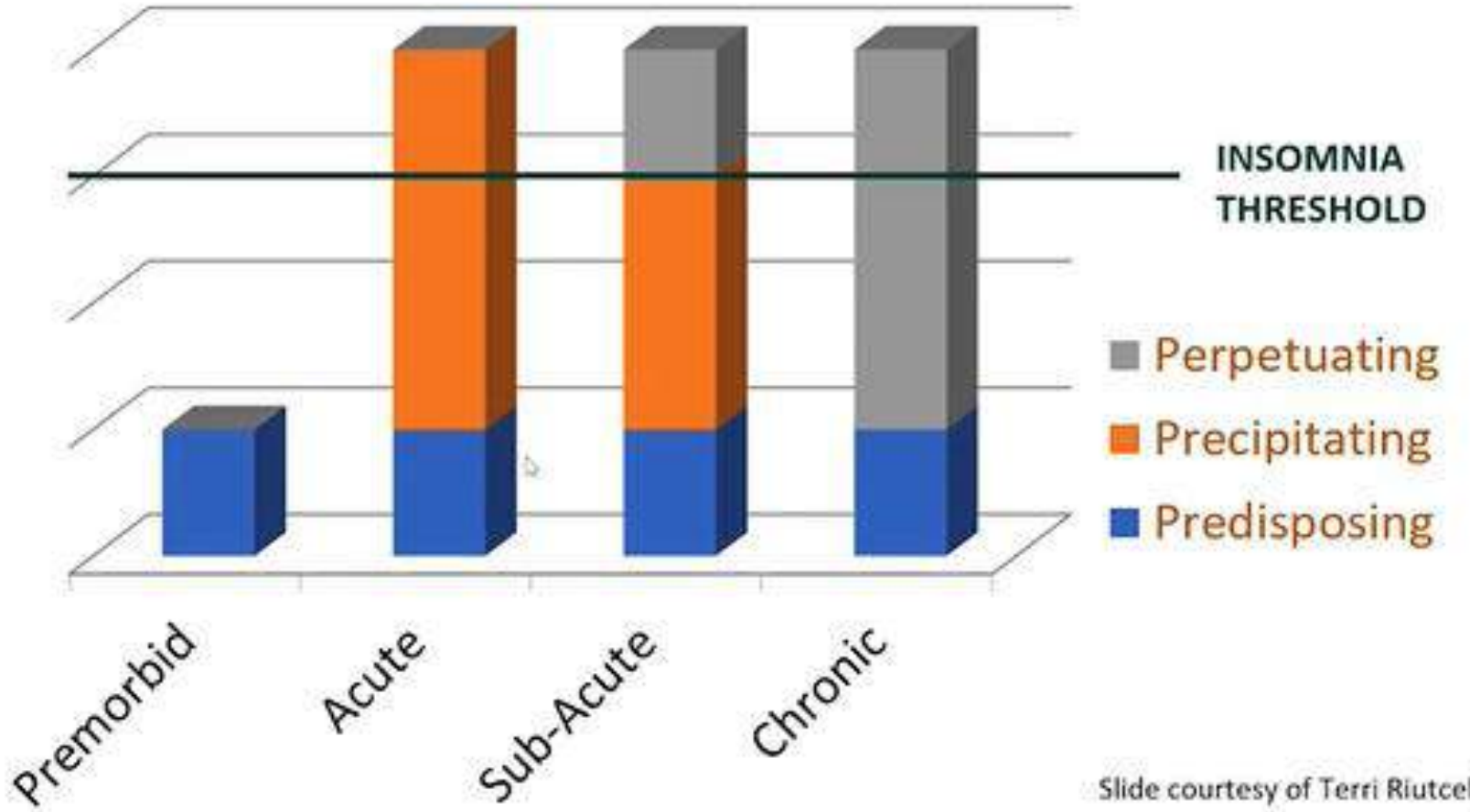
- Psychophysiologic or “learned” insomnia

Insomnia: ICSD-3 Definition

- A complaint of:
  - Difficulty initiating sleep
  - Difficulty maintaining sleep
  - Waking up too early
- Occurs despite adequate opportunity for sleep
- Produces deficits in daytime function
- For chronic insomnia symptoms at 3 times a week for at least 3 months

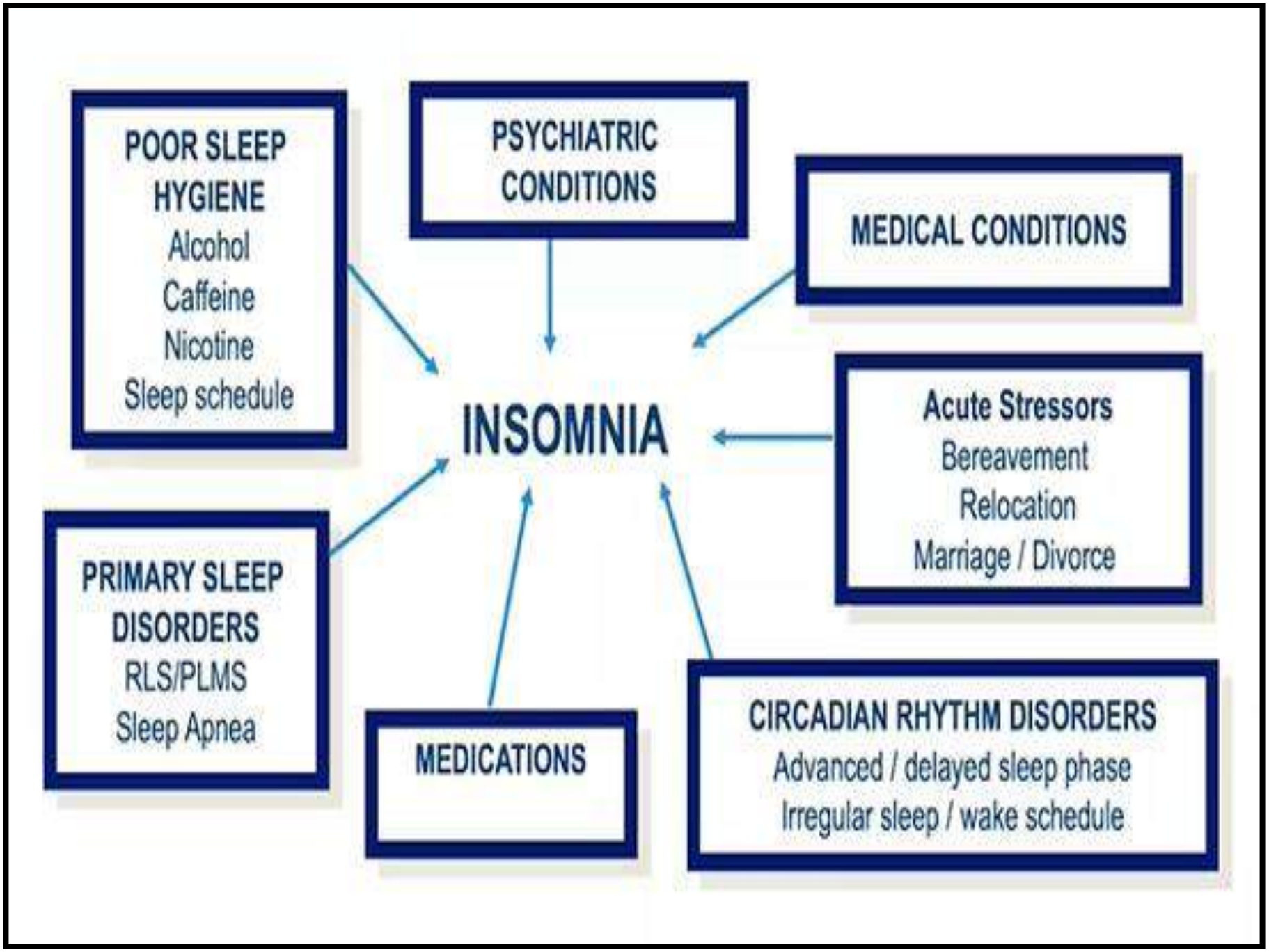
- No more “primary” and “secondary” insomnia terminology
- Secondary insomnia is consider “comorbid” insomnia
- No more childhood diagnosis

Spielman's Three Factor Model for the Evolution of Chronic Insomnia



Slide courtesy of Terri Riutcel, MD

Insomnia does increase mortality especially in those with short sleep duration


POOR SLEEP HYGIENE
Alcohol
Caffeine
Nicotine
Sleep schedule
PSYCHIATRIC CONDITIONS
MEDICAL CONDITIONS
INSOMNIA
Acute Stressors
Bereavement
Relocation
Marriage / Divorce
PRIMARY SLEEP DISORDERS
RLS/PLMS
Sleep Apnea
MEDICATIONS
CIRCADIAN RHYTHM DISORDERS
Advanced / delayed sleep phase
Irregular sleep / wake schedule

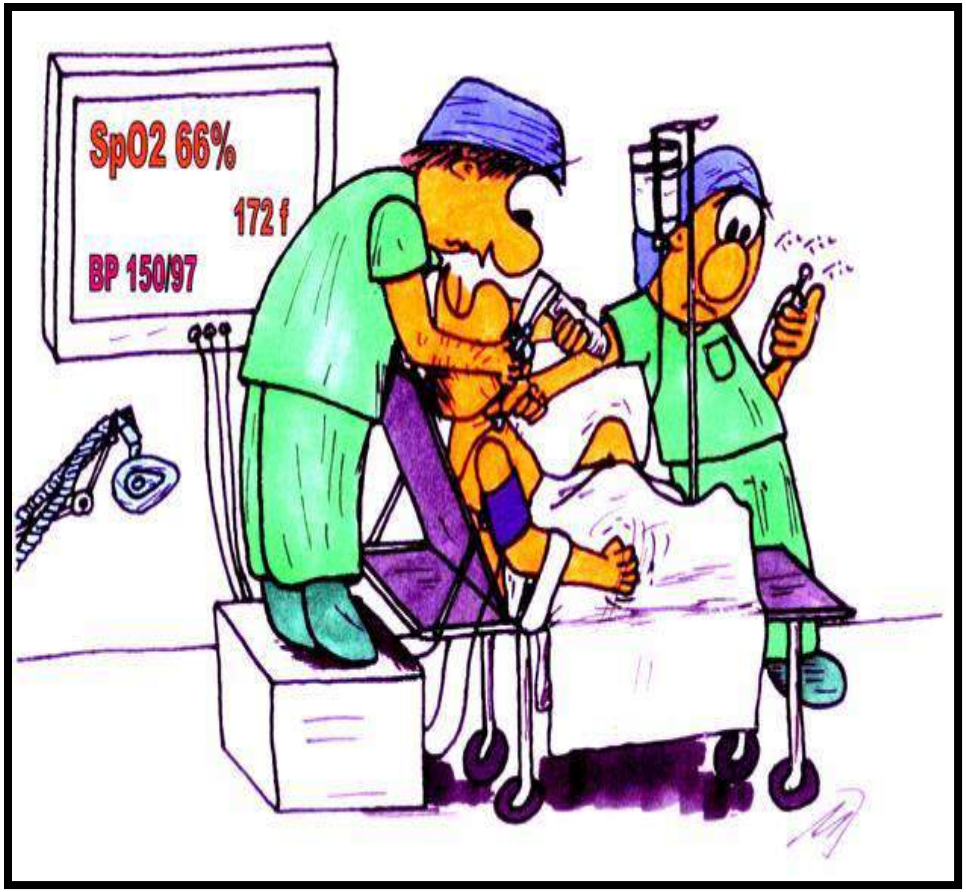
Sub-Types of Chronic Insomnia

- Idiopathic insomnia
- Inadequate sleep hygiene
- Paradoxical insomnia
- Psychophysiologic insomnia
- Behavioral insomnia of childhood
  - Sleep onset association
  - Limit setting

*DSM-V-TR, ***Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition***

Acute Adjustment Insomnia

- Sleep disturbance due to an acute stressor
  - Momentous life event
  - Change in sleeping environment
  - Acute illness
- Sleep improves with resolution of acute stressor or with adaptation



Idiopathic Insomnia

- No identifiable etiology
- Usually onset during infancy or early childhood
- Chronic life-long course
- Previously called **childhood-onset insomnia**

Sleep Pearl: Fatal Familial Insomnia is a prion disease with a mutation in codon 178 of the prion protein gene

Inadequate Sleep hygiene

- Activities or behavior that increases arousal or decreases sleep propensity
  - Television
    - Technology
  - Clock watching
  - Late night snacks
    - Leptin
      - Released during sleep
    - Ghrelin

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Binge Viewing, Sleep, and the Role of Pre-Sleep Arousal

Liese Exelmans, MA[1]; Jan Van den Bulck, DSc, PhD[2]

[1]Leuven School for Mass Communication Research, KU Leuven, Leuven, Belgium; [2]Department of Communication Studies, University of Michigan, Ann Arbor, Michigan

Paradoxical Insomnia

- Sleep **misperception**
- Subjective reports minimal or no sleep during most night
  - Normal sleep quality and architecture during PSG
- No daytime napping or impairment of daytime functioning

Psychophysiologic Insomnia

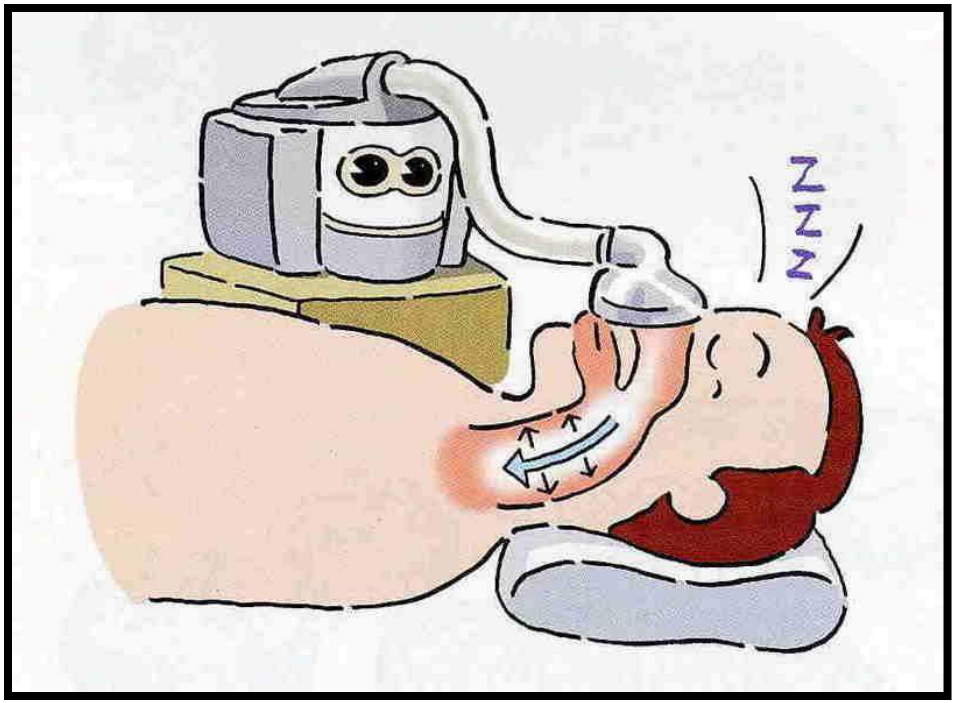
- Associated with excessive worrying
  - Focused on not being able to sleep
  - They also worry about being tired the next day (ruminate)
  - As a result, they become tense and anxious as bedtime approaches
  - May engage in bad behaviors to try to fall asleep
    - Taking sleeping pills, drinking alcohol or spending too much time in bed hoping to get more sleep

Common medications that can cause insomnia

- Antidepressants
  - SSRI & SNRI ex. fluoxetine (Prozac) & venlafaxine
  - Stimulating TCA's ex. protriptyline (Vivactil)
- Beta-blockers
  - Blocks melatonin
  - Drugs with coincident alpha activity (ex.carvedilol) have more fatigue
- Bronchodilators
- Decongestants
  - Pseudoephedrine
- Steroids
- Stimulants
  - Caffeine, nicotine, amphetamines, ecstasy

Insomnia: Evaluation

- History and sleep diary or log
- PSG, actigraphy and laboratory tests are **not** routinely indicated
- Possible indications for PSG
  - To exclude OSA

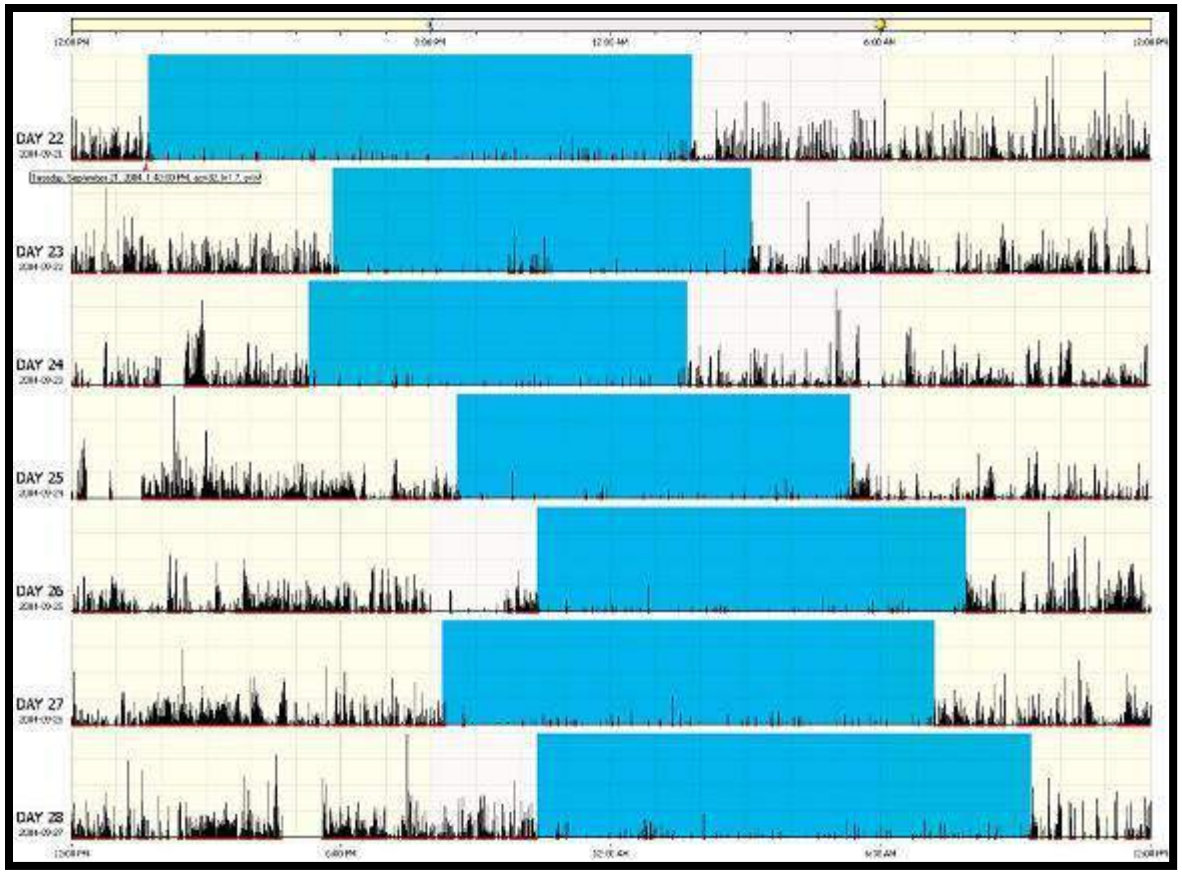


Question

- What is actigraphy ?

Actigraphy

Small instrument worn on the wrist or ankle to measure body movement



New Technology for Monitoring Sleep and Evaluating Insomnia

Insomnia: Cognitive Behavioral Treatments (CBT)

- Helps you:
  - Change actions or thoughts that hurt your ability to sleep well
  - Develop habits that promote a healthy pattern of sleep
- Short-term benefits are comparable to pharmacologic therapy
- Beneficial effects are sustained over time

Sleep hygiene by itself is not a treatment for insomnia as per the AASM

CBT for Acute Insomnia

Participants

- 40 adults DSM-5 defined insomnia disorder with symptoms less than 3 mo who reported no previous exposure to CBT and were not currently taking medication for sleep

Conclusion

- Single session of cognitive behavioral therapy for insomnia is sufficiently efficacious for a significant proportion of those with acute insomnia

VOLUME 38, ISSUE 06

TREATING ACUTE INSOMNIA WITH A SINGLE SESSION OF CBT-I

Treating Acute Insomnia: A Randomized Controlled Trial of a "Single-Shot" of Cognitive Behavioral Therapy for Insomnia

http://dx.doi.org/10.5665/sleep.4752

Jason G. Ellis, PhD[1,2]; Toby Cushing, BSc[1]; Anne Germain, PhD[3]

[1]Northumbria Centre for Sleep Research, Northumbria University, Newcastle, UK; [2]Newcastle Fatigue Research Centre, Newcastle University, Newcastle, UK; [3]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

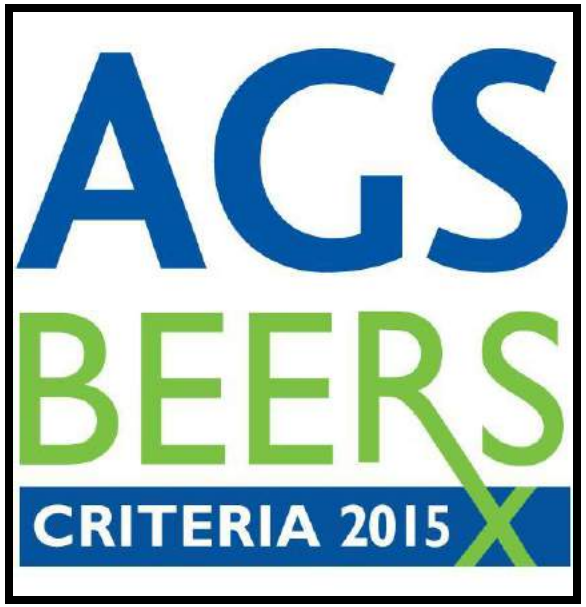
Insomnia: Cognitive Behavioral Treatments

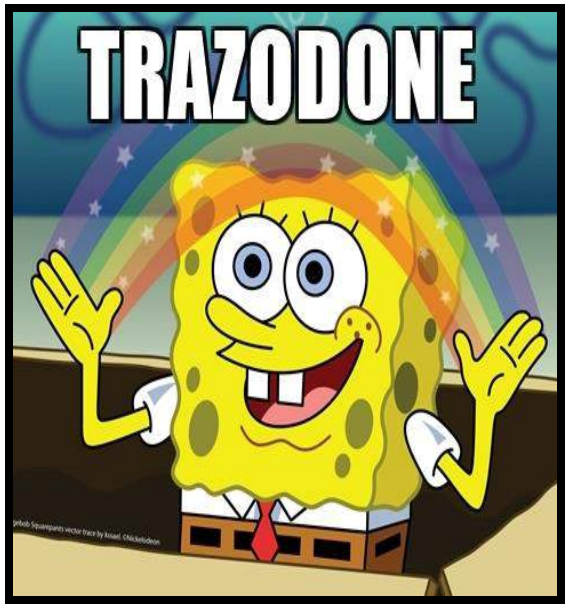
- **Common forms of CBT:**

1. Cognitive therapy
   - Addresses dysfunctional beliefs & negative thoughts related to insomnia
     - Irrational expectations
     - Excessive worry
     - Unrealistic concern
2. Paradoxical intention
   - Example: “Stay awake as long as you can”
3. Relaxation techniques & Biofeedback
   - Galvanic skin response, heart rate
4. Sleep restriction
5. Stimulus control

Insomnia: Pharmacotherapy

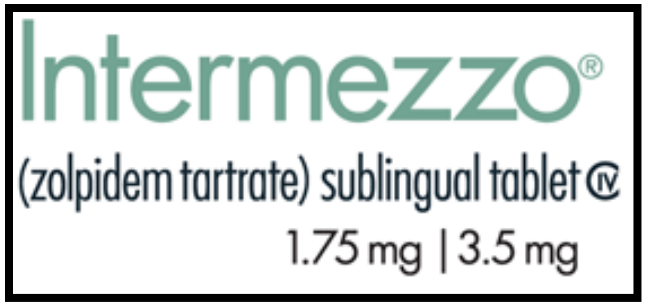
- May enhance sleep but often **do not** improve daytime performance
- Minimal long-term beneficial effect on sleep following drug discontinuation

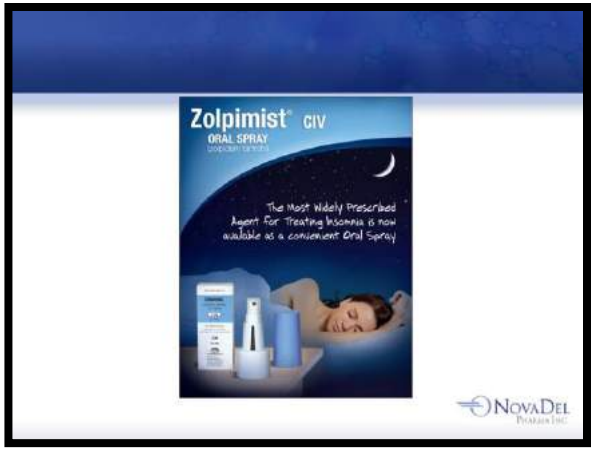




Non-Benzodiazepine BZ Receptor Agonists

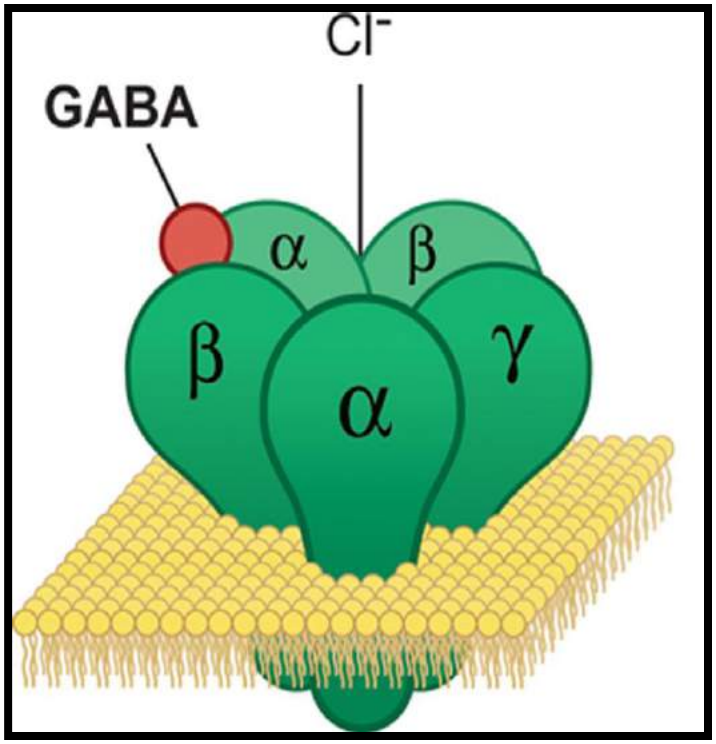
- Selectively bind to the BZ1 receptor subunit
- Duration of action (shortest to longest)
  - Zaleplon<zolpidem<eszopiclone





Non-Benzodiazepine BZ Receptor Agonists

- Compared to conventional benzodiazepines
  - Similar hypnotic action
  - No muscle relaxant, anticonvulsant or anxiolytic properties
  - Less likely to cause rebound insomnia, withdrawal symptoms or tolerance
  - Less likely to alter sleep architecture



Other Hypnotic Agents

- **Melatonin**
  - Used primarily for insomnia associated with circadian rhythm sleep disorders
  - .5-3 mg
  - Short half-life 20-30 minutes

- **Ramelteon (Rozerem)**
  - Selective agonist for the SCN (suprachiasmatic nucleus) melatonin receptor
  - Short half-life
    - Indicated for sleep-onset insomnia
  - Good for COPD
  - MT1 > MT2 receptor

Other Hypnotic Agents: FDA Approved TCA

- **Doxepin**
  - TCA
    - Anti-cholinergic
      - Dry mouth
      - Constipation
      - Tachycardia
    - Anti-histamine
    - Serotonin syndrome

Sedating TCAs: "ACID": Amitriptyline, Clomipramine, Imipramine, Doxepin

Other Hypnotic Agents: The Orexin Battle

- **Suvorexant & Lemborexant**
  - Selective antagonist for orexin receptors
  - Orexin is a neurotransmitter found in a specific part of the brain that can help keep a person awake
  - No taper recommended
  - Less dependance and addiction
  - Avoid in liver disease

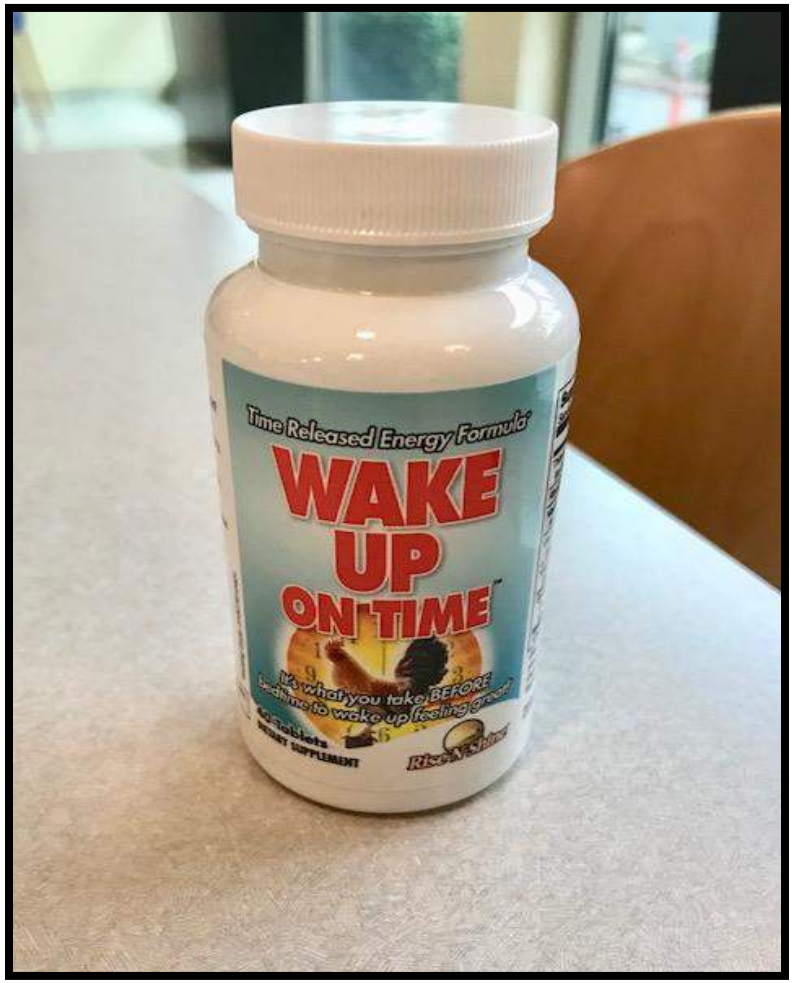
Orexin a hot topic in Alzheimer's patients

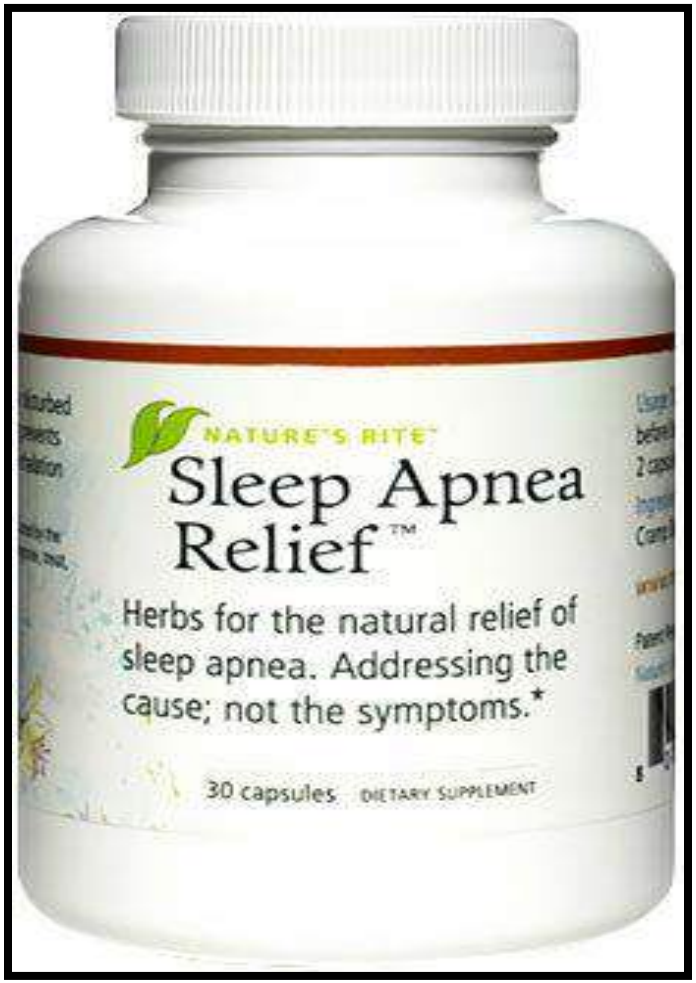
Herbal Remedies

- Valerian
- Chamomile tea
- Kava-kava
- Lavender
- Passion fruit
- Hops
- Tryptophan
- Ginseng
- CBD

THE Doctors

Be careful of non-FDA approved sleep products !!!





Beyond the Pearls: “Sleep Medications Review”

Beyond the Pearls: Medications and Sleep Questions

- Know your benzodiazepine and Z-drug half-lives
  - Triazolam (Halcion) shortest BZ vs. Flurazepam (Dalmane) longest
- Remember the sedating TCA's (ACID)
- MAOIs are the most potent REM sleep inhibitors
- "Prozac eyes" with SSRIs
- Reports of RBD with SSRIs and SNRIs
- Bupropion atypical as it increases REM and decreases PLMs
- Donepezil causes insomnia and vivid dreams
  - Acetylcholinesterase inhibitor for Alzheimer's disease
- Aripiprazole (Abilify) as a minimally-sedating antipsychotic
- Buspirone as a non-sedating anxiolytic
- Prazosin not for nightmares anymore

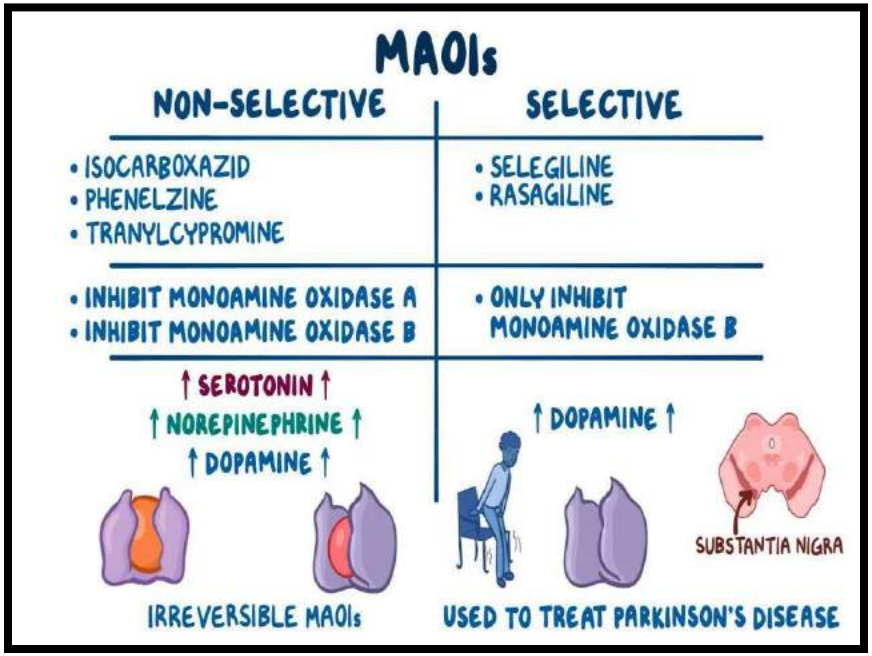
Beyond the Pearls: Question

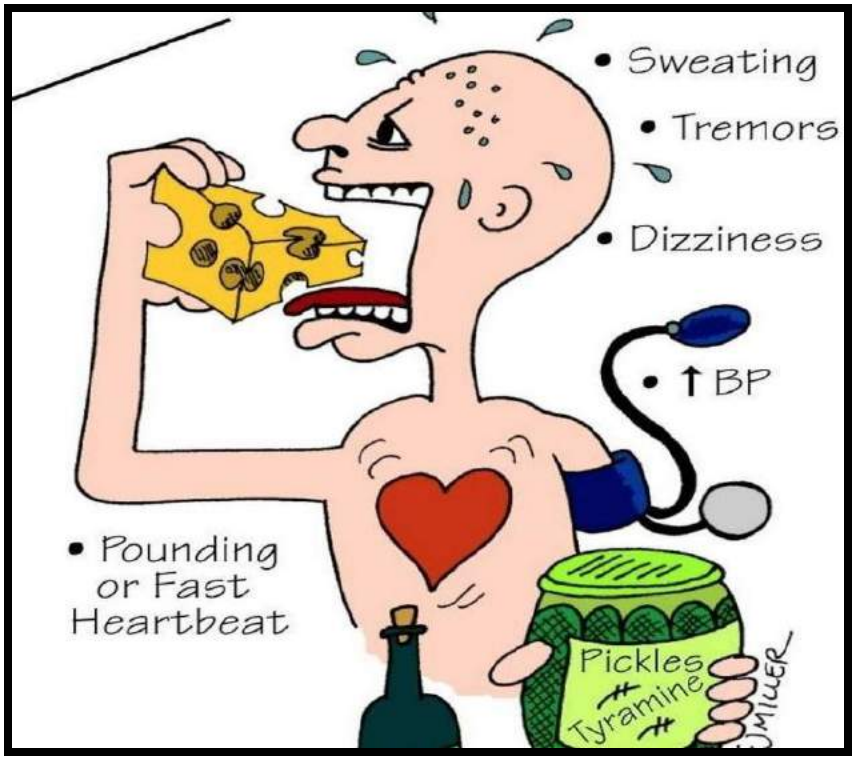
- 29 year old woman with a history of depression is referred for PSG and MSLT to evaluate hypersomnia. Key findings from her nocturnal PSG are listed. Which of the following medications is most likely to be the cause of these findings?
  A. Protriptyline
  B. Fluoxetine
  C. Citalopram
  D. Phenelzine
  E. Trazodone

- TST: 430 minutes
- Sleep efficiency: 92%
- Arousal index: 14/hour
- AHI: 1.5/hour
- Stage: N1 7%
- Stage: N2 73%
- Stage: N3 20%
- Stage: R 0%

Answer: D

- For anti-depressants, MAOIs are the most potent inhibitors of REM sleep





Tyramine is compound produced by the breakdown of an AA called tyrosine that increases your blood pressure and is broken down by monoamine oxidase

Beyond the Pearls: Question

- Which of the following has been most commonly described as a sleep-related consequence of lithium use?

  A. Sleep walking

  B. REM sleep without atonia

  C. Narcolepsy

  D. Sleep-disordered breathing

  E. Restless legs syndrome

Answer: A

- Improved nocturnal sleep and daytime sleepiness
- Increases slow wave sleep, decreases REM sleep
- Somnambulism reported in 7% of users in a lithium clinic (Landry et al, 1999)

Beyond the Pearls: Question

- 64 year old woman has been diagnosed with depression and is complaining of difficulty sleeping. Which of the following agents would be most likely to address both of these concerns?
  A. Bupropion
  B. Mirtazapine
  C. Sertraline
  D. Venlafaxine
  E. Fluoxetine

Answer: B

- Antagonist of H1 and 5 HT2 receptors
- Highly sedating and reports of excessive daytime sleepiness
- Exacerbation of RLS

REMERON®
(mirtazapine) Tablets

Narcolepsy & Excessive Daytime Sleepiness

Narcolepsy: Outline

- Excessive Daytime Sleepiness
- What is Narcolepsy ?
- Evaluation & Diagnosis
- Treatment
- Clinical Questions

Beyond the Pearls: Question

- 24 year old **medical student** seeks your advice about an episode that happened over her brief summer vacation. She was staying with some friends at the beach and fell asleep while sunbathing one afternoon after staying up until 3 am the night before
- She was awakened by some shouting and **could not move** for several seconds. She was aware of her surroundings and did not lose bladder or bowel control during this episode. This has happened once in the past. Her **Epworth Sleepiness Scale score is 8**. She is otherwise healthy, takes no medications, and is doing reasonably well in school.

Beyond the Pearls: Question

- Which of the following do you recommend?
  - A. Evaluation for narcolepsy
  - B. Referral to a psychiatrist
  - C. Reassurance
  - D. Evaluation for possible seizures


#THEDOCTORS
Dr's

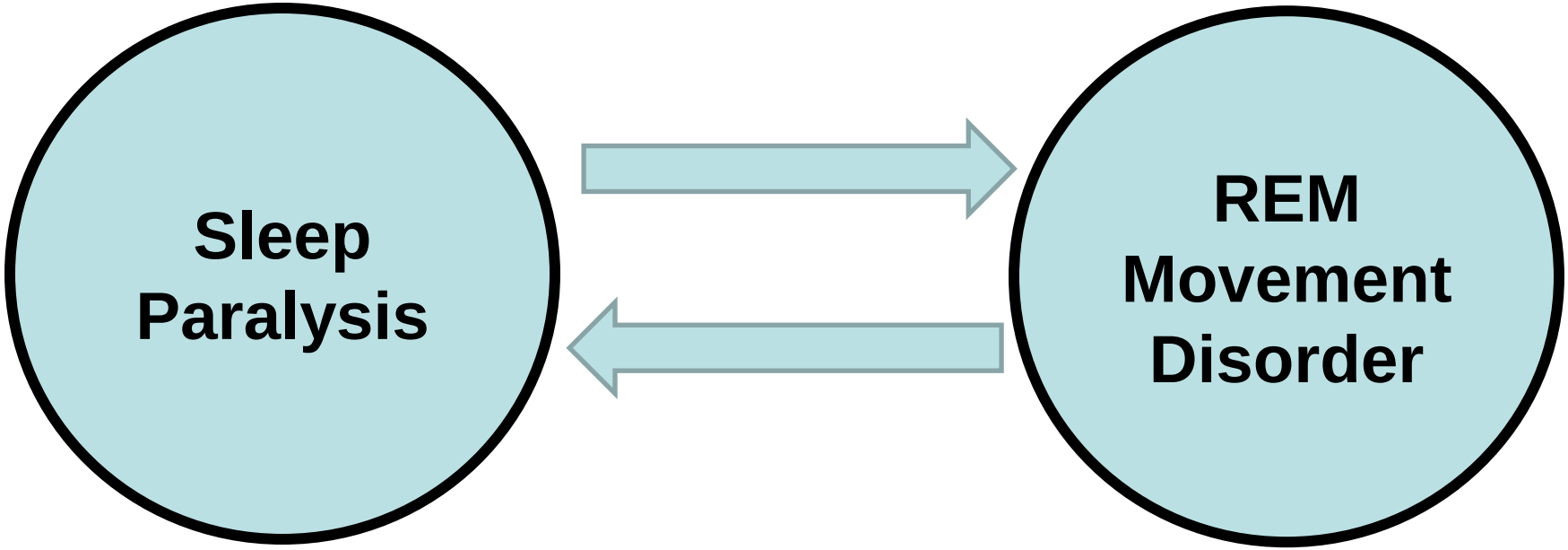

#THEDOCTORS
Dr's
Kendall Jenner's Sleep Paralysis Explained!


THE Doctors
ALL NEW
THE Dr's
What Is Sleep Paralysis?

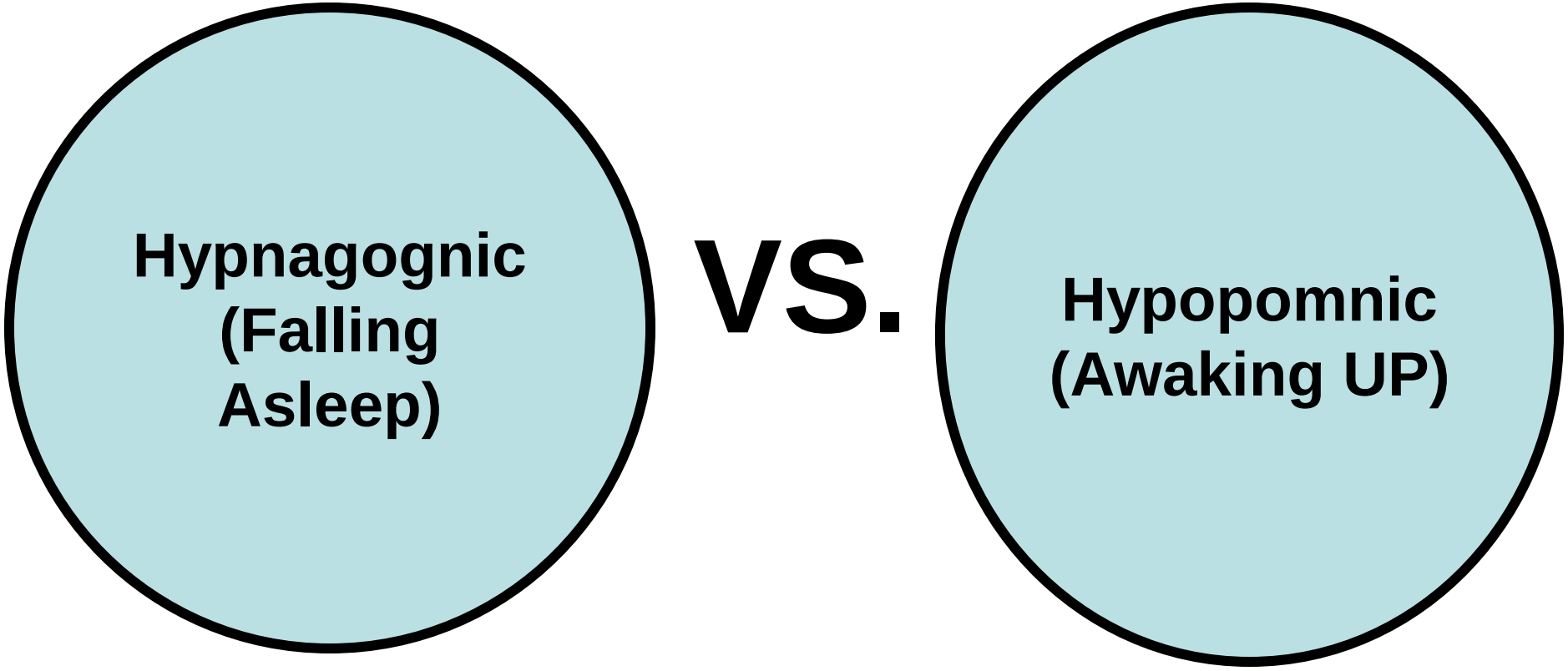

#THEDOCTORS
Dr's

Is Sleep Paralysis Bad ?

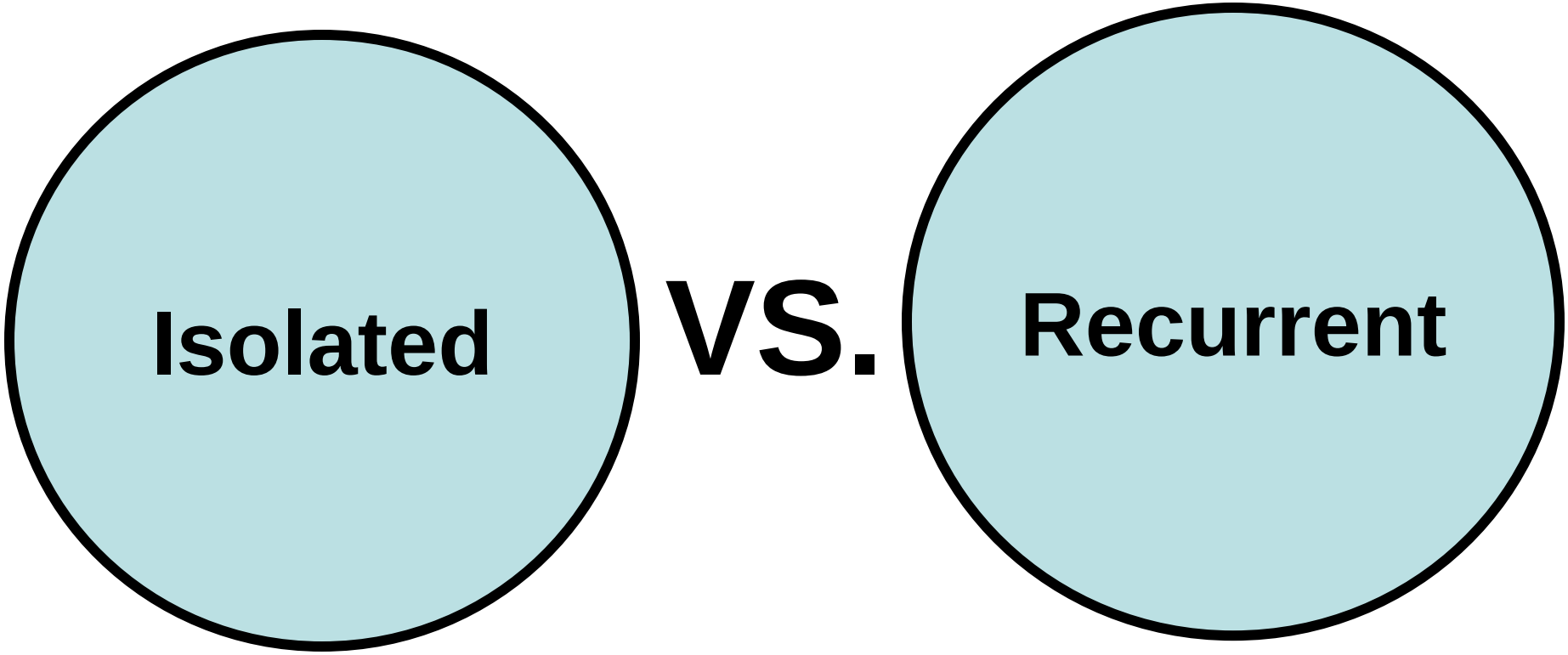
- We are normally paralyzed in REM sleep as a protective mechanism so we don't reenact our dreams



How is Sleep Paralysis Characterized?



How is Sleep Paralysis Characterized?



- Sleep deprivation
- Jet Lag
- Alcohol
- GERD

- Sleep apnea
- Narcolepsy

Sleep Paralysis: Why Am I Seeing Aliens ?

- A hyper-vigilant state created in the midbrain may further contribute to hallucinations

Sleep Paralysis: Why Is There A Demon Sitting On My Chest ?

- Several features of REM breathing patterns exacerbate the feeling of suffocation
- These include shallow rapid breathing, hypercapnia, and slight blockage of the airway, which is a symptom prevalent in sleep apnea patients

Excessive Daytime Sleepiness

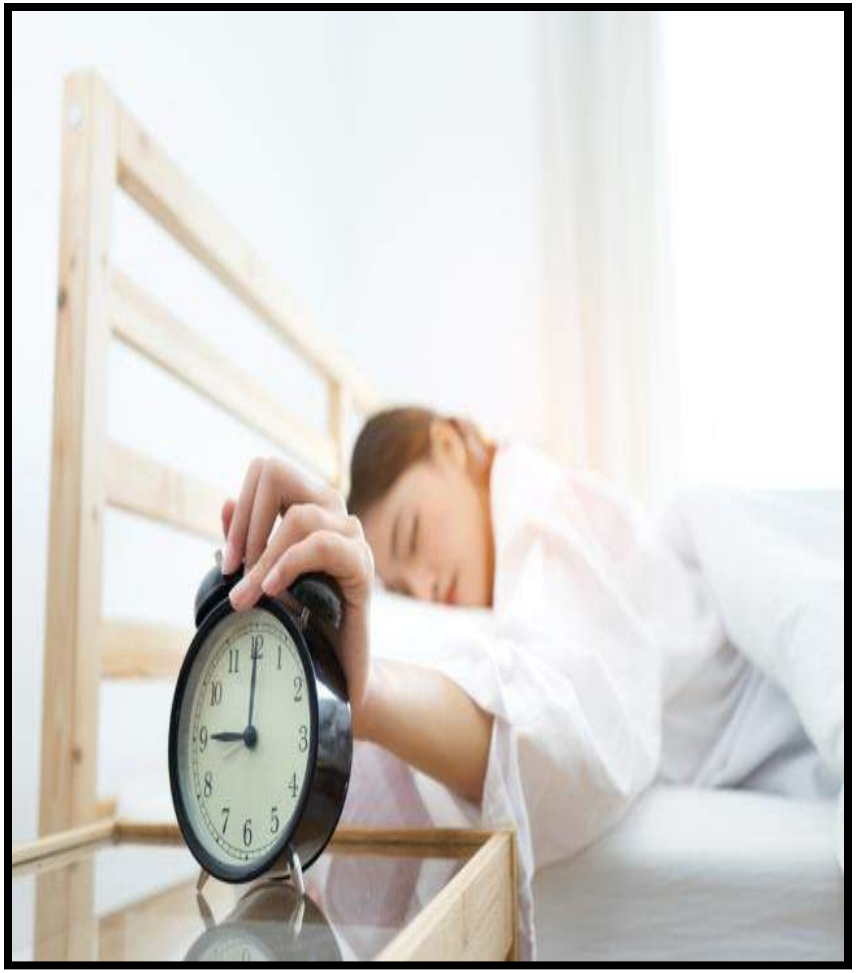
- Inability to consistently achieve and sustain wakefulness and alertness to accomplish the tasks of daily living
- Manifestations:
  - **Frequent napping**
  - **Sleep attacks**
    - Marked by sudden irresistible sleepiness
  - **Microsleep**
    - Episode of sleep which may last for a fraction of a second or up to 30 seconds
  - **Automatic behavior**
    - Spontaneous production of often purposeless verbal or motor behavior without conscious self-control or self-censorship

Question

- Define a “nap”

Answer

- Prolonged naps, those exceeding 30 minutes, could lead to **sleep inertia**, causing the subject to be groggy after the nap
- Naps are not recommended for those suffering from insomnia

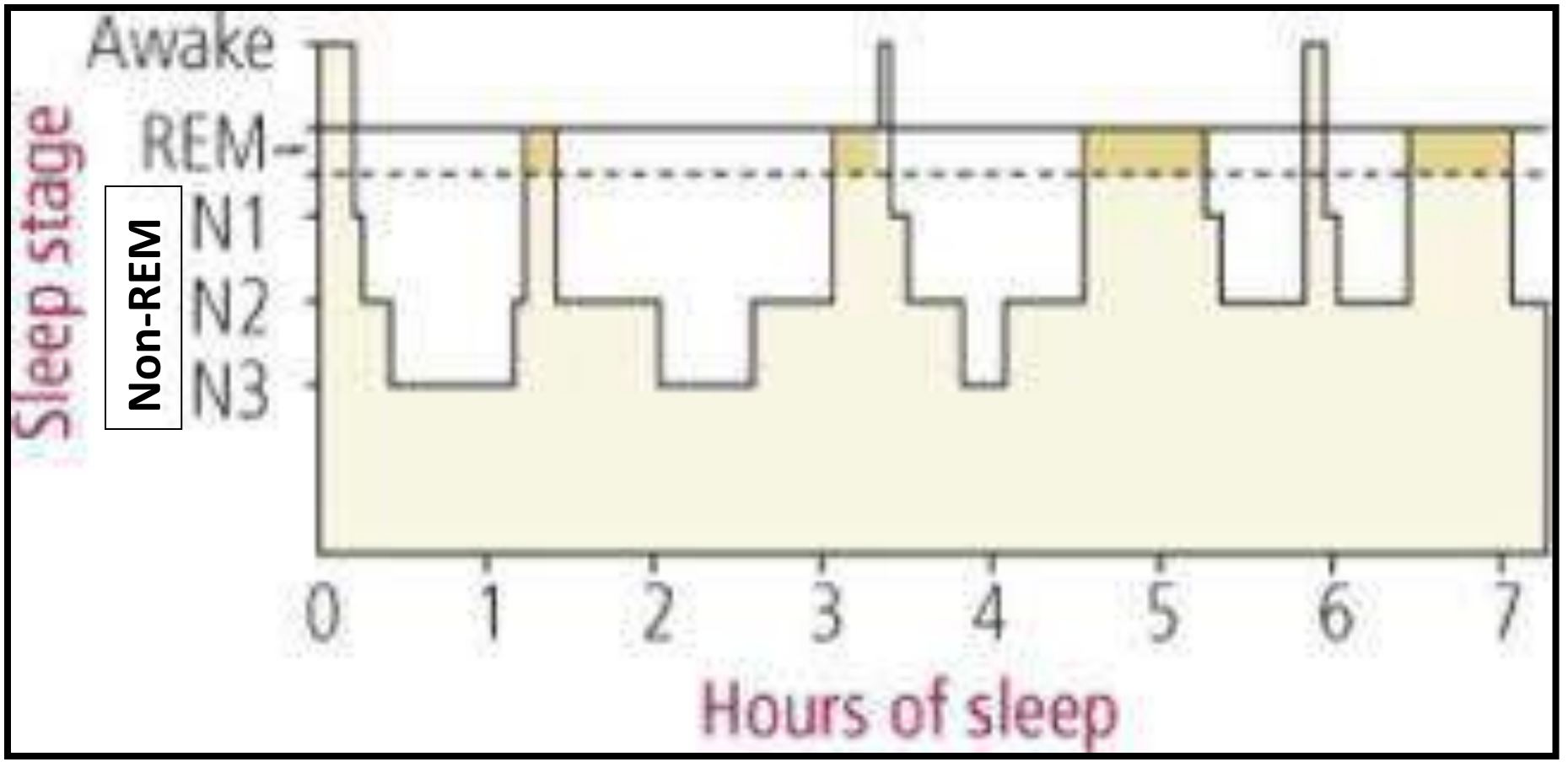


Excessive Daytime Sleepiness: General Causes

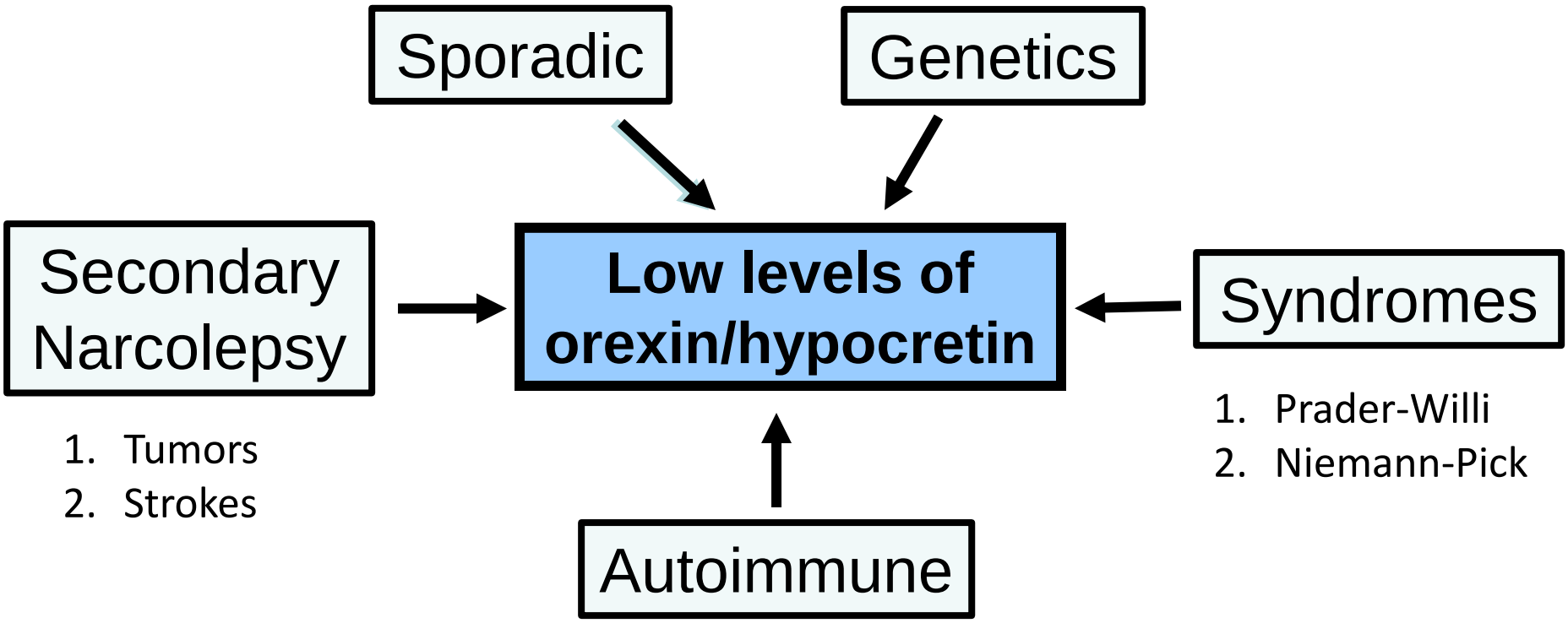
1. **Insufficient sleep syndrome**
2. **Narcolepsy**
3. **Idiopathic hypersomnia**
   - No longer a distinction based on long sleep time
     - ICSD-2: Without LST (<10 hours) & With LST (>10 hours)
4. **Recurrent hypersomnia**
   - **Kleine-Levin syndrome**
     - At least 2 episodes of excessive sleepiness lasting 2 days to 5 weeks with a mean duration of 13 days
     - Recurrences at least once every 18 months
     - Lasts approximately 15 years
     - Triggers: Infection, alcohol, stress, head trauma and sleep deprivation
     - Treat with lithium, clarithromycin
   - **Menstruation-associated**
5. **Hypersomnia due to medical disorders**
6. **Hypersomnia due to drugs or substance**

What is Narcolepsy?

Narcolepsy is a chronic neurologic sleep disorder caused by the brain's inability to regulate the sleep-wake cycle



What causes narcolepsy?

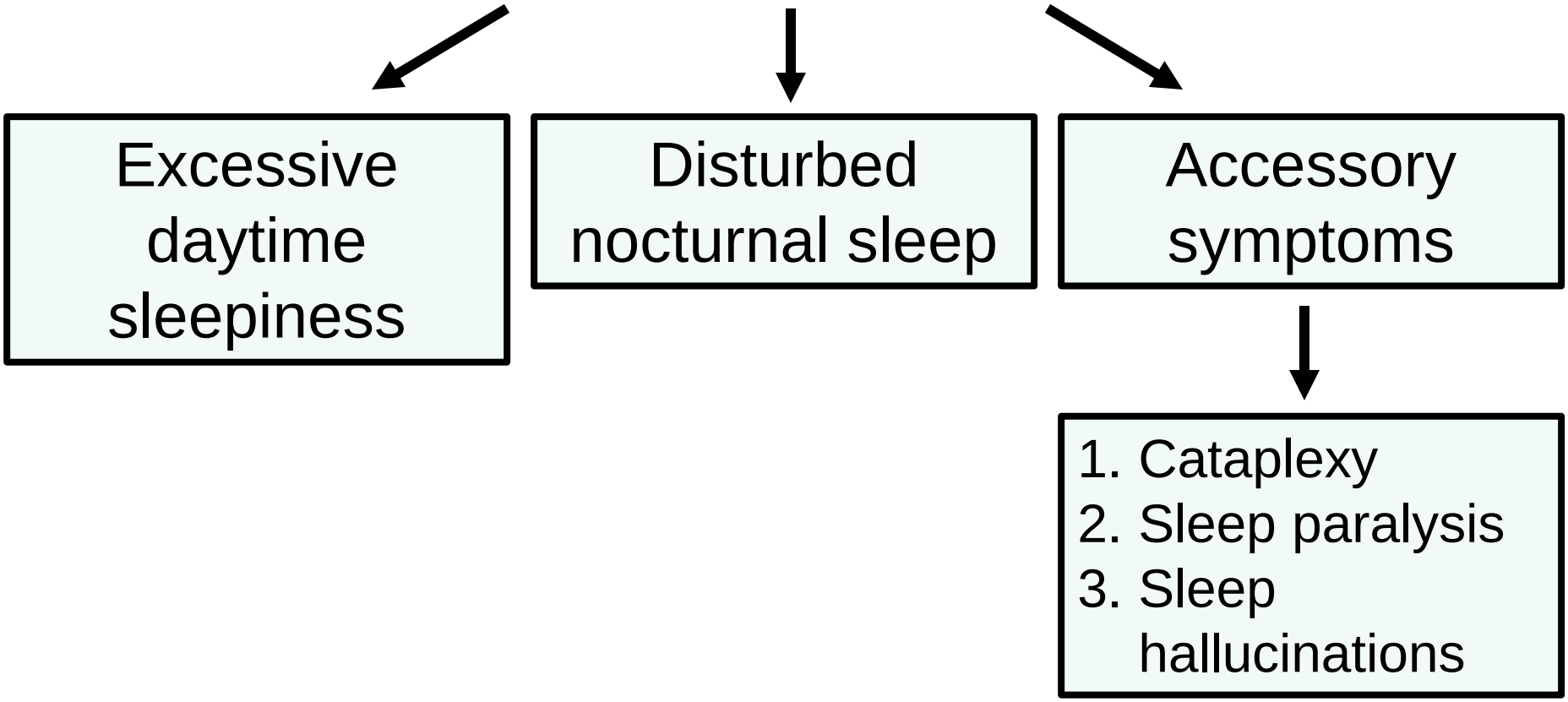


1. Tumors
2. Strokes

1. Prader-Willi
2. Niemann-Pick

1. Strep throat
2. Influenza A (H1N1)
3. H1N1 vaccine (Europe 2009)

Symptoms of Narcolepsy



Narcolepsy: Pentad

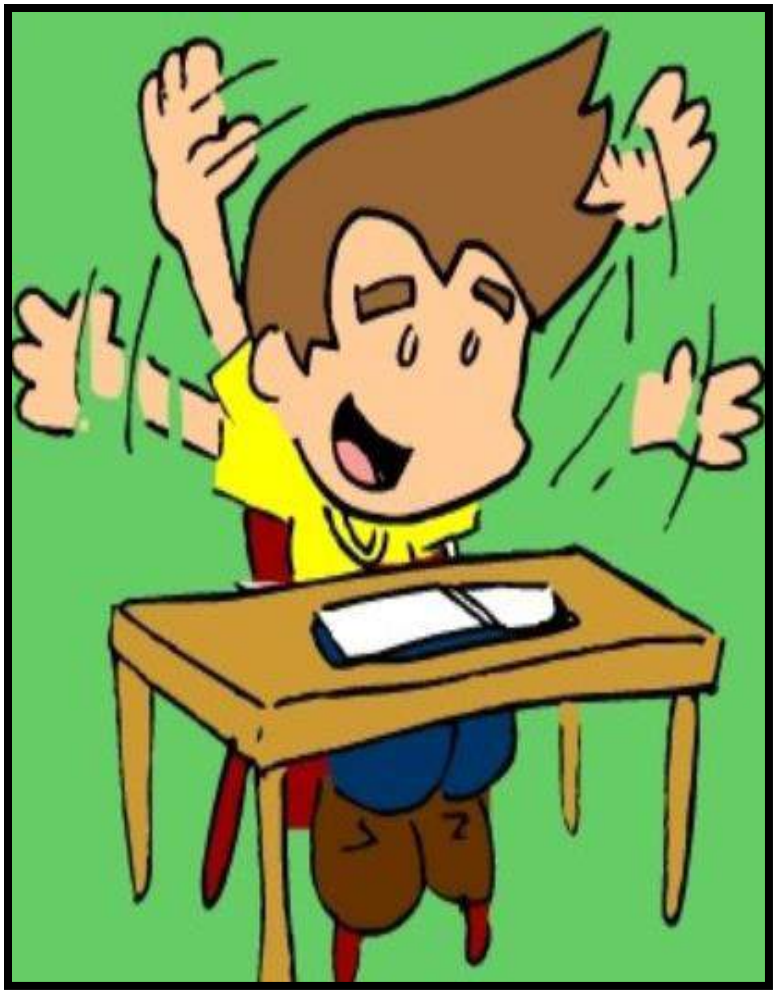
- Neurological disorder characterized by the clinical pentad of:
  1. Excessive sleepiness
  2. Cataplexy
  3. Sleep paralysis
  4. Sleep hallucinations
  5. Fragmented nocturnal sleep
- Only **10-15%** of patients demonstrate this full pentad

Narcolepsy: Demographics in Children

- Typically begins in the teens and early twenties
- Can occur as early as 5 years of age
- Narcolepsy often not spotted until well into adulthood

Narcolepsy: Clinical Features: in Children

- Delays in diagnosis are common due to unique features that are not typically observed in adults
  - Irritability
  - Frequent napping leading to the perception of “lazy”
  - Hyperactivity and learning disability
  - Depression & anxiety
  - Defiant behavior



Evaluation & Diagnosis of Narcolepsy

Narcolepsy: Evaluation

- Sleep history
- Sleep log +/- actigraphy
- Subjective tests of sleepiness
  - Epworth, Stanford and Karolinska sleepiness scale
- PSG
  - To exclude OSA and PLMD
  - Include SOREM
- MSLT
  - Mean **SOL < 8 minutes** and **2 SOREMS**
  - Include PSG SOREM
  - Drug screening
- MWT
  - Mean SOL < 40 minutes

Narcolepsy: MSLT Limitations

1) MSLT is not validated as a diagnostic test in children **< 6 years** of age

2) Normal and abnormal sleep latencies have not been established outside the usual testing hours of **8:00 pm to 6:00 am**
   - Individuals with circadian rhythm sleep disorders are difficult to interpret

3) MSLT is sensitive to **sleep deprivation**

4) 6 h of nocturnal sleep required by the testing guidelines may also be **too little** for pediatrics

Narcolepsy: Evaluation

Clinical History

- Narcolepsy with cataplexy can not be diagnosed by history alone now
- This is a change in the AASM guidelines

New AASM Guidelines

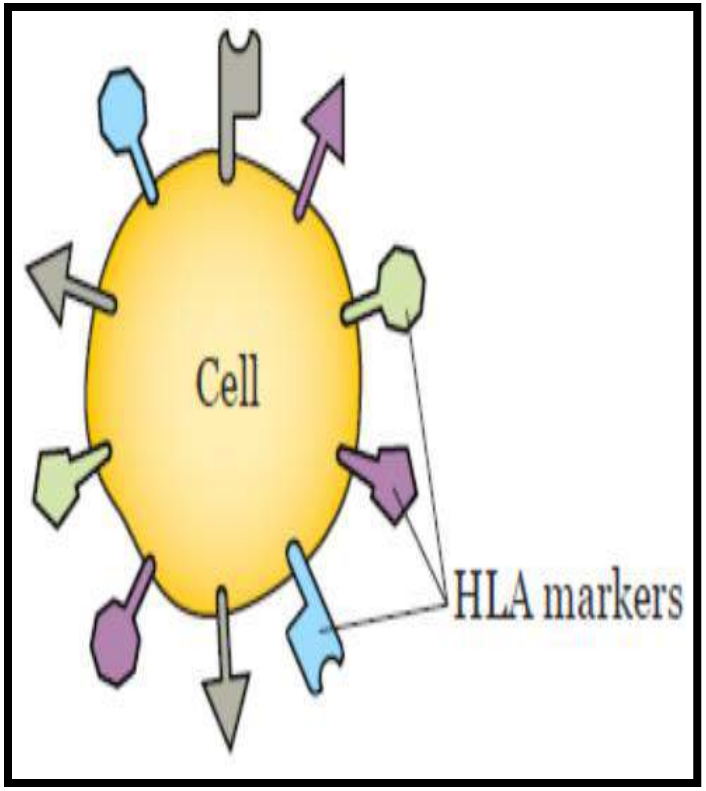
- PSG followed by MSLT is now required to confirm the diagnosis
- Type 1 narcolepsy can be diagnosed with a low hypocretin level in the CSF

Narcolepsy Evaluation: CSF Hypocretin-1

- CSF orexin/hypocretin-1 levels < 110pg/mL or 1/3 of mean normal control values
  - Low with cataplexy
- For the diagnosis of Type 1 narcolepsy

Narcolepsy Evaluation: HLA Typing

- Limited diagnostic utility
  - HLA-DQB1*0602
- Bottom line:
  - Narcolepsy type 1 is likely a T-cell mediated autoimmune disease, occurring in people with HLA DQB1*06:02 following an environmental trigger



Beyond the Pearls: Question

- Which of the following statements concerning the MSLT is true?
  a. The mean sleep latency discriminates normal individuals from those with abnormal sleepiness
  b. A mean sleep latency of greater than 10 minutes is considered normal
  c. Its utility in the diagnosis of narcolepsy is mainly based on the presence of sleep onset REM periods (SOREMPs)
  d. It is indicated to help predict a sleepy individual's ability to safely drive a motor vehicle

Answer: C

- The MSLT is an objective measure of the tendency to fall asleep in the absence of physiologic arousal
- Its main indication in clinical practice is as part of the evaluation of patients with suspected narcolepsy
- The utility of the MSLT in the diagnosis of narcolepsy is mainly based on the presence of SOREMPs, which are common in narcolepsy

Diagnostic Summary

	NT1	NT2	IH
Excessive daytime sleepiness, daily x 3+ months	Mandatory	Mandatory	Mandatory
Cataplexy	May be present. If MSLT used for diagnosis, MUST be present	Never present	Never present
MSLT required for diagnosis?	No (although typically performed)	Yes	No (although typically performed)
MSLT mean sleep latency (if MSLT used for diagnosis)	MSL $\leq$ 8 minutes	MSL $\leq$ 8 minutes	MSL $\leq$ 8 minutes
PSG + MSLT SOREMS (if MSLT used for diagnosis)	2+	2+	0-1
Non-MSLT diagnostic criteria	Low CSF hypocretin (<110 or <1/3 controls)	N/A	PSG TST > 660 minutes or 1+ week actigraphy showing >660 min average estimated TST

Diagnostic Summary

	NT1	NT2	IH
CSF hypocretin, IF MEASURED	Low (< 110 or < 1/3 control values)	Normal	Normal
Rule out of other causes	Not mandated	Necessary	Necessary
Summary of criteria	EDS plus either A OR B: A) Cataplexy AND MSL ≤ 8 min AND 2+ SOREMs B) Low CSF hypocretin	EDS plus MSL ≤ 8 min AND 2+ SOREMs; no cataplexy, no low hypocretin (if measured), no other explanation	EDS plus either A, B, OR C: A) MSL ≤ 8 min with 0-1 SOREM B) PSG TST > 660 min C) Actigraphy (1+wk) daily TST > 660; no cataplexy, no low hypocretin (if measured), no other explanation

- **HLA DQB1*0602 can be seen in people with NT1, NT2, or IH, but is most commonly seen in people with NT1**
- **HLA has a limited role as a diagnostic test**

Treatment

Beyond the Pearls: Question

- 24 year old woman presents with several years of excessive daytime sleepiness associated with bilateral lower extremity weakness precipitated by **laughter**. Her typical bedtime is 10:30pm with a subjective total sleep time of 8 hours on most nights. She has no medical problems and takes no medications
- Following a relatively normal overnight PSG, an MSLT demonstrates a mean sleep latency of 3 minutes with 3 sleep onset REM periods out of 4 nap trials supporting a diagnosis of narcolepsy
- Therapy with modafinil 200mg taken each morning is initiated and later increased to 400mg taken each morning

Beyond the Pearls: Question

- After 4 weeks of therapy, she continues to have significant residual daytime sleepiness, as well as cataplexy. Which of the following could you recommend to better treat the patient's symptoms

A. Increase modafinil 400mg from once a day to twice a day dosing

B. Add methamphetamine or dextroamphetamine

C. Add sodium oxybate

D. Add methylphenidate SR or dextroamphetamine XR

Answer: C

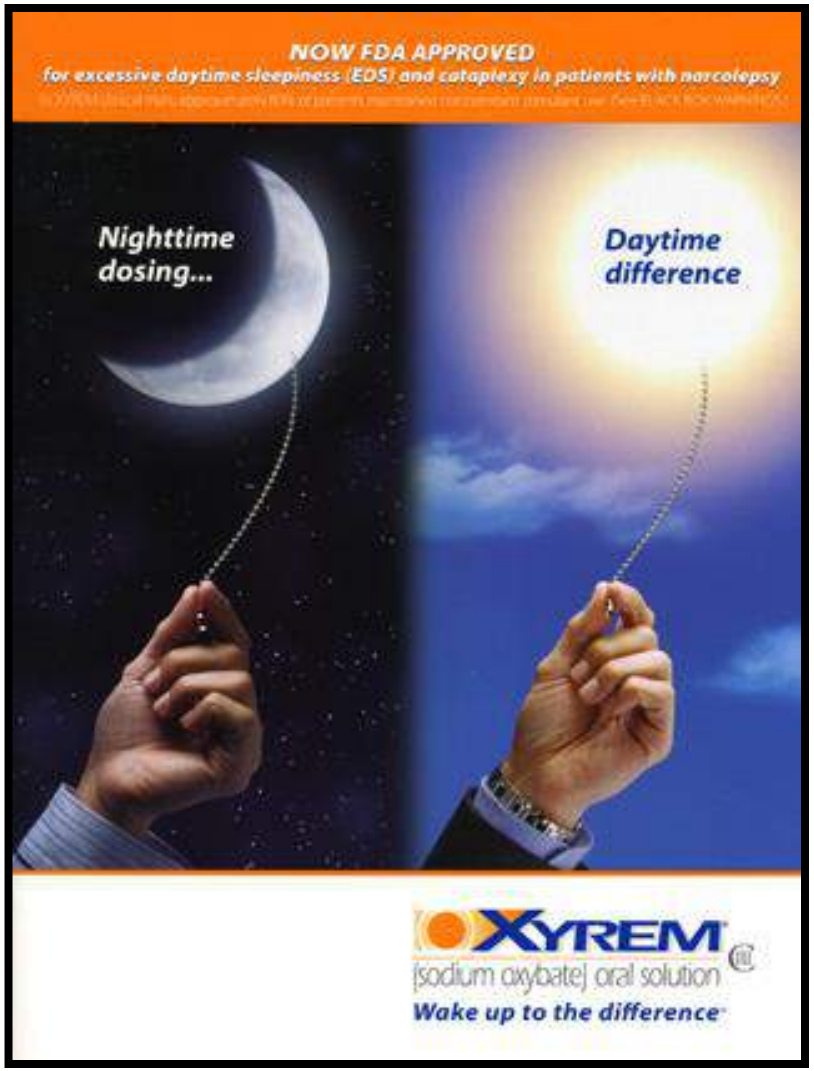
- Sodium oxybate which is derived from gamma hydroxybutyrate is the only FDA approved treatment for all the core symptoms of narcolepsy, including cataplexy

Narcolepsy: Pharmacologic Treatment of Excessive Sleepiness

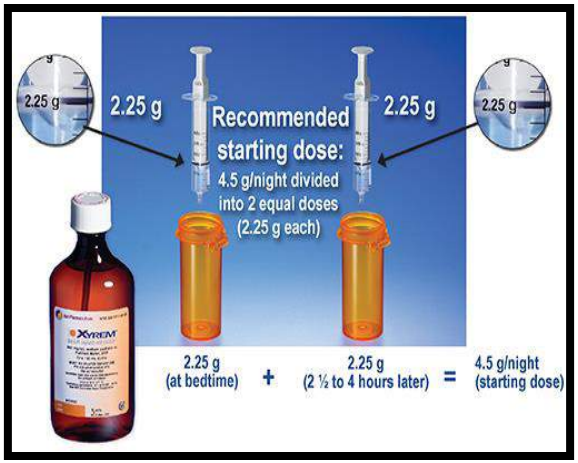
- Modafinil (Provigil)
- Armodafinil (Nuvigil)
- Dextroamphetamine
  - Adderall & XR
  - Dexedrine
  - Vyvanse
- Methylphenidate
  - Ritalin
  - Ritalin long-acting (Concerta)

Narcolepsy: Treatment of Cataplexy

- REM sleep suppressant agents
  - SSRI
  - SNRI
    - Venlafaxine
  - MAOI
  - TCA
- Gamma hydroxybutyrate (1st line)
  - **Xyrem**
- Pitolisant (Wakix)



Narcolepsy: Xyrem



What's New ?

- **Jazz Pharma: Ca2+/Mg2+/K+/Na+ Oxybate**
  - 92% less sodium
  - Same dosing as Sodium Oxybate (Xyrem)
  - FDA approved for idiopathic hypersomnia
- **Jazz Pharma: Solriamfetol**
  - Norepinephrine–dopamine reuptake inhibitor
  - Obstructive sleep apnea, narcolepsy and hypersomnia
- **Harmony Biosciences: Pitolisant**
  - Histamine 3 inverse agonist
  - For EDS and cataplexy
- **Avadel Pharmaceuticals**
  - Once-daily Sodium Oxybate
  - "REST-ON" study is a Phase III clinical trial

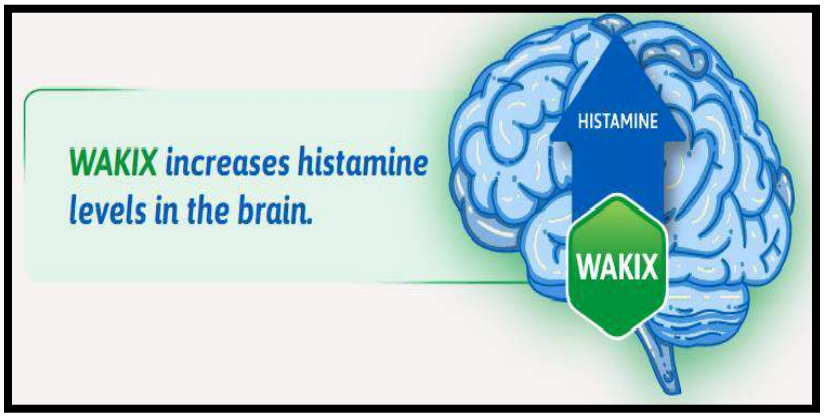
xywav™
(calcium, magnesium, potassium, and sodium oxybates) oral solution

Solriamfetol (Sunosi)

- FDA approved March 20th 2019 for OSA and Narcolepsy
- Dosing 37.5 to 150 mg daily
  - Narcolepsy start at 75mg
  - Increased in intervals of 3 days
- Careful in renal impairment

Pitolisant (Wakix)

- FDA approved in August 15th 2019 for EDS and cataplexy
- Only FDA-approved treatment for narcolepsy that is not a controlled substance
- Dosing starts at 4.45 mg tabs x 2 daily for 1 week then 17.8 mg once daily for 1 week then 17.8 mg x 2 thereafter
- Takes up to 8 weeks to get clinical response
- Studied in patient taking Xyrem and Provigil



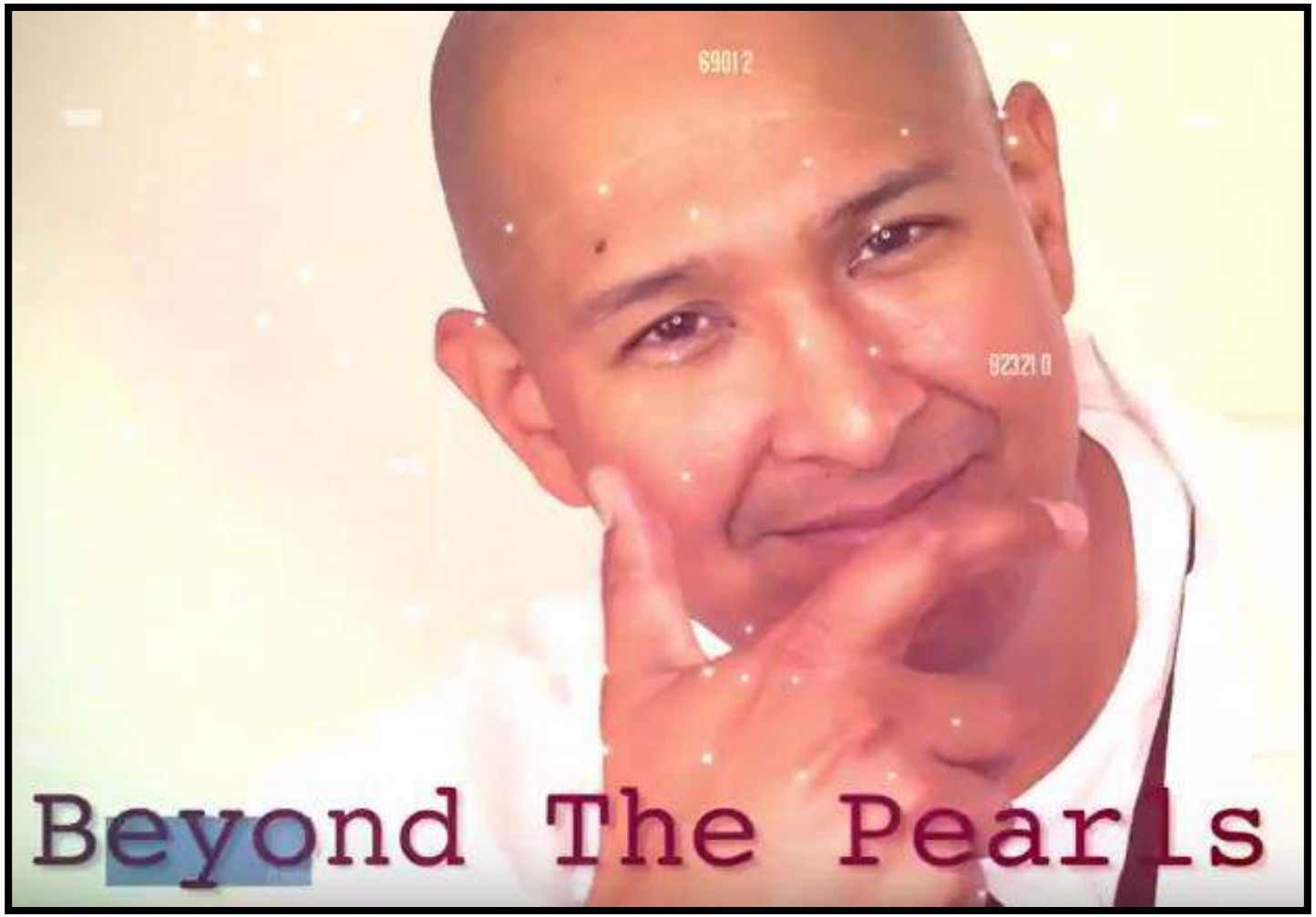
Medications for Narcolepsy Summary

Medication	MOA	Treats sleepiness?	Treats cataplexy?
Modafinil	Dopamine reuptake inhibition	Yes	No
Armodafinil	Dopamine reuptake inhibition (r-enantiomer of racemic modafinil)	Yes	No
Solriamfetol	Dopamine & norepinephrine reuptake inhibition	Yes	No
Methylphenidate & amphetamines	Dopamine & norepinephrine reuptake inhibition & release of monoamines	Yes	No
Pitolisant	H3 antagonist/inverse agonist	Yes	Yes
Oxybates	GABA-B/GHB agonists	Yes	Yes
SNRIs (venlafaxine)/SSRIs (fluoxetine)	Not FDA approved for this indication; REM suppression/modulation	No	Yes

Medications for Idiopathic Hypersomnia Summary

Medication	Evidence in IH
Modafinil	2 IH-specific RCTs, effective for reducing ESS & increasing MWT vs placebo
Armodafinil	Presumably similar to modafinil; not studied
Solriamfetol	Not studied
Methylphenidate & amphetamines	Clinical series suggest benefit
Pitolisant	Clinical series suggest benefit in 1/3 of refractory IH patients; hard to access in US without narcolepsy diagnosis
Oxybates	RCT publication pending; presented abstracts show benefits on ESS, PGI-C, IH severity
Clarithromycin	Small RCT showing benefit on ESS; possibly consider for carefully selected, treatment-refractory patients

Hypersomnia: Clinical Practice Questions



Beyond the Pearls: Question

- 23 year old man is having difficulty waking in the morning and staying awake at work despite getting between 8-9 hours of sleep per night. He recently graduated from college and, despite having been employed for only 3 months, has already been written up twice for napping at his desk. He reports having required more sleep than most of his friends as a child. In college, he was able to function without difficulty because he never scheduled early morning or late evening classes and so was able to get between 10-11 hours of sleep per night consistently.
- He has had 2 episodes of sleep paralysis in the past, but he denies symptoms of cataplexy. His ESS score is 12/24. His medical history is remarkable only for seasonal allergies. He consumes 32 oz of caffeinated coffee per day. PSG showed a normal sleep architecture with a TST 8.5 hours, a sleep efficiency of 92%, a sleep latency of 7 min, and REM sleep latency of 30 min. Results of a following-day multiple sleep latency test (MSLT) are shown in Figure 1.

- What is the most likely diagnosis?
  - A. Narcolepsy
  - B. Kleine-Levin syndrome
  - C. Idiopathic hypersomnia
  - D. Long sleeper

Nap	1	2	3	4	5
Sleep latency (min)	8	5	8	2	3
REM latency (min)	-	8	-	-	-

Answer: D


Which are you?
SHORT SLEEPERS
thrive with less than
5 hours of sleep
REGULAR SLEEPERS
need between
7 – 9 hours of sleep
LONG SLEEPERS
average
10 –12 hours of sleep
providencehospitals@provhospsc

Beyond the Pearls: Question

- 30 year old man presents with longstanding symptoms of EDS (**ESS 17**) that date back to adolescence. He sleeps for 11 to 12 hours based on 7 day actigraphy, without improvement in his symptoms. His typical bedtime is 9 pm, with an awakening time between 8 am and 9 am
- During the day, he notes frequent prolonged **unrefreshing naps**. He denies muscle weakness associated with emotion, snoring or witnessed apneas, restless leg symptoms, medications use, or any history of head trauma. He complains of “sleep drunkenness” when he wakes up in the morning
- His physical examination is normal. The PSG data are shown below, and the MSLT are also shown

Beyond the Pearls: Question

- **PSG data:**
  - Total sleep time: 550 minutes
  - Sleep efficiency: 95%
  - Sleep latency: 1 minute
  - REM latency: 110 minutes
  - % sleep stages:
    - Stage 1 (15%)
    - Stage 2 (55%)
    - Stage 3 (12%)
    - REM (18%)
  - Total AHI: 1 event/hour
  - PLM index: 3.2 events/hour
  - Lowest oxygen saturation: 93%

MSLT Data:

NAP	Sleep latency	SOREM
1	7	(-)
2	9	(+)
3	9	(-)
4	10	(-)
5	8	(-)

- Mean sleep latency: 8.6 minutes
- Urine toxicology: Negative
- 7 day actigraphy shows 11 to 12 hours of sleep per night

Beyond the Pearls: Question

- Based on his clinical history and objective testing, which of the following statements concerning this patient's disorder is correct?

A. The mean sleep latency on the MSLT is typically greater than that observed in patients with narcolepsy

B. A family history of EDS is uncommon

C. Spontaneous resolution of symptoms is commonly observed

D. The diagnosis may be confirmed by the MWT test

Answer: A

- Most patients with idiopathic hypersomnia demonstrates mean sleep latencies on the MSLT that are **higher** than those of patients with narcolepsy
- Idiopathic hypersomnia patients have an average mean sleep latency values of **6.2 +/-3.0 minutes** vs. 3.0 +/- 3.0 minutes for patients with narcolepsy
- Other important supportive features:
  - Severe & prolonged sleep inertia (sleep drunkenness)
  - Unrefreshing naps > 1 hour
  - PSG sleep efficiency >90%

Beyond the Pearls: Questions

- A 35 year old woman without significant medical history presents with symptoms of EDS (**ESS 16**) that have progressed over the past 3 years. She works as a secretary and homemaker and subjectively **estimates her total sleep time at 7 hours per night**, with a typical sleep schedule of a bedtime at 12 midnight and an out of bed time at 7 am
- She notes that her symptoms are relatively consistent throughout the month. She denies snoring, RLS, cataplexy-like symptoms, or medications use. She notes that she has 2 sisters who have similar complaints of daytime sleepiness.
- She is instructed to keep a **sleep log for a week** and is then scheduled for an overnight PSG followed by a MSLT, and the results are as follows:

Beyond the Pearls: Question

- **PSG data:**
  - Total sleep time: 420 minutes
  - Sleep efficiency: 95%
  - Sleep latency: 1 minute
  - REM latency: 54 minutes
  - % sleep stages:
    - Stage 1 (5%)
    - Stage 2 (55%)
    - Stage 3 (32%)
    - REM (8%)
  - Total AHI: 0 events/hour
  - PLM Index: 1.2 events/hour
  - Lowest oxygen saturation: 93%

- **MSLT Data**

Nap	Sleep Latency (min)	SOREM
1	2	(+)
2	4	(-)
3	7	(-)
4	9	(-)
5	14	(-)

- Mean sleep latency is 7.2 minutes
- Urine toxicology screen is negative

- Sleep log data shows nightly sleep times averaging 5.5 hours

Beyond the Pearls: Question

- Which of the following is the correct diagnosis based on her clinical history and objective testing?

  a. Narcolepsy without cataplexy

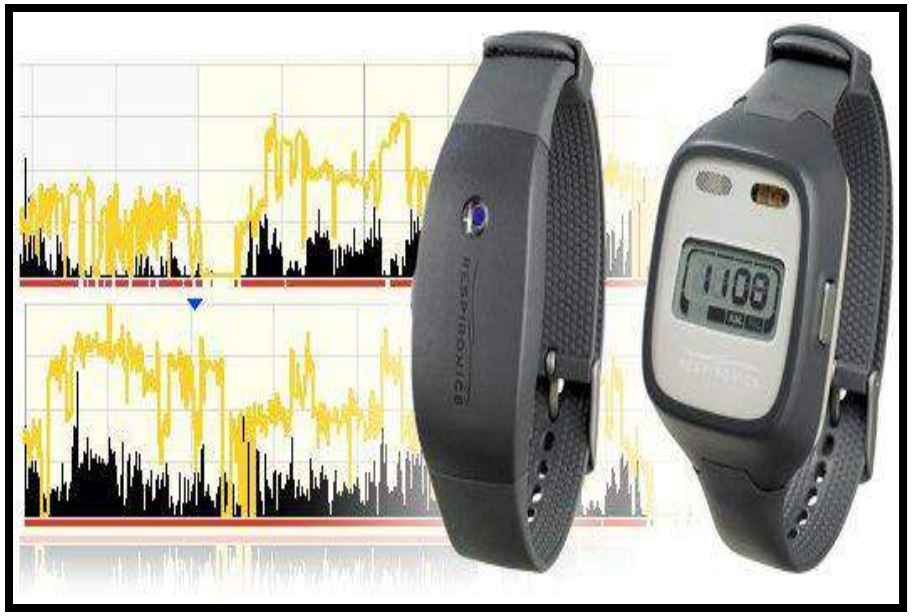
  b. Idiopathic hypersomnia

  c. Behaviorally induced insufficient sleep syndrome

  d. Menstrual related recurrent hypersomnia

Answer: C

- The primary etiology of the patient's complaints of daytime sleepiness is chronic partial sleep deprivation, resulting in a behaviorally induced insufficient sleep syndrome
- While her MSLT data alone could be interpreted as being consistent with idiopathic hypersomnia, her clinical presentation is not consistent with the diagnosis, given her sleep log data



Circadian Rhythm Sleep Disorders

Circadian Disorders: Overview

- Diseases of incorrect sleep timing
- Each person has a circadian cycle referred to as "**tao**" that is approximately 24 hours
  - This value can be +/- 24 hours but the most common value is 24.2
- Synchronization between the 24 hour solar day and each person's circadian cycle (**entrainment**) is accomplished via external circadian cues (**zeitgebers**)
- Circadian disorders occur when the circadian system fails to promote sleep and wake at the "correct" times
  - Morning & evening circadian types by itself are not disorders

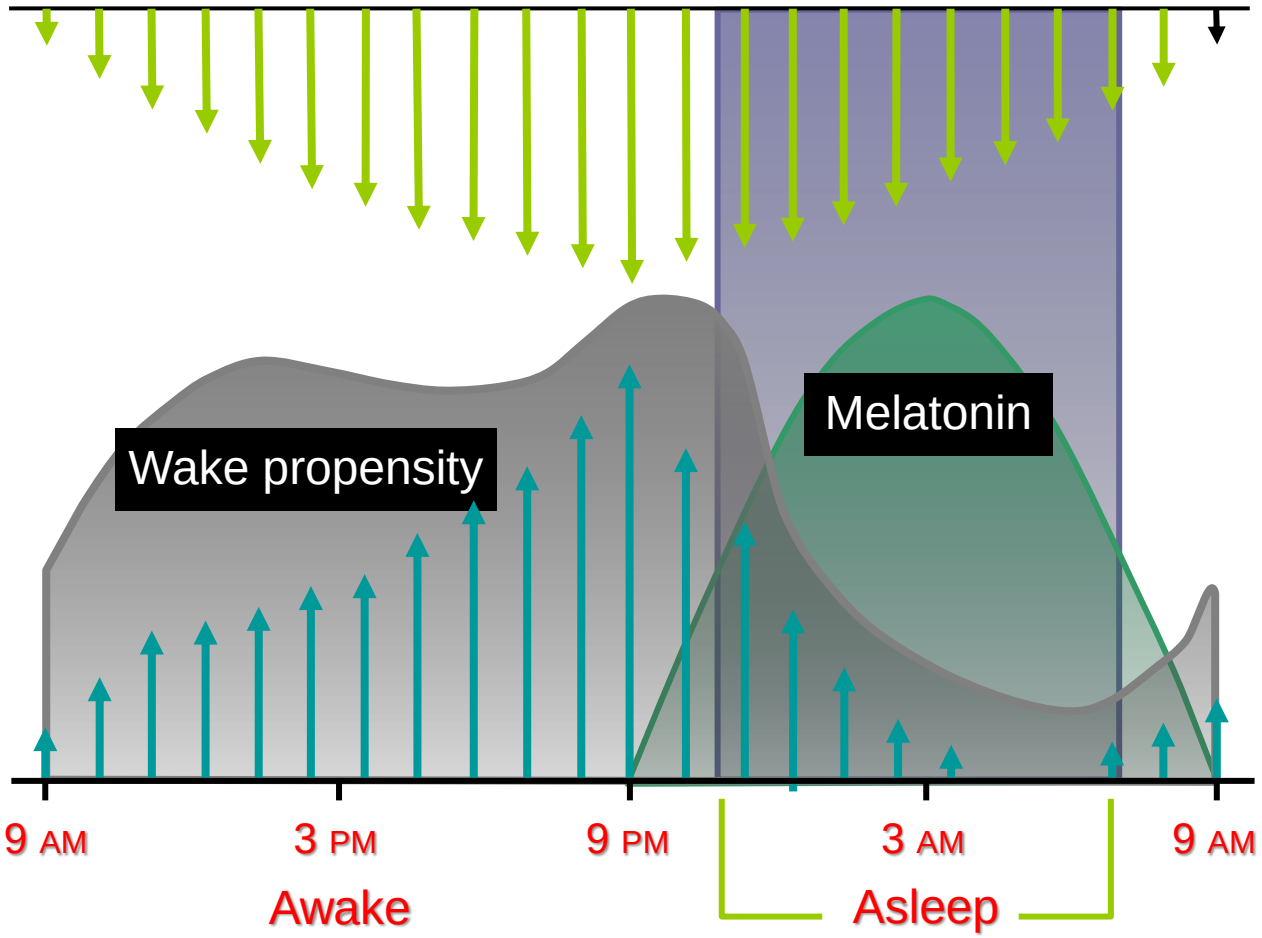
Circadian Regulation of Sleep/Wake Cycle

Homeostatic sleep drive

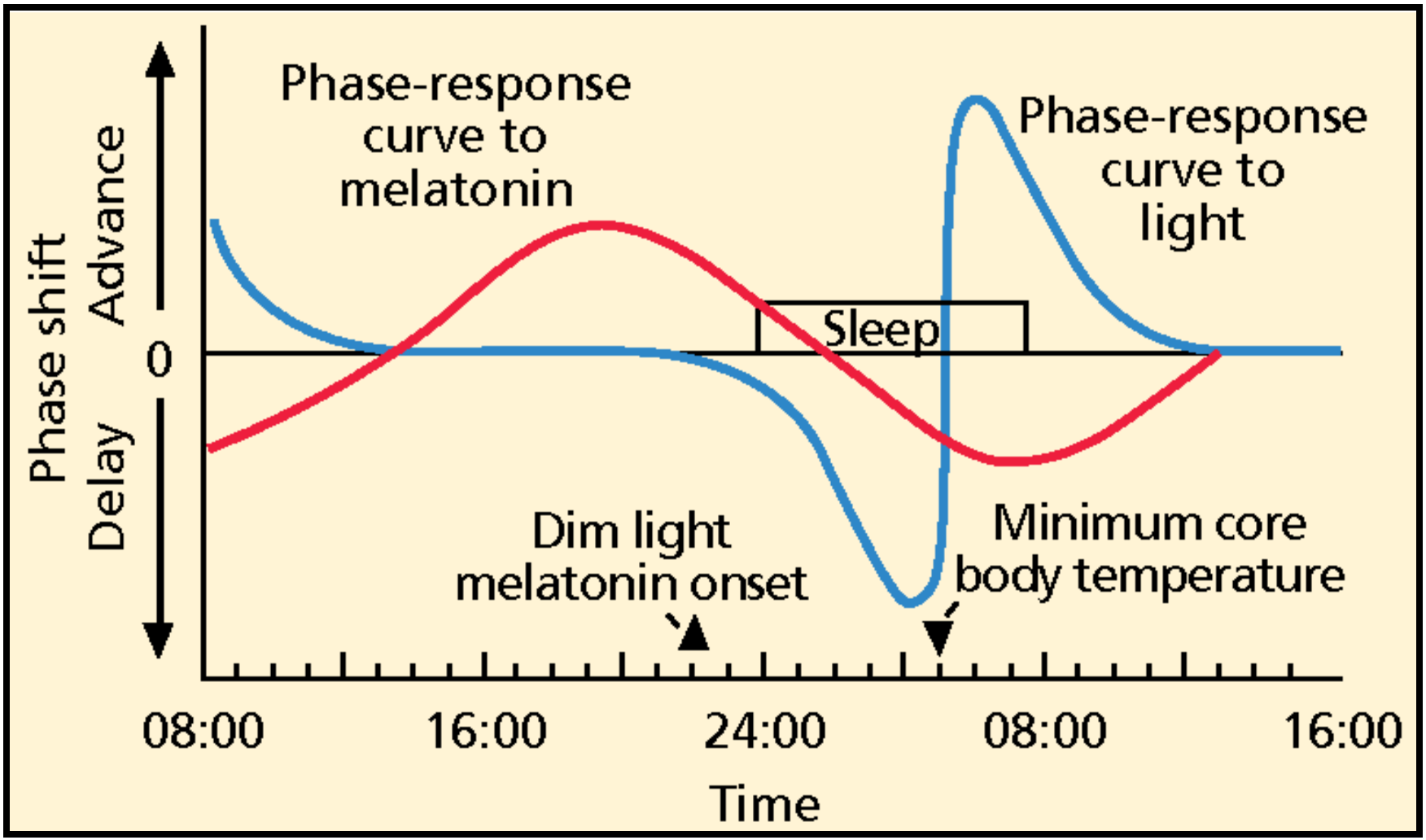
Sleep Drive (**Process S**): Adenosine accumulates during wakefulness

Circadian alerting signal

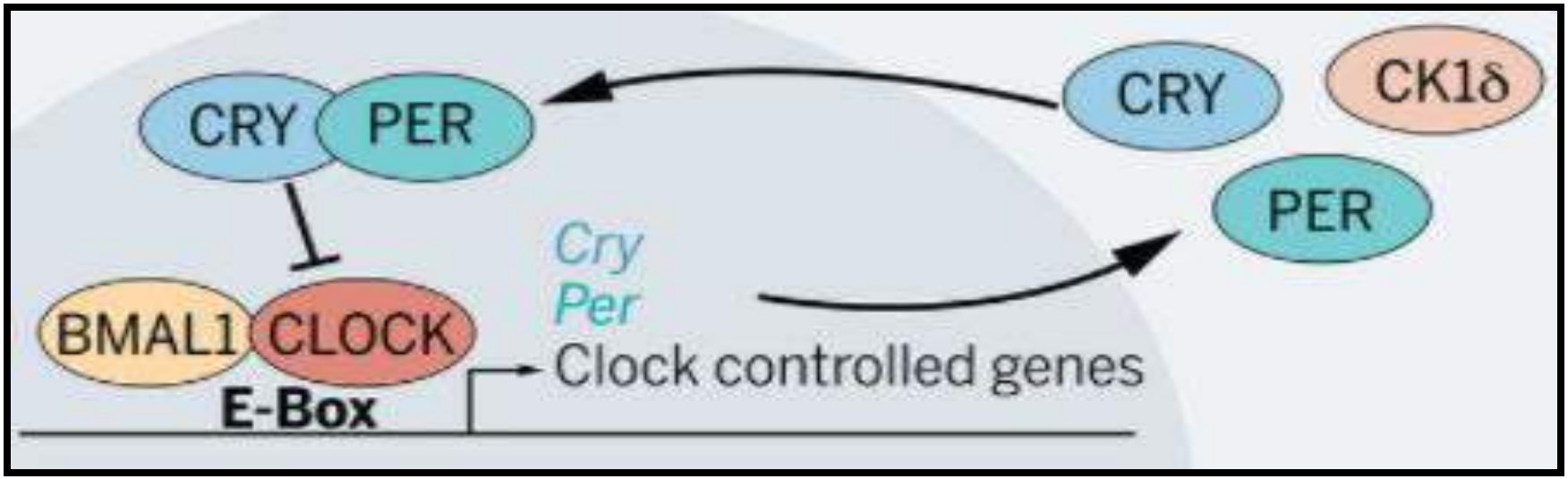
Wake Drive (**Process C**): Oscillating promotion of arousal



Double Plot Phase Response Curve to Light & Melatonin



The molecular basis of circadian rhythm is cyclic transcription of proteins which in turn provide negative feedback



For Sleep Boards:

- Advance Sleep Phase Syndrome: hPER2
- Delayed Sleep Phase Syndrome: Cry1

Circadian rhythm sleep disorder

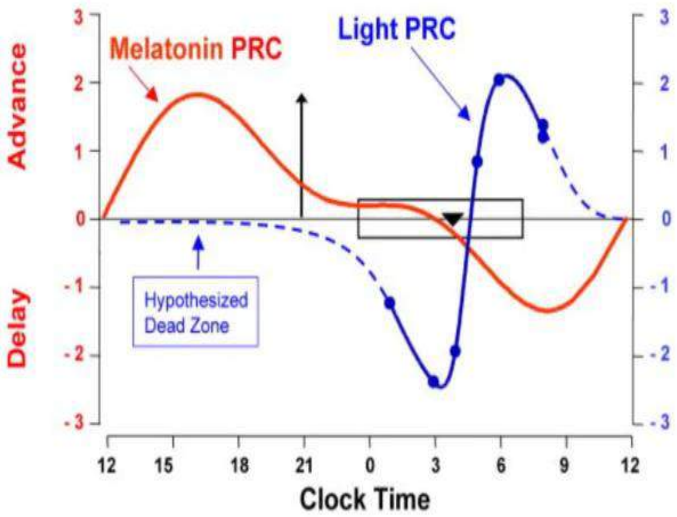
- Family of sleep disorders affecting the **timing of sleep**
- Patients unable to sleep and wake **at the times required** for normal work, school, and social needs
- Able to get enough sleep if allowed to wake at the times **dictated** by their **body clocks**

Circadian rhythm sleep disorder

- **Extrinsic type**
  - Jet lag (at least 2 time zones)
    - Easier to travel West
  - Shift work

East
Clock later & go to bed earlier

West
Clock earlier & go to bed later



- **Intrinsic type**
  - Advance sleep phase disorder
    - Morning lark
  - Delayed sleep phase disorder
    - Night owl
  - Free-Running Circadian Disorder
    - Blind
  - Irregular Sleep-Wake Rhythm
    - Rare
    - Alzheimer's dementia

Limited evidence based trials for the treatment of ASPD & DSPD. For diagnosis symptoms must be present for at least 3 months and supported by 1-2 weeks of sleep diaries or actigraphy

Free-Running Circadian Disorder

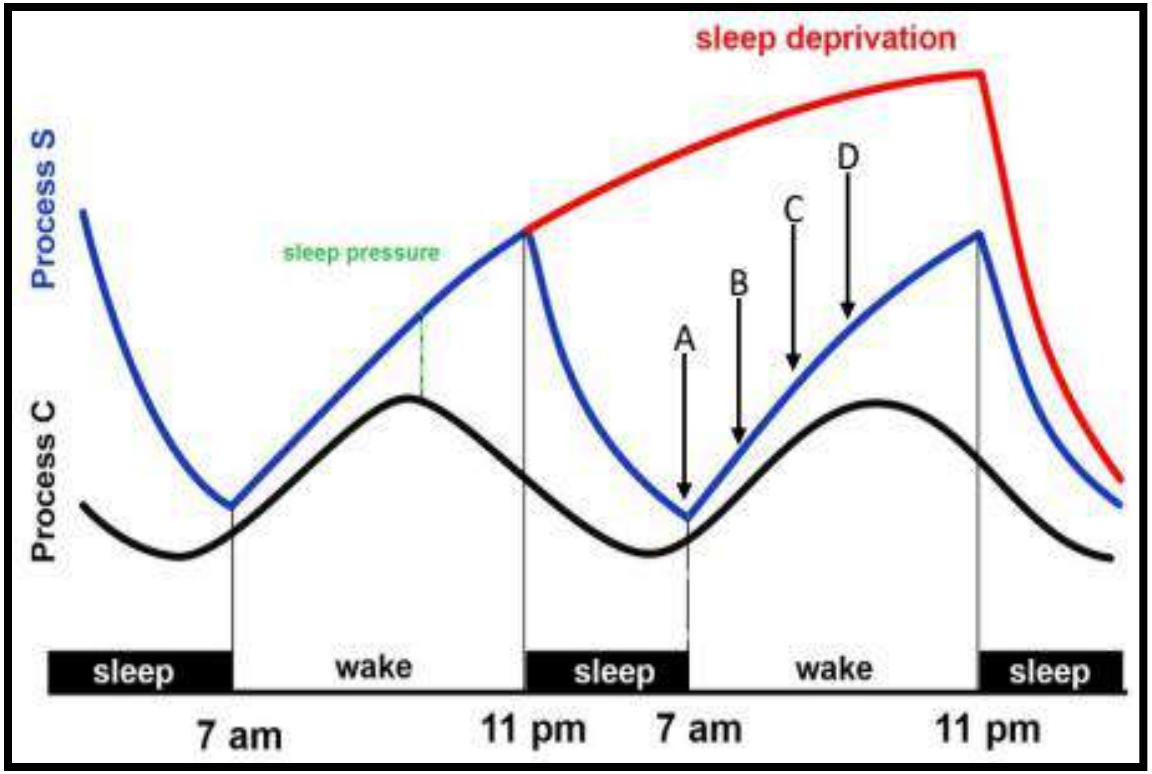
- An old disorder under a more user-friendly name
- The prevalence of non-24 is particularly high in totally blind persons
- In the case of sighted persons, the cause of non-24 is complex and multifactorial

Hetlioz recently FDA approved for Smith Magenis Syndrome (SMS) a rare developmental disorder which inversion of the melatonin cycle

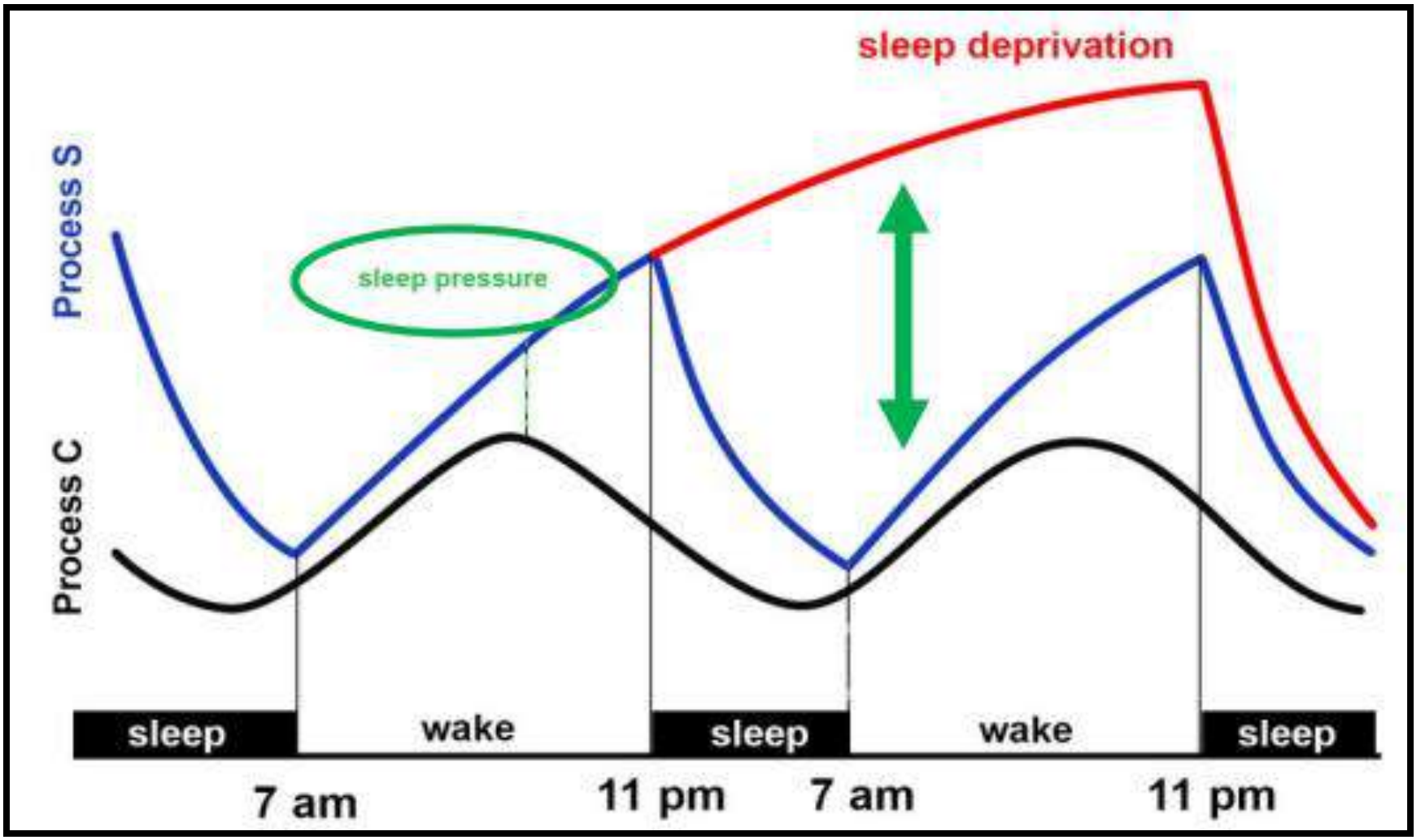
MT2 receptor mainly for circadian rhythm shifting
MT1 receptor mainly for sleep

Beyond the Pearls: Question

- Assuming daytime work and nighttime sleep as the habitual schedule. What is the safest time to drive home following an overnight shift?
  A. Time A
  B. Time B
  C. Time C
  D. Time D

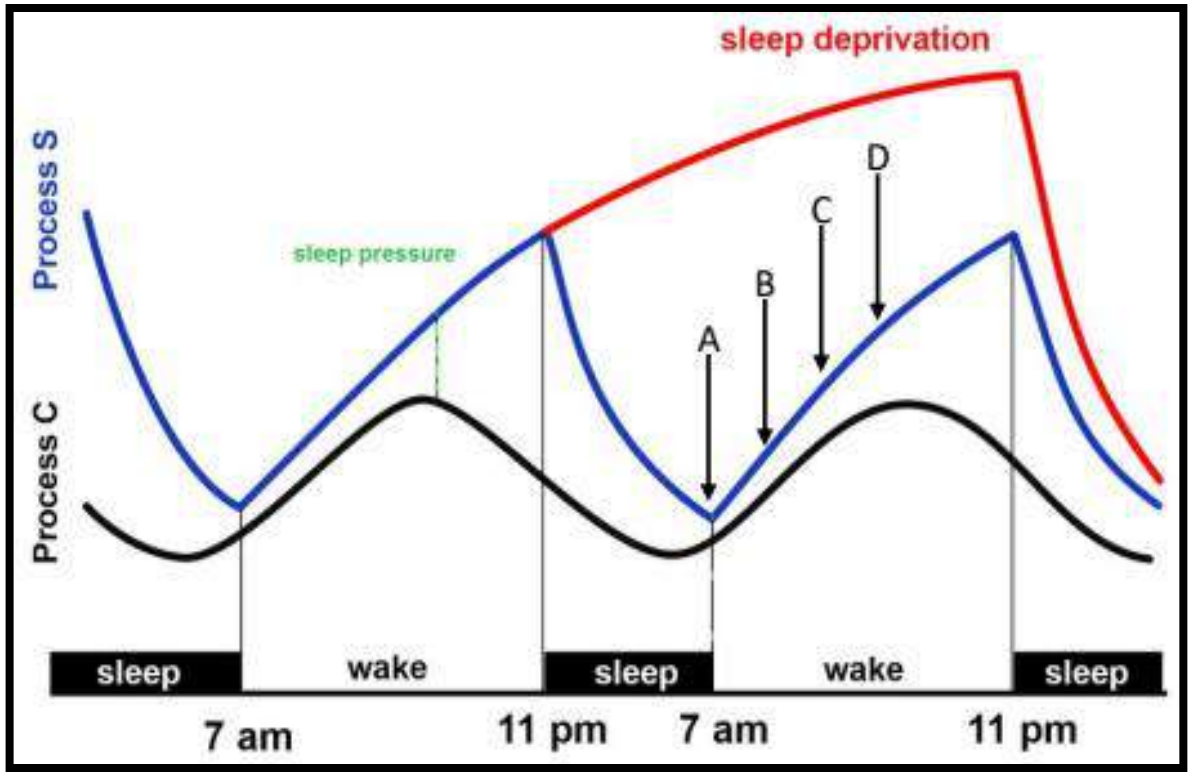


Answer: D

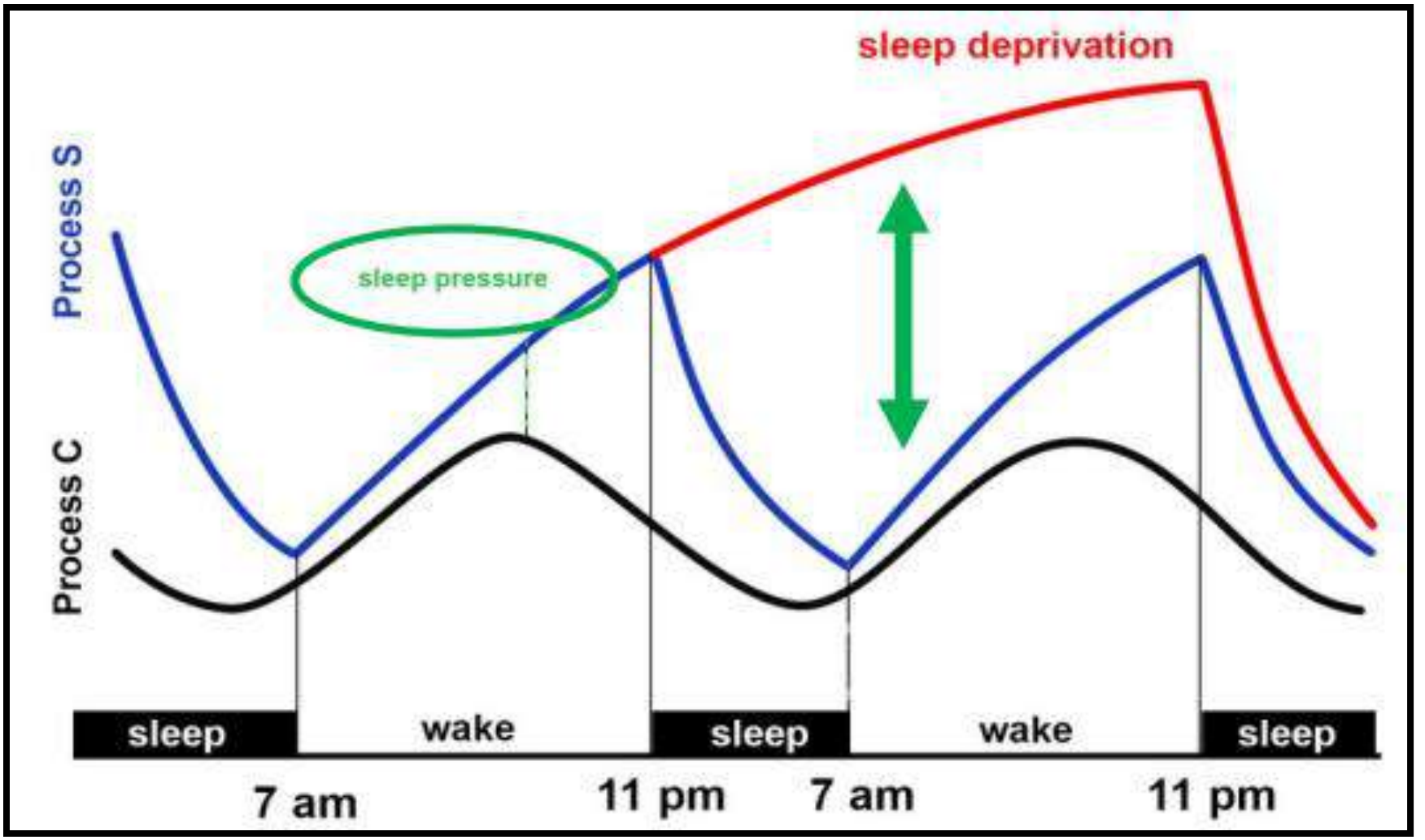

sleep deprivation
Process S
sleep pressure
Process C
sleep
wake
sleep
wake
sleep
7 am
11 pm
7 am
11 pm

Beyond the Pearls: Question

- Assuming daytime work and nighttime sleep as the habitual schedule. What is the best time to initiate sleep after an overnight shift?
  A. Time A
  B. Time B
  C. Time C
  D. Time D



Answer: A


sleep deprivation
Process S
sleep pressure
Process C
sleep
wake
sleep
wake
sleep
7 am
11 pm
7 am
11 pm

Parasomnias

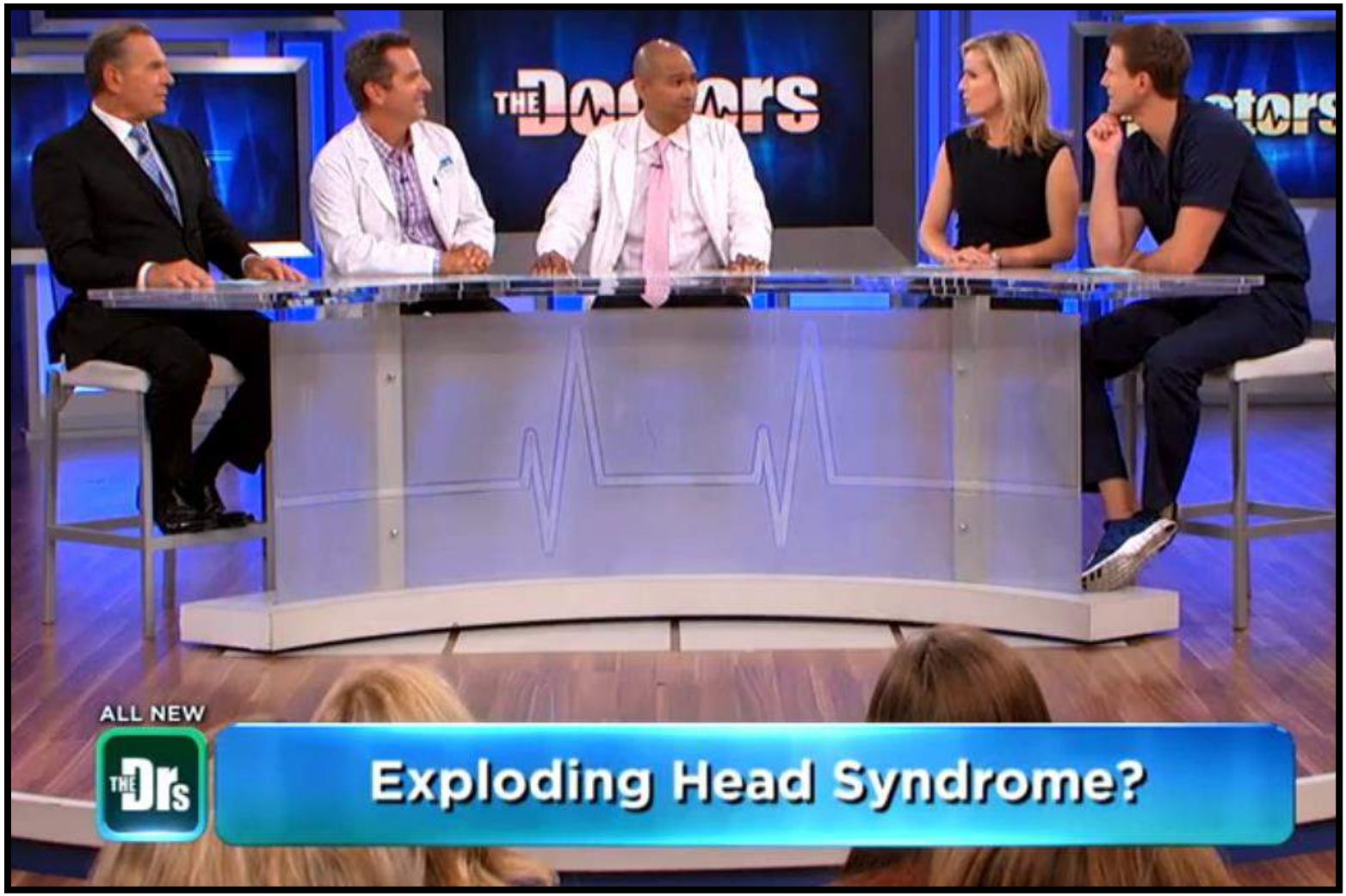
Beyond the Pearls: Question

- 58 year old woman complains of a **sudden loud noise** in her head during wake-sleep transition or on awakening during the night. Once awake, she denies headache, any pain complaints, neurologic deficits, incontinence, or amnesia for the events. She has complaints of **difficulty falling asleep** at bedtime and after routine awakenings because of concern that these episodes will recur. She denies other medical history and is currently taking no medications. Results of her physical examination, including a neurologic examination are normal.

Beyond the Pearls: Question

- Based on the history and exam, the best initial recommendation would be:
  a) MRI of the brain
  b) Clomipramine prior to bedtime
  c) Reassurance
  d) Ibuprofen prior to bedtime

Answer: C



Exploding Head Syndrome

- Form of hypnagogic auditory hallucination that is an uncommon parasomnia
- The subject experiences a loud bang in their head similar to a:
  - Bomb exploding
  - Gun going off
  - Clash of cymbals
  - Ringing
- Usually not accompanied by pain

Parasomnias: Definition

- “Undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousal from sleep”
  - Definition from The International Classification of Sleep Disorders, 3rd Edition

Parasomnias: Definition

- Category of sleep disorders that involve abnormal and unnatural:
  1. Movements
  2. Behaviors
  3. Emotions
  4. Perceptions
  5. Dreams

- Most parasomnias are treatable

Parasomnias

- **2 main categories**
  - Parasomnias occurring during NREM sleep (disorders of arousal)
    - Confusional arousals
    - Sleep terrors
    - Sleepwalking
      - Ambien
  - Parasomnias occurring during REM sleep
    - Nightmares
    - REM sleep behavior disorder (RBD)

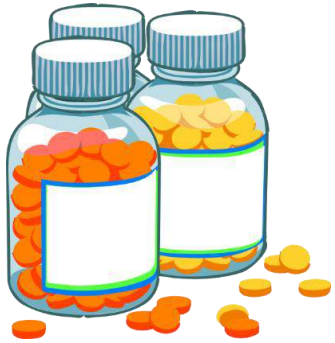
Sleepwalking would put her 6-month old in danger

Sexual Assault Defense is Sleep Apnea?

Man Attacks Wife after Dreaming She Cheated!

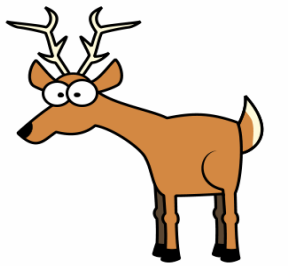
Sleep Thrashing

The Worst Combination



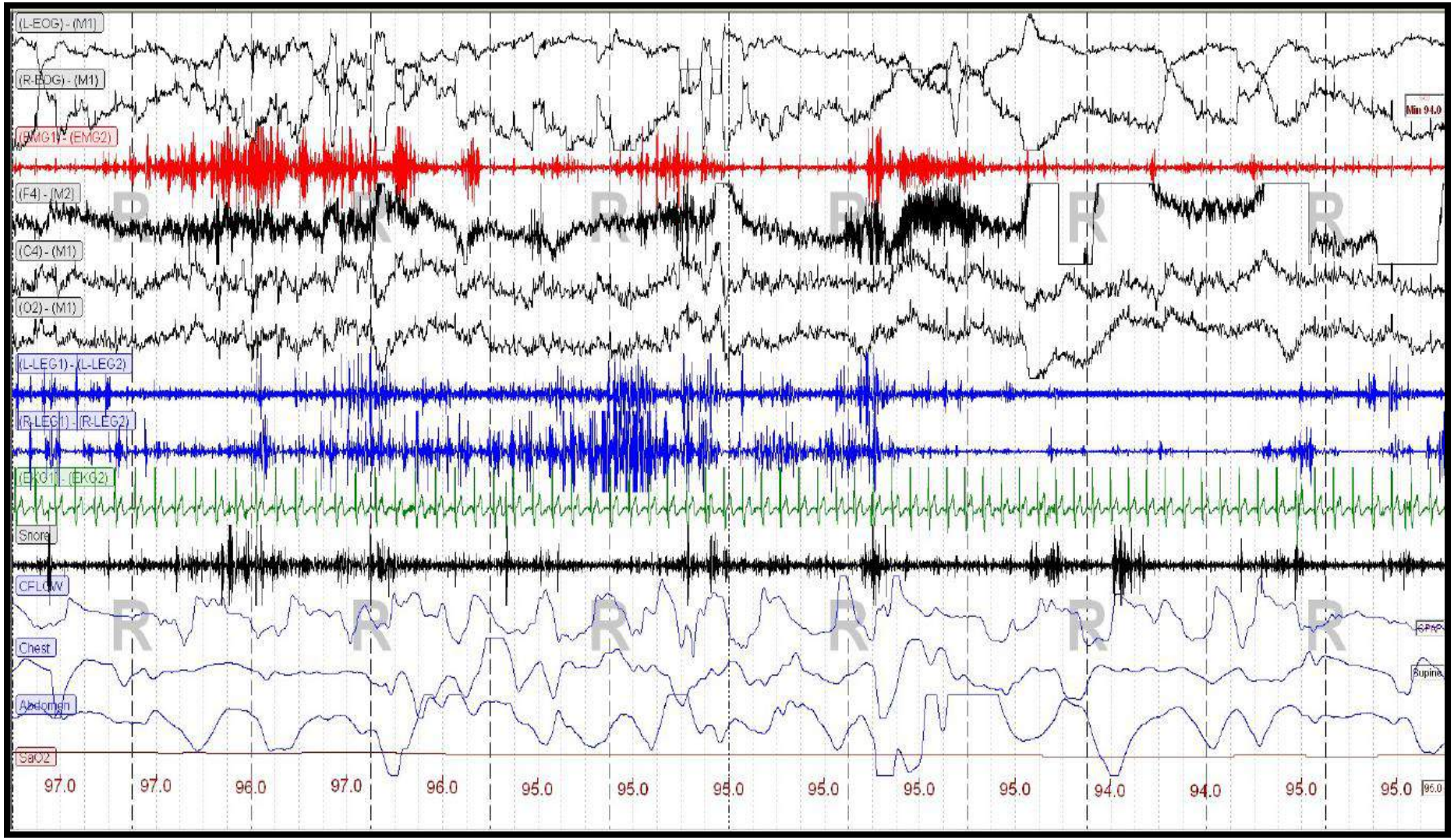
REM Sleep Behavior Disorder

- Abnormal "dream enacting" behavior during REM sleep
  - Loss of REM-related muscle atonia
- More common in older male adults (>50 years of age)
- Can result in injuries to patient or bed partner



- Treatment and Associations
  1. Low-dose clonazepam at bedtime
     - 0.5-2mg
     - Works by suppressing phasic REM
  2. High-dose melatonin
     - 3-12mg
     - Restores tonic REM
  3. Environmental precautions
  4. Associated with the development of alpha-synucleinopathies
     - Parkinson's disease, lewy body dementia, multiple system atrophy & pure autonomic failure

Epoch of REM Sleep Without Atonia



Question for the G.O.A.T

- 18 year old high school student complains of abnormal **sleep-related behaviors**. His parents accompany him to the evaluation. They report that over the previous 4 months, the patient had repeatedly been found to be **wandering**, seemingly aimlessly, in the house at night. One time, he urinated in the hallway outside his bedroom. When confronted by his parents, he just stares past them and **does not respond** to their questions. However, he does not resist when he is led back to his bedroom, where he would get into bed and promptly return to sleep. These nighttime wanderings usually occur between **1:00 am and 2:00 am**.

Question for the G.O.A.T

- He typically goes to bed shortly before **12:30 am** and falls asleep within a few minutes. He wakes up at **6:00 am** on school days and as late as **11:00 am** on weekends. He has **no recollection** of any of the abnormal nighttime events when asked by his parents the following day. He describes being sleepy during his morning classes and has **fallen asleep** in class on several occasions. He has no medical or medications history

Question for the G.O.A.T: Part 1

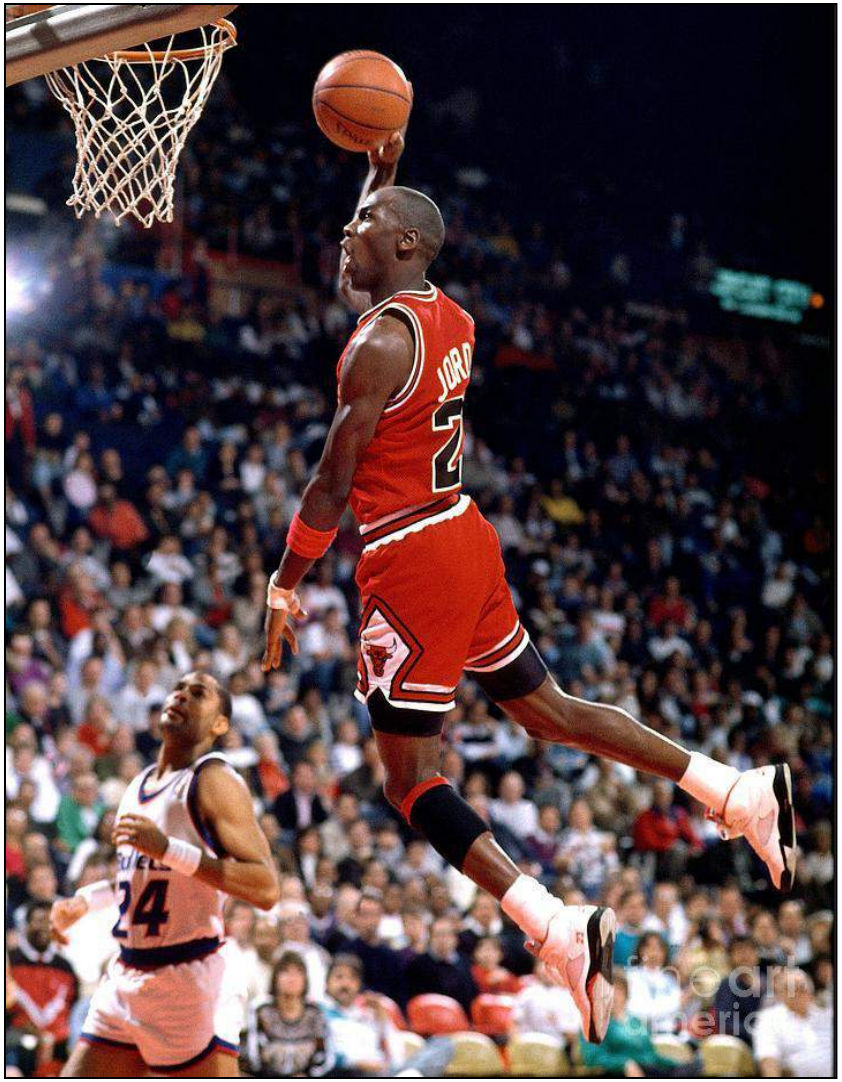
- A polysomnographic study with video recording is performed and captures one episode of **unusual behavior** that is similar to the ones described by his parents. During which of the following sleep epochs is this abnormal sleep-related behavior **most likely** to develop ?

  A. Epoch 1

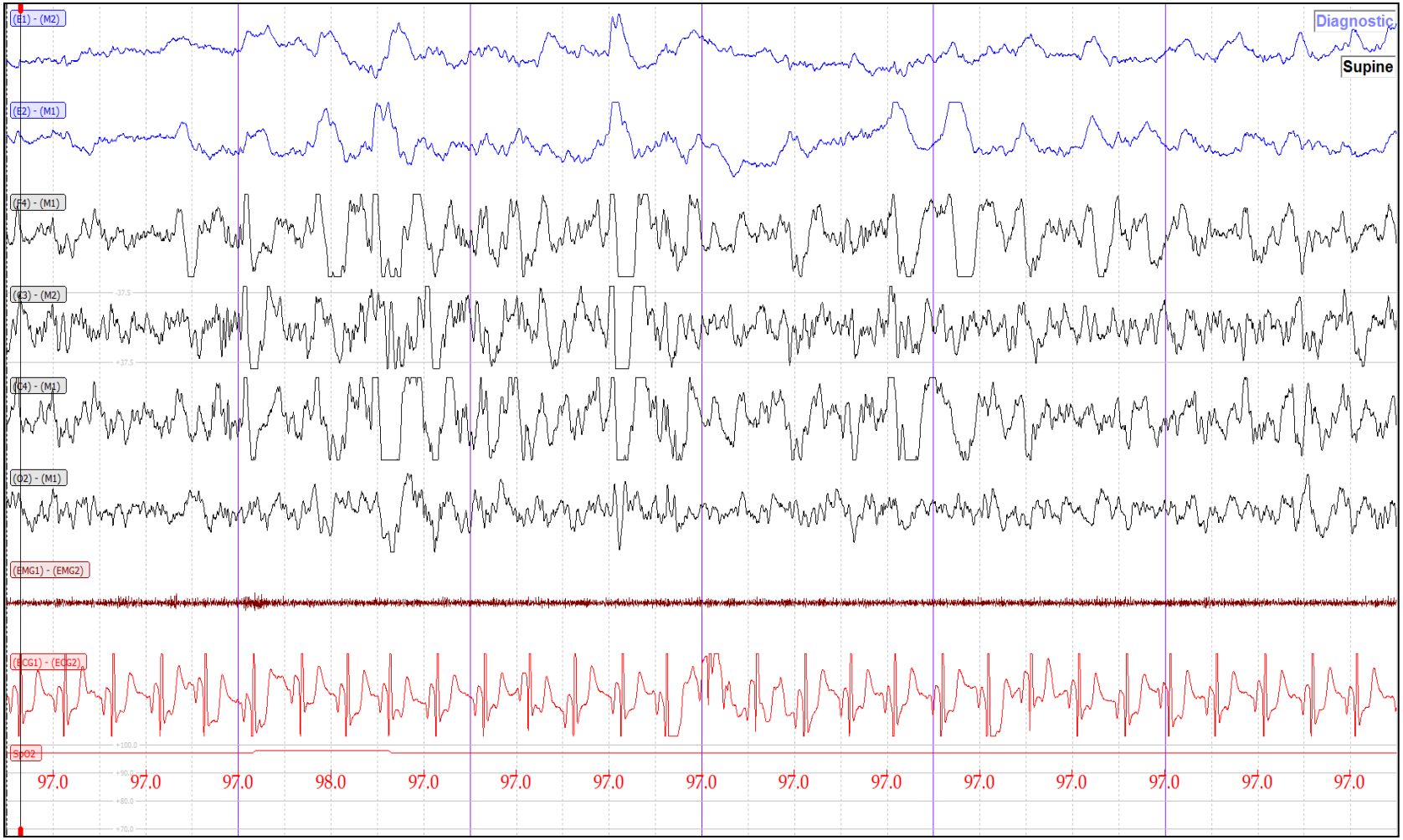
  B. Epoch 2

  C. Epoch 3

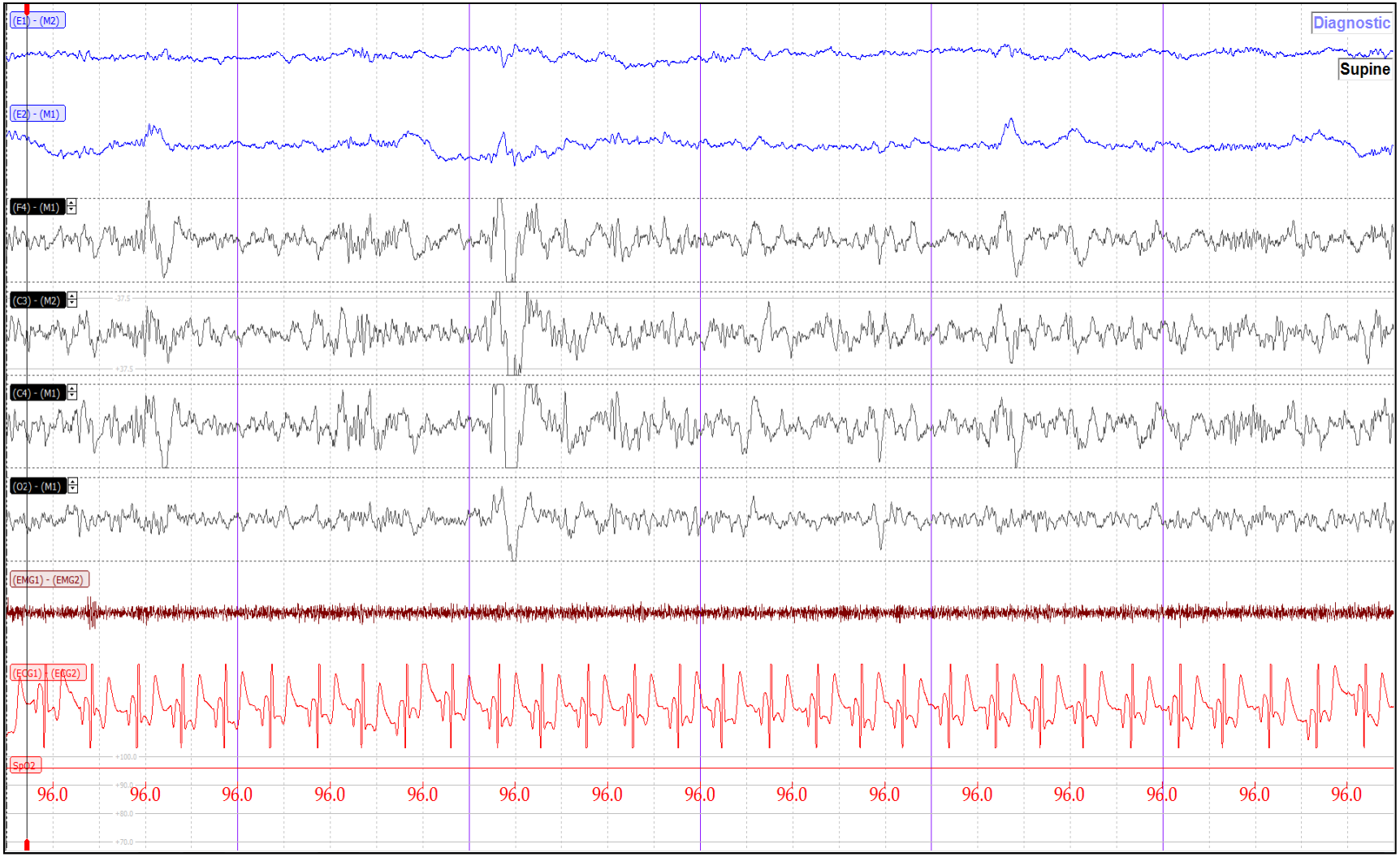
  D. Epoch 4



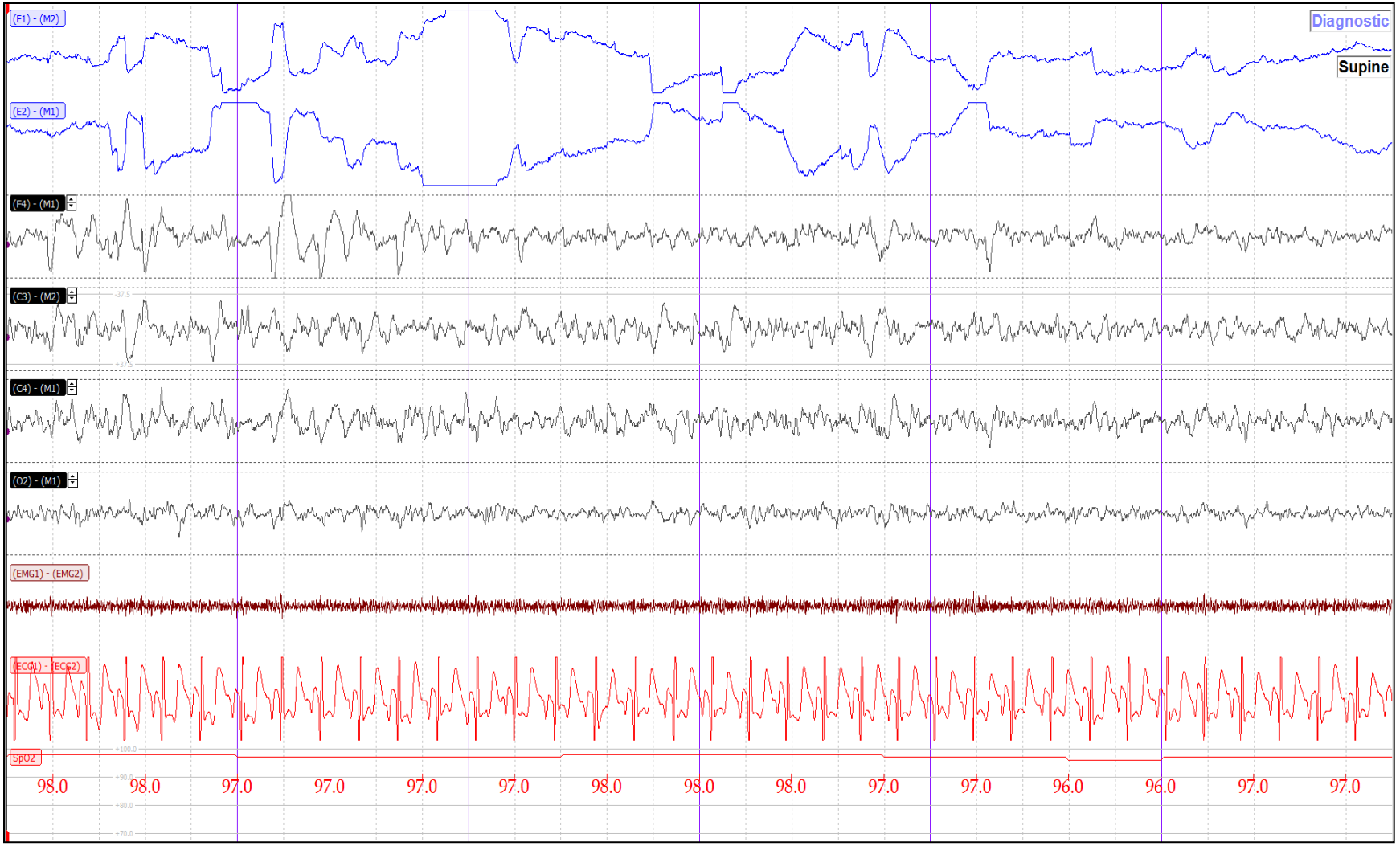
Epoch 1


(E1) - (M2)
(E2) - (M1)
(F4) - (M1)
(C3) - (M2)
(C4) - (M1)
(O2) - (M1)
(EMG1) - (EMG2)
(ECG1) - (ECG2)
SpO2
Diagnostic
Supine
97.0 97.0 97.0 98.0 97.0 97.0 97.0 97.0 97.0 97.0 97.0 97.0 97.0 97.0 97.0

Epoch 2


(E1) - (M2)
Diagnostic
Supine
(E2) - (M1)
(F4) - (M1)
(C3) - (M2)
(C4) - (M1)
(O2) - (M1)
(EMG1) - (EMG2)
(ECG1) - (ECG2)
SpO2
96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0 96.0

Epoch 3


(E1) - (M2)
(E2) - (M1)
Diagnostic
Supine
(F4) - (M1)
(C3) - (M2)
(C4) - (M1)
(O2) - (M1)
(EMG1) - (EMG2)
(ECG1) - (ECG2)
SpO2
98.0
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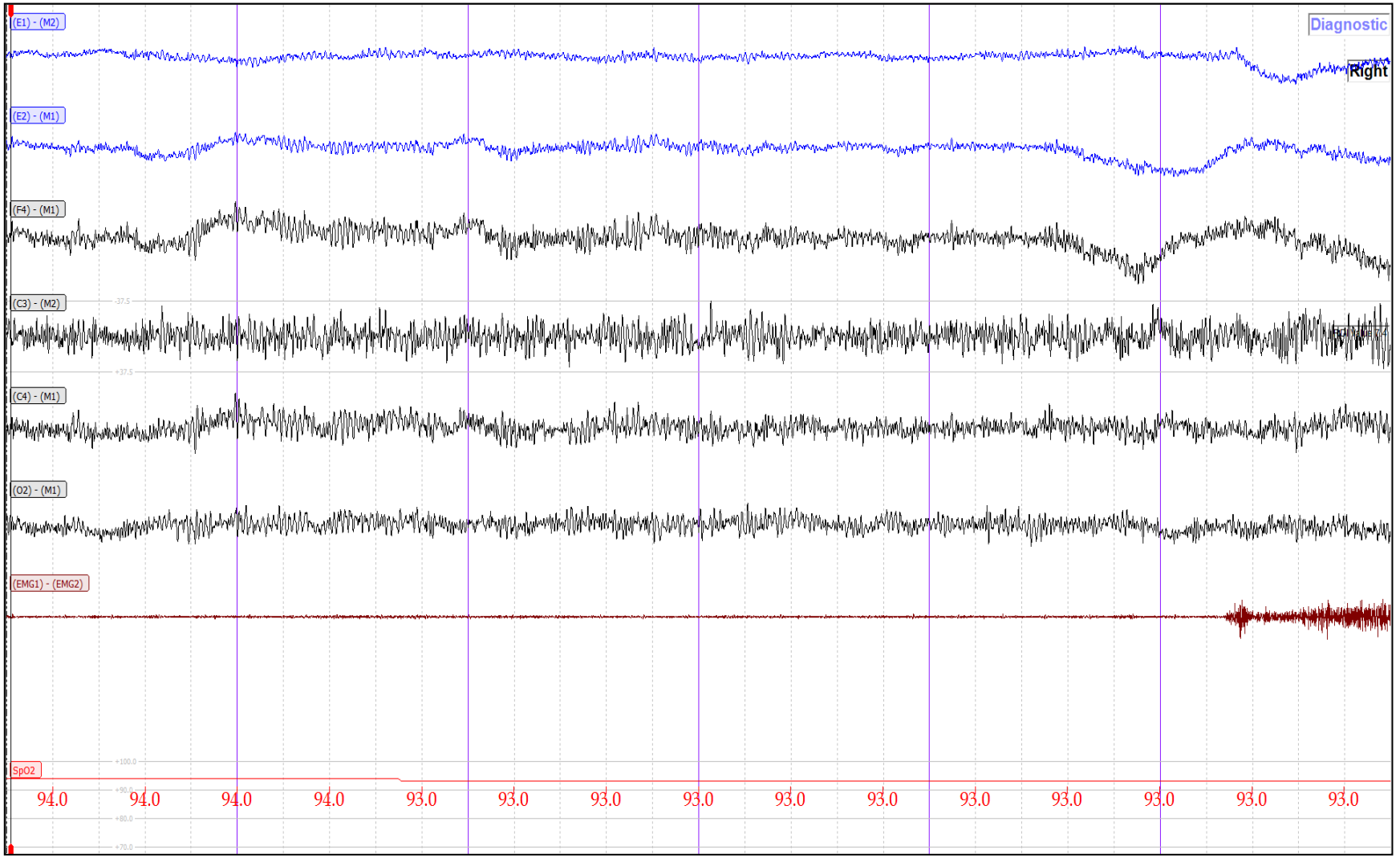
97.0

Epoch 4


(E1) - (M2)
Diagnostic
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(E2) - (M1)
(F4) - (M1)
(C3) - (M2)
(C4) - (M1)
(O2) - (M1)
(EMG1) - (EMG2)
SpO2
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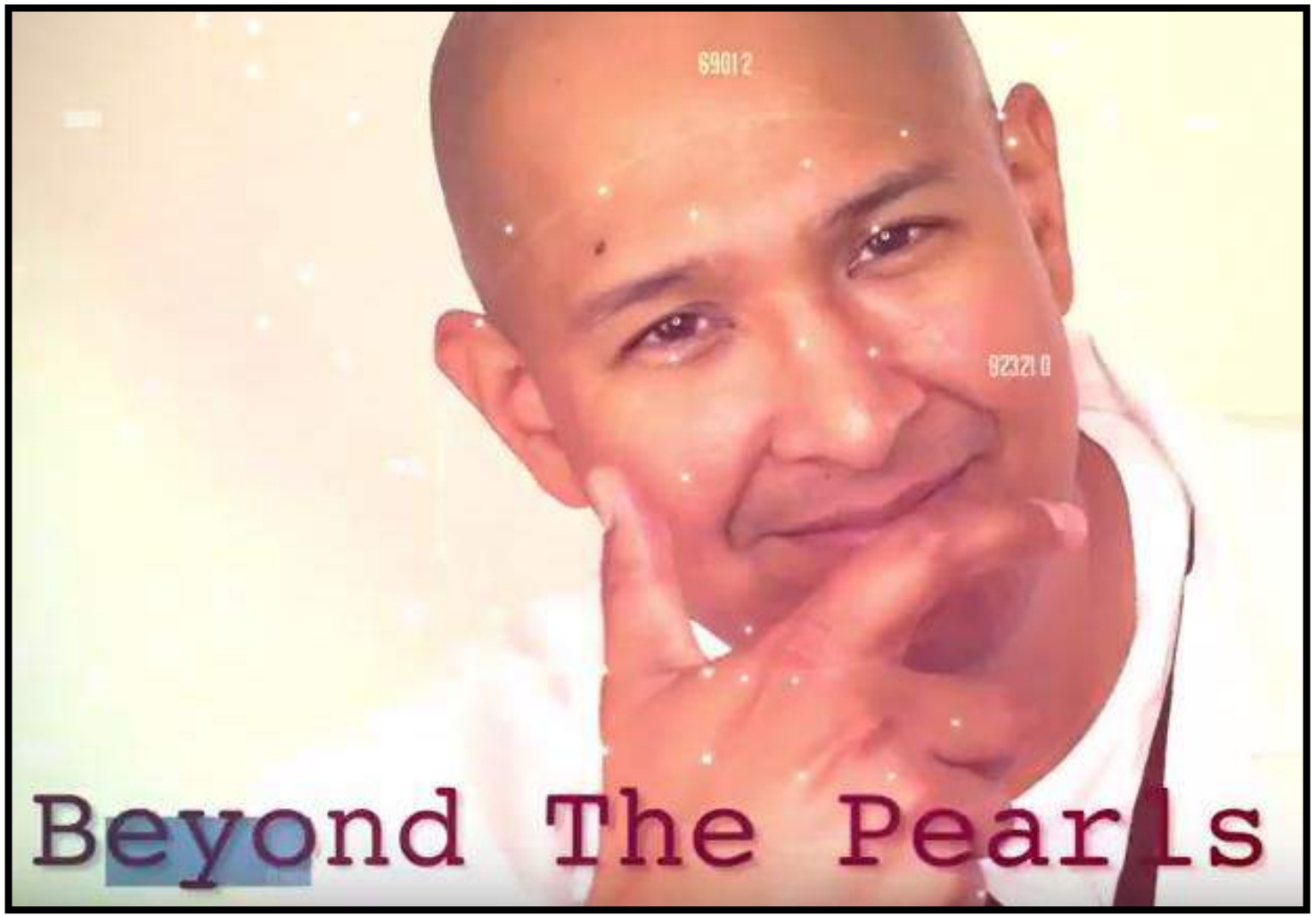
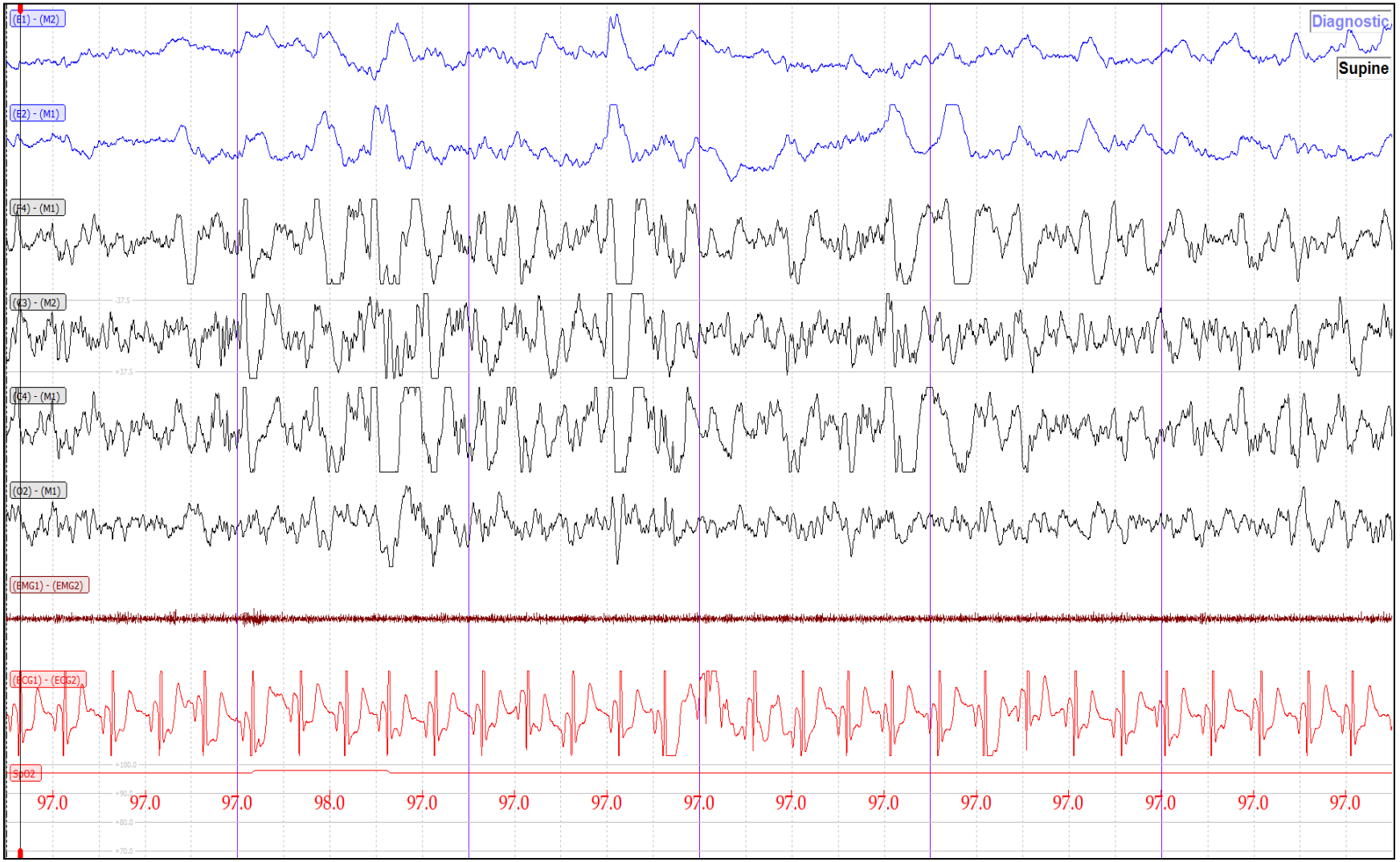
93.0

What is the answer?



Answer: A


(E1) - (M2)
(E2) - (M1)
(F4) - (M1)
(C3) - (M2)
(C4) - (M1)
(O2) - (M1)
(EMG1) - (EMG2)
(ECG1) - (ECG2)
SpO2
Diagnostic
Supine
97.0
97.0
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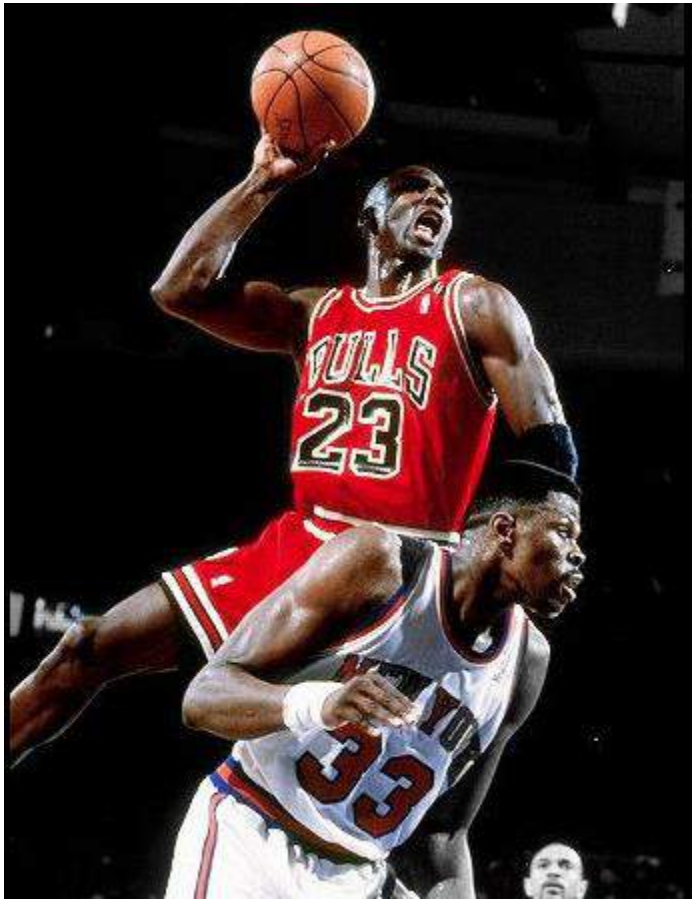
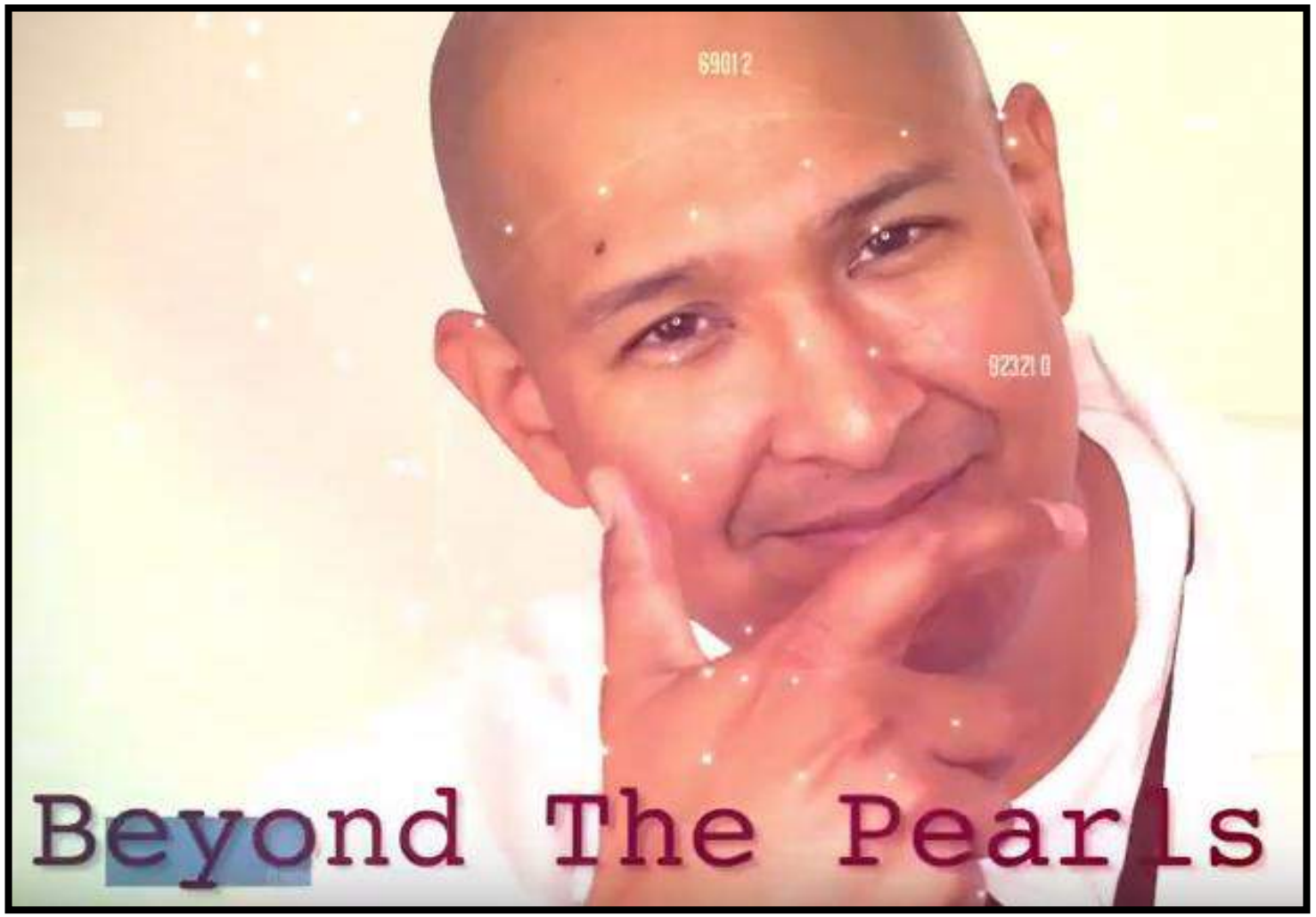
97.0
97.0

Question for the G.O.A.T: Part 2

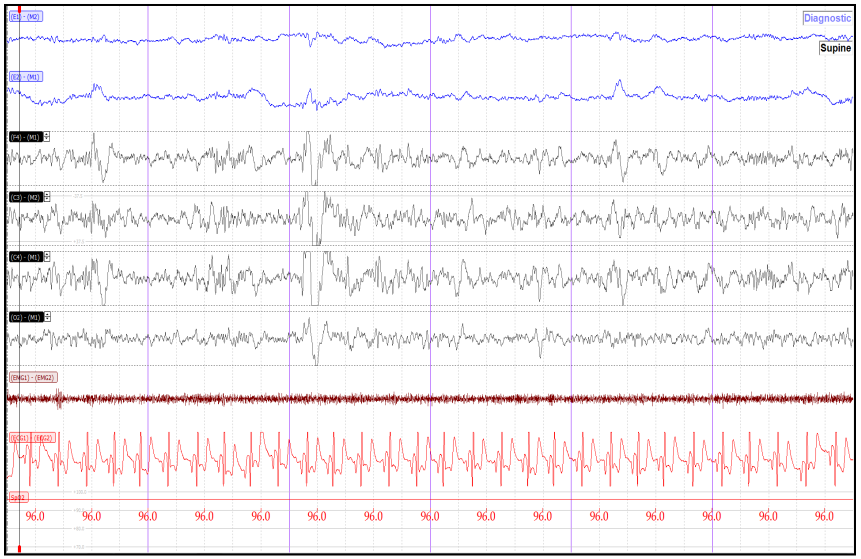
- What Epoch combination represents the stage of sleep that seizures occurs the most and the least
  - A. Epoch 1 & 2
  - B. Epoch 2 & 3
  - C. Epoch 3 & 1
  - D. Epoch 3 & 4



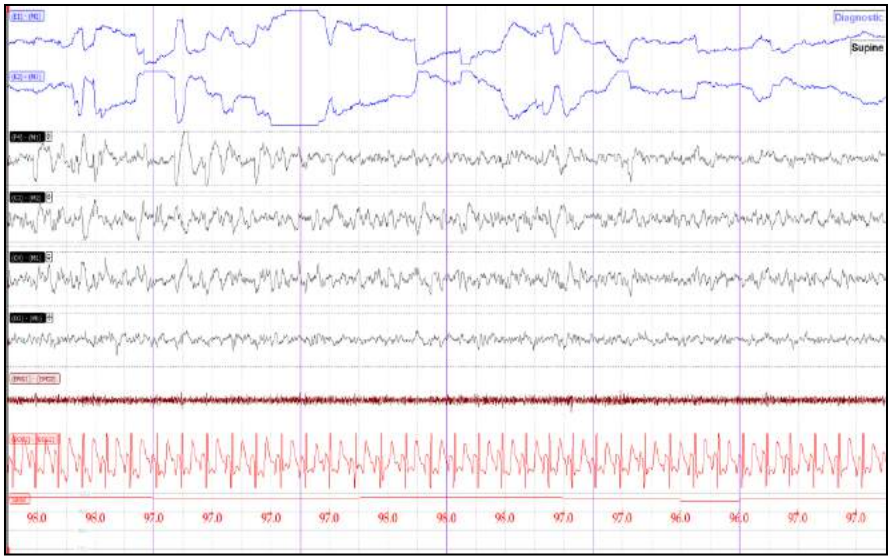
What is the answer?



Answer: B



Stage N2



Stage R

Sleep and Epilepsy: High Yield Points

- Increased sleep latency and awakenings
- Sleep deprivation can worsen seizures
- Untreated OSA can worsen seizures and treatment with CPAP can reduce seizures in epileptics

Excessive Daytime Sleepiness in Epilepsy

- Very common in epilepsy patients
- Incorrectly blamed solely on AED's, but typically multifactorial
- 1/3 of medically refractory epileptics found to have sleep apnea

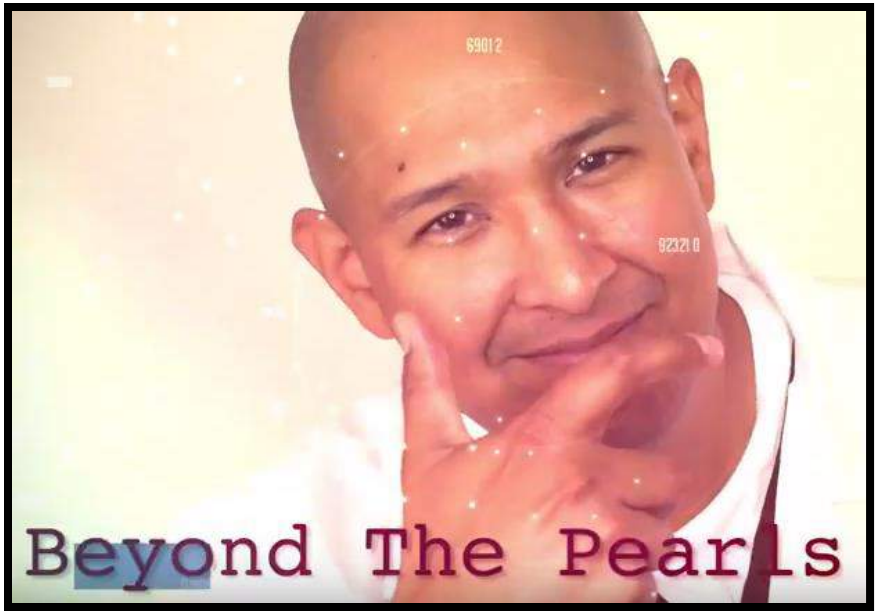
Sleep Related Movement Disorders

Beyond the Pearls: Question

- 56-year-old woman is evaluated for a 6-month history of nocturnal leg movements. According to her husband, she frequently kicks her legs during sleep but does not exhibit vocalizations or complex movements while asleep. The patient is unaware of these movements and has not had any sensory discomfort or urge to move the legs. She **snores** at night but has had no sudden loss of muscle tone, **sleep attacks**, or excessive daytime sleepiness.
- Results of physical exam and labs are unremarkable.
- A PSG shows good **sleep efficiency**, a low apnea-hypopnea index, and **absence of motor activity** during REM sleep; no sleep fragmentation is evident, despite frequent leg movements. A video recording of her movements reveals slow flexion movements of the ankles, knees, and hips that repeats every **20 seconds** in a stereotyped manner

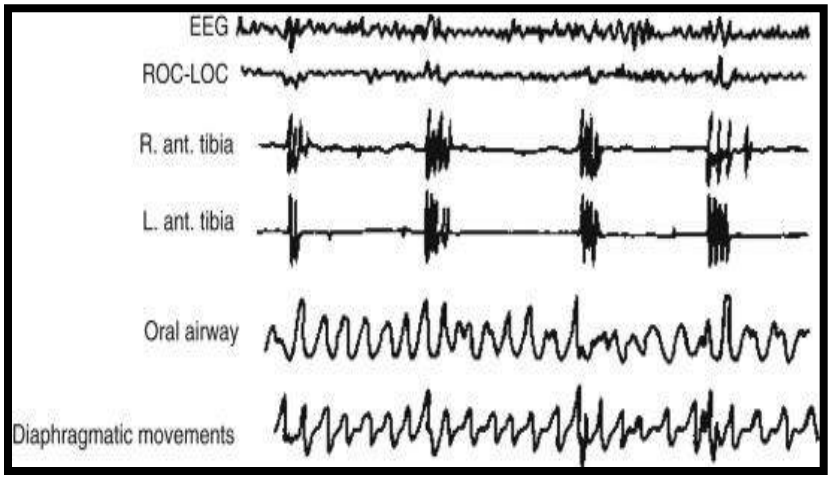
Beyond the Pearls: Question

- Which of the following is the most appropriate next step in management?
  A. Clonazepam administration
  B. Electroencephalography
  C. Ferritin level measurement
  D. No treatment is necessary



Answer: D

- **Periodic limb movements of sleep (PLMS)** is characterized by periodic leg kicks that often exhibit a stereotyped flexion repeating periodically during sleep
- When PLM was first described in the 1950s, it was called **nocturnal myoclonus**
- If no associated sleep disorder is present, **reassurance** is the best management
- Do not confuse with **PLMD**



Beyond the Pearls: Question

- Which of the following statements regarding periodic leg movements of sleep (PLMS) is correct?
  a. Patients generally present with complaints of repetitive leg movements during sleep
  b. A PLM index greater than 15 should always be treated
  c. Prevalence is increased in patients with REM sleep behavior disorder
  d. They commonly respond to dopamine agonists

Answer: C

- Prevalence of PLMS increases with age, most commonly affecting patients older than **60 years** of age
- It can be associated with:
  - RLS
  - REM sleep behavior disorder
  - Narcolepsy
  - OSA
- They can occasionally cause **arousals**, but patients are generally unaware of the movements

Beyond the Pearls: Question

- Which of the waves listed below defines “arousal” on a EEG that must last at least 3 seconds and usually seen in the occipital leads ?

  A.Alpha & Theta

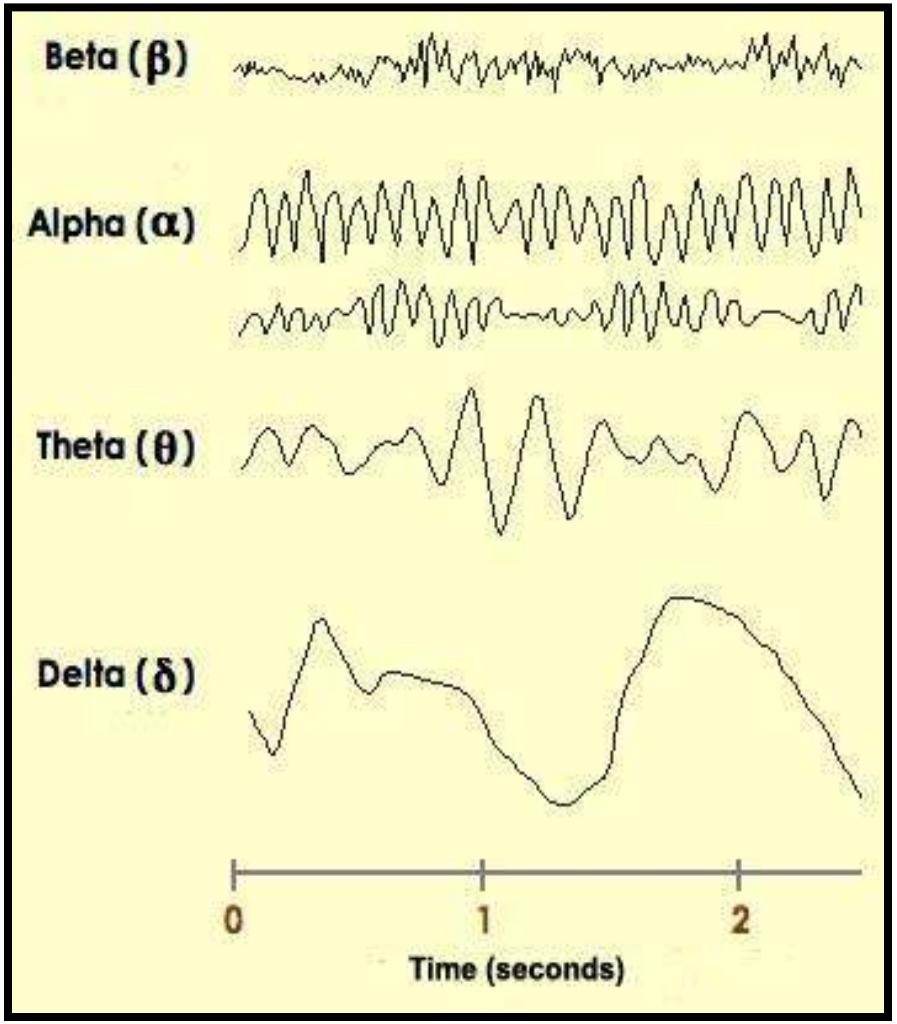
  B.K-complex

  C.Sleep spindles

  D.Delta

Answer: A

- Score arousals during sleep stages N1, N2, N3 or REM if there is an abrupt shift in EEG frequency including:
  - Alpha
  - Theta
  - Frequencies > 16Hz (but not spindles)
- Arousal last 3 seconds with at least 10 seconds of stable sleep preceding the change



High Yield: PLMS vs. PLMD

- PLMS do **not** have a consistent relationship with symptoms such as insomnia or excessive daytime sleepiness or with PSG variables of sleep disruption

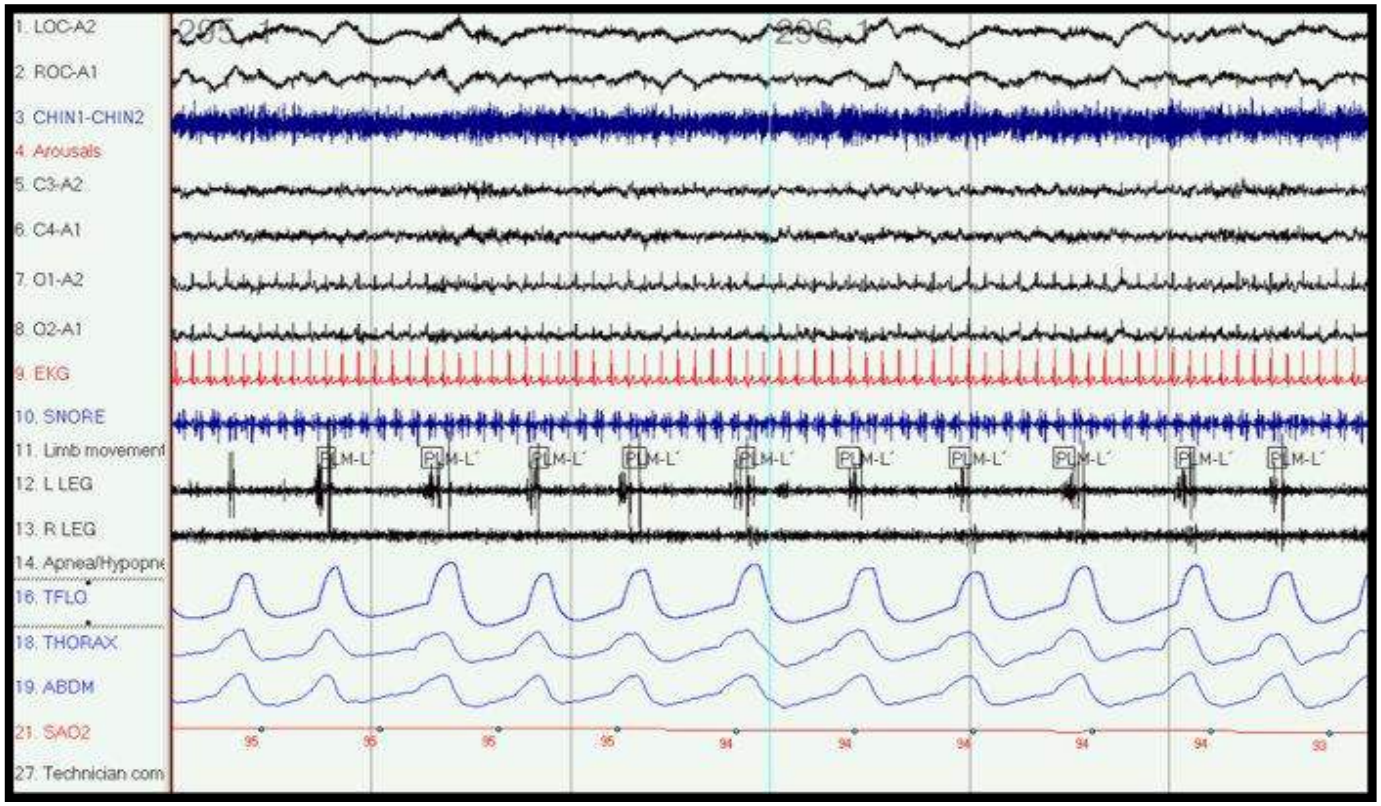
- PLMS are generally considered to be:
  - Age-related phenomenon
  - Response to arousals
  - Byproduct of other disorders

- Occasionally they occur with frequent **EEG arousals** in the absence of other disorders, leading the clinician to suspect that they are **directly** responsible for complaints of excessive sleepiness or insomnia. The term periodic limb movement disorder (**PLMD**) should be restricted to this subgroup

Periodic Limb Movements: Diagnosis

- PSG is required for diagnosis
- The arousal index **(ARI)**
  - Total number of arousals per hour of sleep
  - Generally **lower** than the AHI or RDI because approximately 20% of apneas or hypopneas are **not** accompanied by arousals that are evident on PSG
  - However, the ARI can be greater than the AHI or RDI if arousals occur due to causes other than apneas or hypopneas
- Periodic limb movement index (PLMI) is abnormal if:
  - > 5 in children
  - > 15 in adults

Periodic Limb Movements on Polysomnography



- PSG demonstrates repetitive movements that are:
  - **0.5 to 5** seconds in duration
  - Separated by an interval of **5 to 90 seconds**
  - Series of **4 or more** consecutive movements

Periodic Limb Movement Disorder: Treatment

- Therapy of PLMD is **similar** to that of RLS but not well studied and no FDA approved drugs
- Specific therapy is not indicated for **PLMS**

Beyond the Pearls: Question

- 52 year old woman presents sleep-onset insomnia, which began shortly after the birth of her **3rd child**
- She has a hard time getting comfortable in the bed and frequently **“thrashes”** her legs, which gives her some relief but disturbs her husband. Except for migraines, she is healthy. She takes a lipid-lowering agent and calcium supplements. She rarely drinks alcohol and quit smoking 25 years ago
- Her physical exam is normal. Lab results shows a creatinine 1.2 mg/dL, glucose of 99, total cholesterol of 176, Hgb 13.2, and ferritin 80

Beyond the Pearls: Question

- Which of the following treatments is most appropriate at this time?
  - A. Iron replacement
  - B. Ropinirole
  - C. Clonazepam
  - D. Sertraline
  - E. Pregabalin

Answer: E

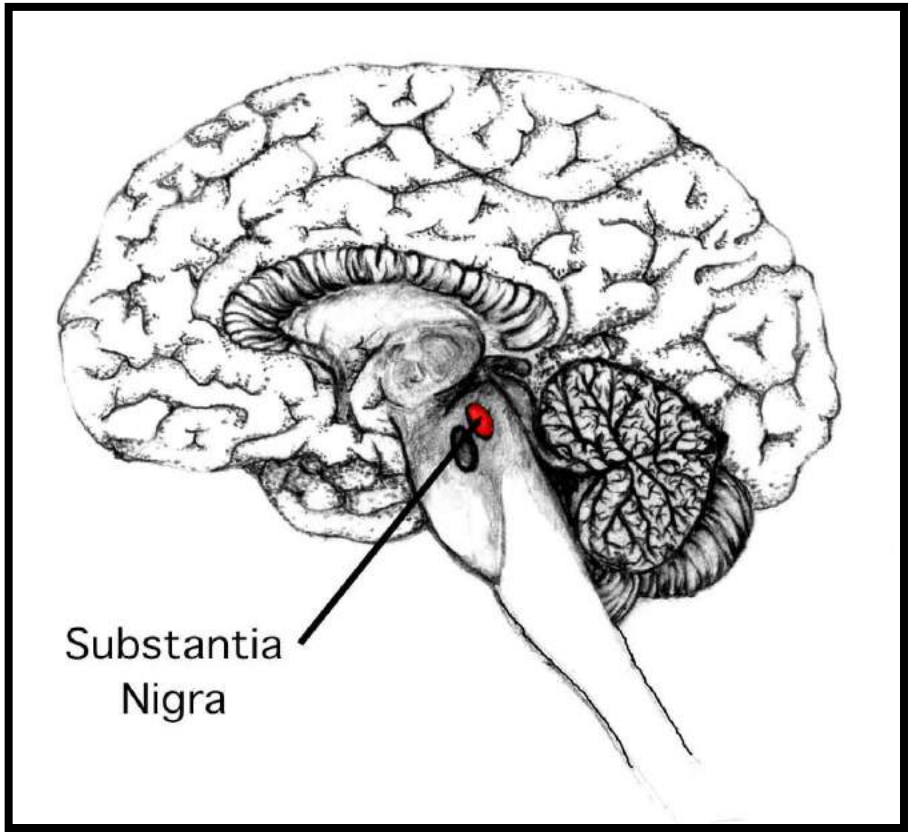
- This women's insomnia is secondary to RLS
- Her "thrashing" gives her temporary relief
- The risk of RLS increases with parity
- Benzodiazepines are not FDA approved for RLS
- New AASM guidelines recommend gabapentinoids as 1st line agents due to no risk for augmentation as seen with dopamine agonist which were historically first line

Beyond the Pearls: Question

- Ekbom, in 1960, noted that RLS occurs commonly in patients with iron deficiency anemia. What is the theoretical association between iron and RLS
  a. Low iron levels interfere with gamma aminobutyric acid (GABA) transmission
  b. Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis
  c. MRI studies show decreased levels of iron in the motor cortex of persons with RLS compared to age-matched control subjects
  d. More recent investigations have failed to show any significant correlation between iron status and RLS

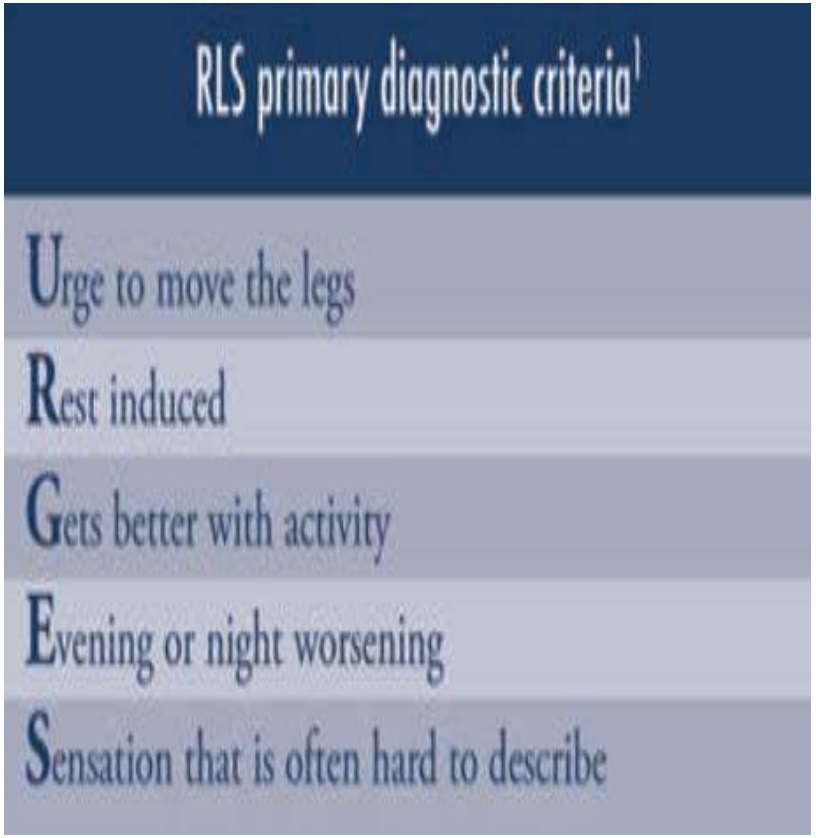
Answer: B

- MRI and autopsy studies have shown a number of iron-related abnormalities in the **substantia nigra** patients with RLS
- Since iron is necessary for the synthesis of **dopamine**, low iron levels can lead to decreased dopamine synthesis in the substantia nigra



Restless Legs Syndrome

- **“Ekbom syndrome”**
  - An urge to move legs
  - Unpleasant sensations in the legs that:
    - Begin or worsen during periods of rest or inactivity
    - Are relieved transiently by movement
    - Are worse, or occur only at night



Terms that patients use to describe the symptoms include: crawling, creeping, pulling, aching, itching, drawing, or stretching, all localized to deep structures rather than the skin

RLS: Diagnosis & Evaluation

- Clinical history
- Laboratory evaluation
- PSG is **not** routinely indicated
- Supportive criteria can help if the diagnosis is unclear:
  - Positive family history in 1st degree relative
  - Periodic limb movements
  - Response to treatment with dopaminergic medications

Primary Restless Legs Syndrome

- The cause of primary RLS is unknown
- Family history consistent with **autosomal dominant** inheritance is present in more than **40%** of patients

Secondary Restless Legs Syndrome

- **Iron deficiency**
  - RLS has been reported in **30-40%** of patients with iron deficiency anemia
- **End-stage renal disease**
  - RLS is common among **hemodialysis patients**, with a reported incidence of approximately 20-30%
- **Pregnancy**
  - The cause of the increased frequency of RLS during pregnancy is **unclear**, but possible causes include iron deficiency, folate deficiency, and hormonal changes
- **Multiple sclerosis**
  - People with MS are more likely to have restless legs syndrome
- **Drugs**
  - A variety of drugs can induce or exacerbate RLS These include nicotine, caffeine, alcohol and several classes of medications including SSRI, SNRI, TCA, anti-psychotics, dopamine-blocking anti-emetics such as **metoclopramide** and anti-histamine meds

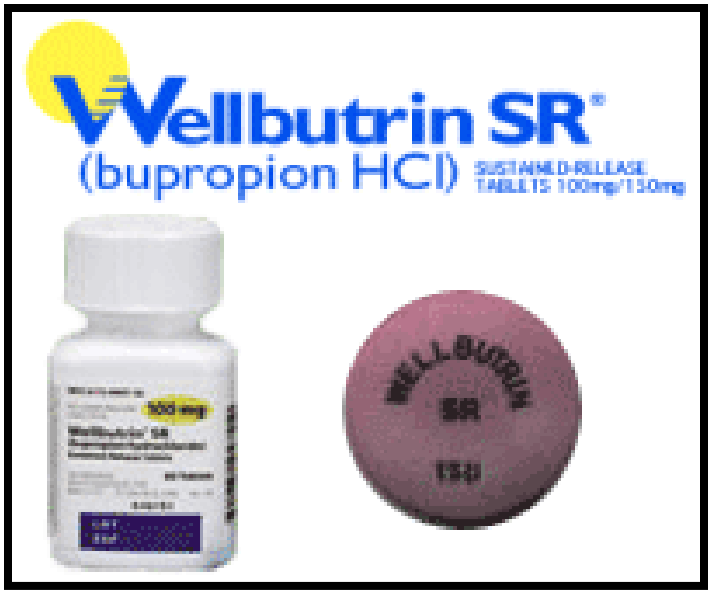
Beyond the Pearls: Question

- 54 year old woman with mild restless legs syndrome (RLS) has developed **depression** and anxiety disorder. Her primary care physician would like your opinion regarding the choice for antidepressant therapy.

- Which of the following antidepressant medications would you
  - A. Sertraline
  - B. Fluoxetine
  - C. Bupropion
  - D. Venlafaxine

Answer: C

- SSRI and SNRI can worsen RLS and increase PLMS
- Small case studies indicate a potential benefit in patients with RLS



RLS Treatment Options

- 1st line: Alpha-2-delta Ca2+ channel ligands (aka gabapentinoids)
  - Gabapentin (Neurontin)
    - 300-3600mg; usually need 900-2400mg for RLS
  - Gabapentin enacarbil (Horizant)
    - Prodrug, not bioequivalent; 600mg fixed dose
    - Only gabapentinoid that is FDA approved (2011)
  - Pregabalin (Lyrica)
    - 50-450mg; 300mg best studied for RLS

Horizant® gabapentin enacarbil extended-release tablets 600 mg·300 mg

LYRICA® PREGABALIN

NEURONTIN® (gabapentin)

RLS Treatment Options

- Dopamine agonists (if alpha-2-delta ligand contraindications)
  - Pramipexole (Mirapex) renally excreted
    - 0.125mg to 0.5mg; max 0.5 to 0.75mg
  - Ropinirole (Requip) hepatic metabolism
    - 0.5mg to 4mg; max 4mg
  - Rotigotine patch (Neupro)
    - 1-3mg; max 3mg
- Opiates for very severe, treatment refractory cases

Neupro® (Rotigotine Transdermal System)

Mirapex® pramipexole dihydrochloride tablets

Requip® (ropinirole HCl)

Dopamine agonist side effects: sleepiness (sleep attacks) & compulsive behaviors. Typical doses much smaller than doses used in Parkinson's disease. All 3 drugs are FDA approved

RLS: Augmentation

- Treatment-induced worsening of RLS related to dopaminergic medication use
  - Highest risk: carbidopa-levodopa, don't use for daily RLS treatment
  - Medium risk: pramipexole, ropinirole (both 8-9% per year)
  - Lowest risk of dopaminergics: rotigotine
- Clues to augmentation: spread to other body parts, symptoms earlier in the day, request for dose increase after chronic stable dosing with symptom control

RLS: Prevention of Augmentation

- Use an alpha-2-delta ligand instead of a dopamine medication to treat RLS first line
- If using dopaminergic medications, use the lowest dose possible
- Avoid iron deficiency; keep ferritin $\geq$ 75 and % saturation $\geq$ 20
  - Most patients start with oral iron
  - Consider IV iron if:
    - Failure or intolerance to PO
    - Impaired absorption of PO
    - RLS symptoms severe enough to need rapid response
    - RCT data strongest for IV ferric carboxymaltose

Beyond the Pearls: Question

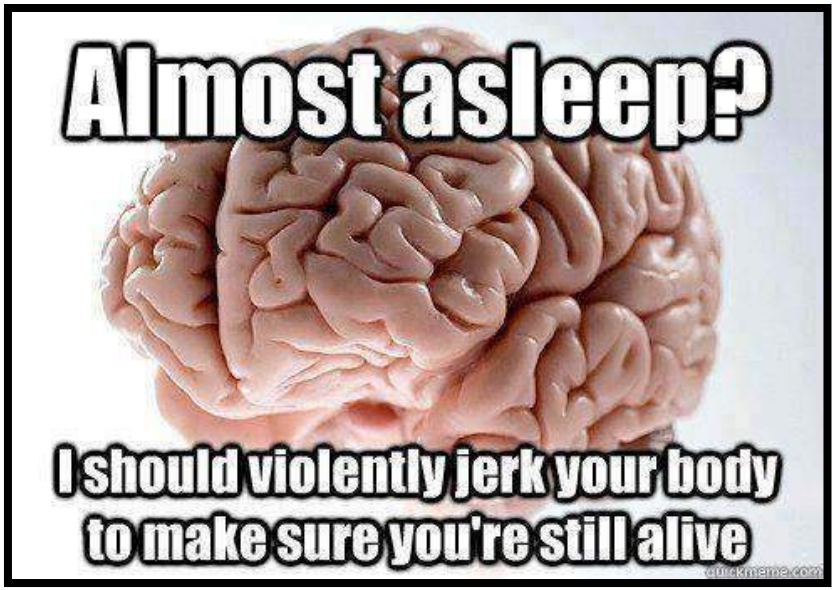
- 20 year old man complains of **sudden** and **brief contractions** of one of his legs when he is trying to fall asleep
- He has been studying for an exam and reports **decreased total sleep time** over the past 2 weeks compared to his usual schedule
- He denies any unpleasant sensation or pain in his legs. He feels otherwise normal and has no other complaints.

Beyond the Pearls: Question

- What is the likely diagnosis ?
  A. Periodic leg movement disorder
  B. Restless legs syndrome
  C. Muscle cramps
  D. Hypnic jerks

Answer: D

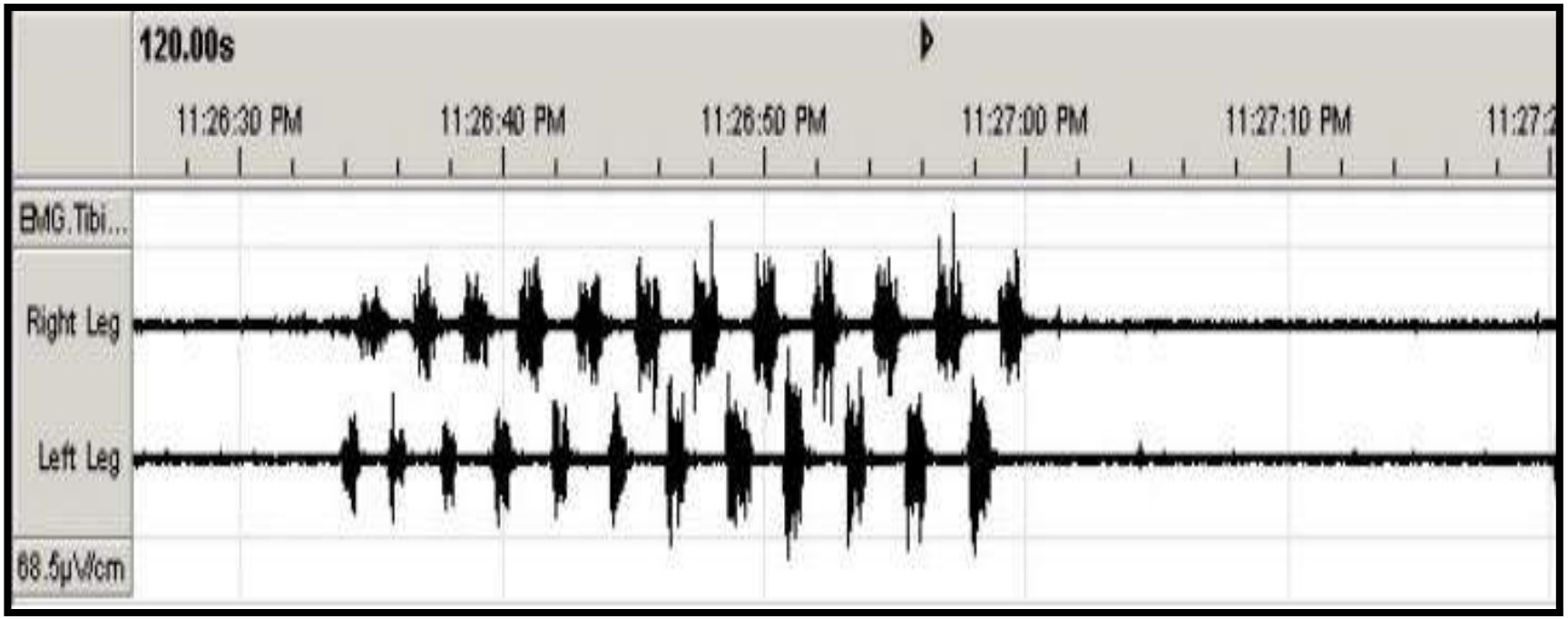
- Hypnic jerks or **sleep starts** occur in up to 70% of the population
  - They consist of sudden and brief contractions of the muscles of the legs or, less commonly, the arms during sleep onset
  - Can precipitate **sleep initiation**
  - Can be associated with an abrupt sensation of falling or vivid dreams
  - Episodes can be aggravated by:
    - Stress
    - Sleep deprivation
    - Excessive caffeine intake



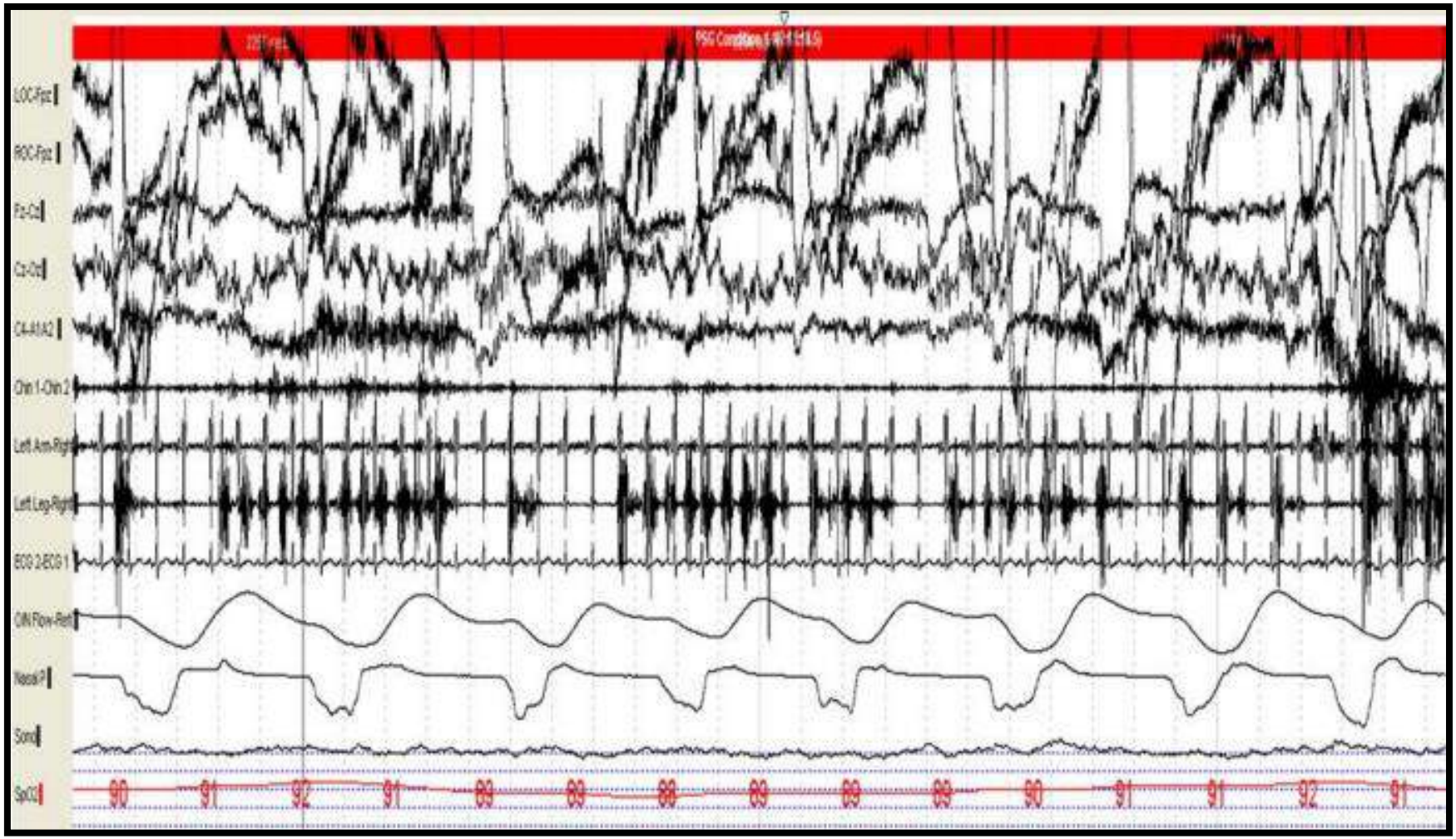
Lesser Known Sleep Related Movements

- Alternating leg movement activity (ALMA)
- Hypnogogic foot tremor
- Propriospinal myoclonus
- Excessive fragmentary myoclonus

Alternating Leg Movement Activity (ALMA)



Hypnogogic foot tremor (HFT)



ALMA & HFT: Clinical Features

- Possibly both variants of the same phenomenon of rhythmic movement disorder
- Usually a benign PSG finding without clinical manifestations
- No obvious movements

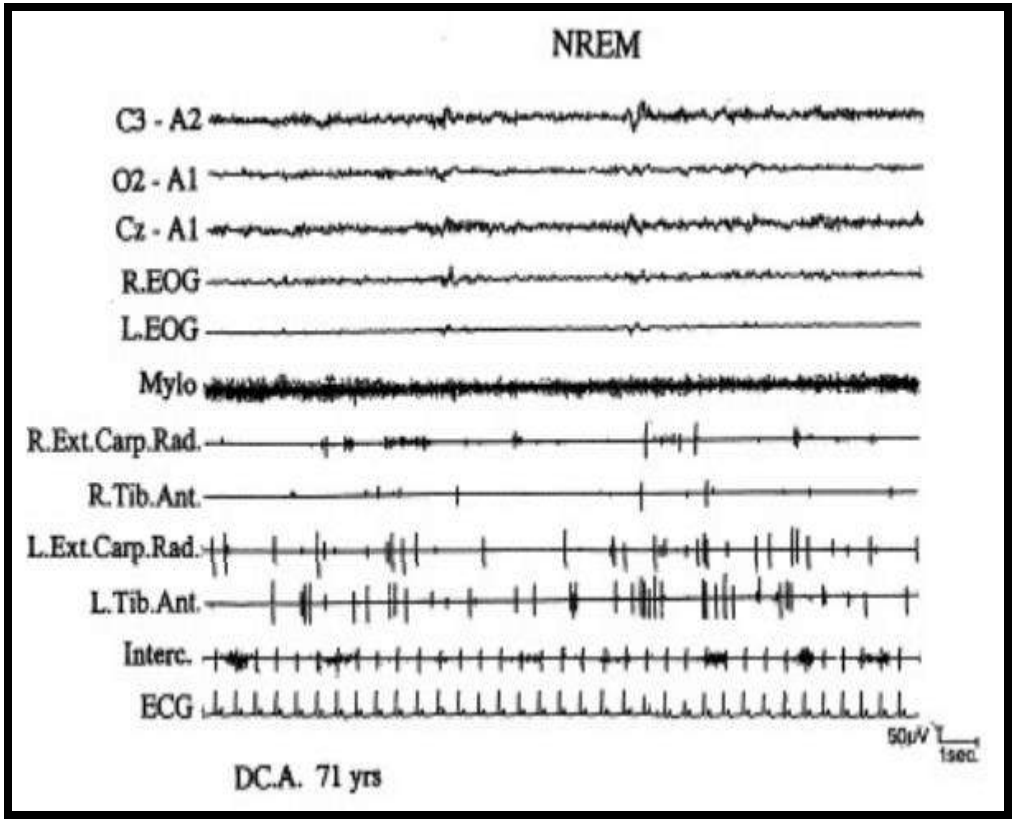
Propriospinal Myoclonus of Sleep Onset

- Sudden jerks of the abdomen, trunk, neck
- Occur during drowsiness, relaxed wakefulness, when trying to fall asleep
- Resolve with either mental activation or stable sleep
- Interfere with sleep onset
- Not better explained by another condition

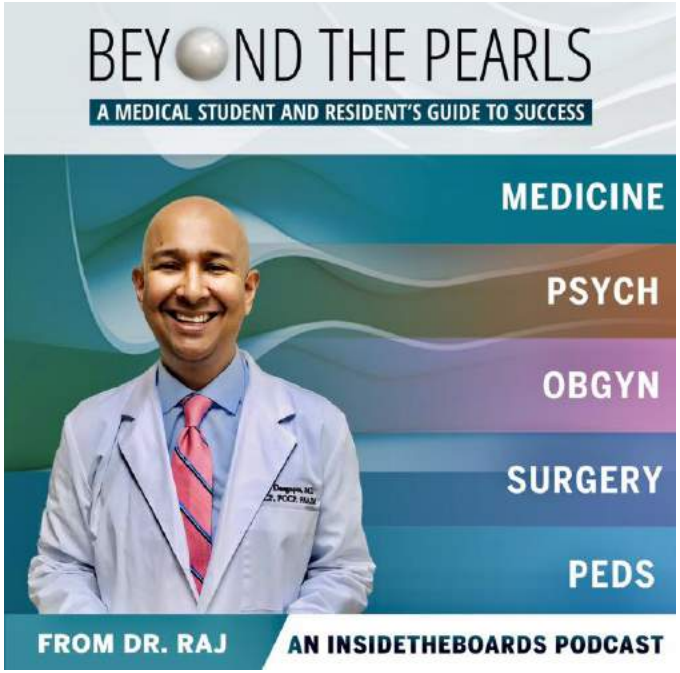
- Most commonly **"jackknife"** flexion of trunk
- Typically starts in axial musculature and propagates up/down
- Can be single or cluster of a few movements
- Unclear relationship to daytime propriospinal myoclonus
- Up to 20% with daytime PSM have spinal cord pathology therefore may consider imaging for cases of sleep-onset PSM
- Rare, probably more common in men, not reported in kids
- Treatment: clonazepam? Anti-epileptics with anti-myoclonus properties?

Excessive Fragmentary Myoclonus

- PSG finding rather than clinical diagnosis/syndrome
- Small twitches may be visible of the mouth, toes and fingers but no large joint movements



Thank You



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