Basics of Sleep Medicine: From A to ZZZZ's

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IM Sleep Lecture
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Objectives

- Normal Sleep
- Physiology of sleep (just briefly)
- Sleep stages
- Introduction to the PSG
- Sleep Disorders
  - Insomnia, OSA, Narcolepsy

Basic Sleep Concepts

- Drive for sleep exceeds the drive for food and water, and freedom from pain
- Sleep deprivation, total or chronic partial, may have serious consequences
  - death in experimental animals
  - impaired perception and microsleeps in humans
- Sleep debt must eventually be repaid

Sleep-Wake Cycle Regulation

- Two related key processes promote sleepiness or mental arousal at different times
  - Homeostatic drive
  - Circadian rhythm
- Together, these determine when sleep can occur under both normal and abnormal circumstances

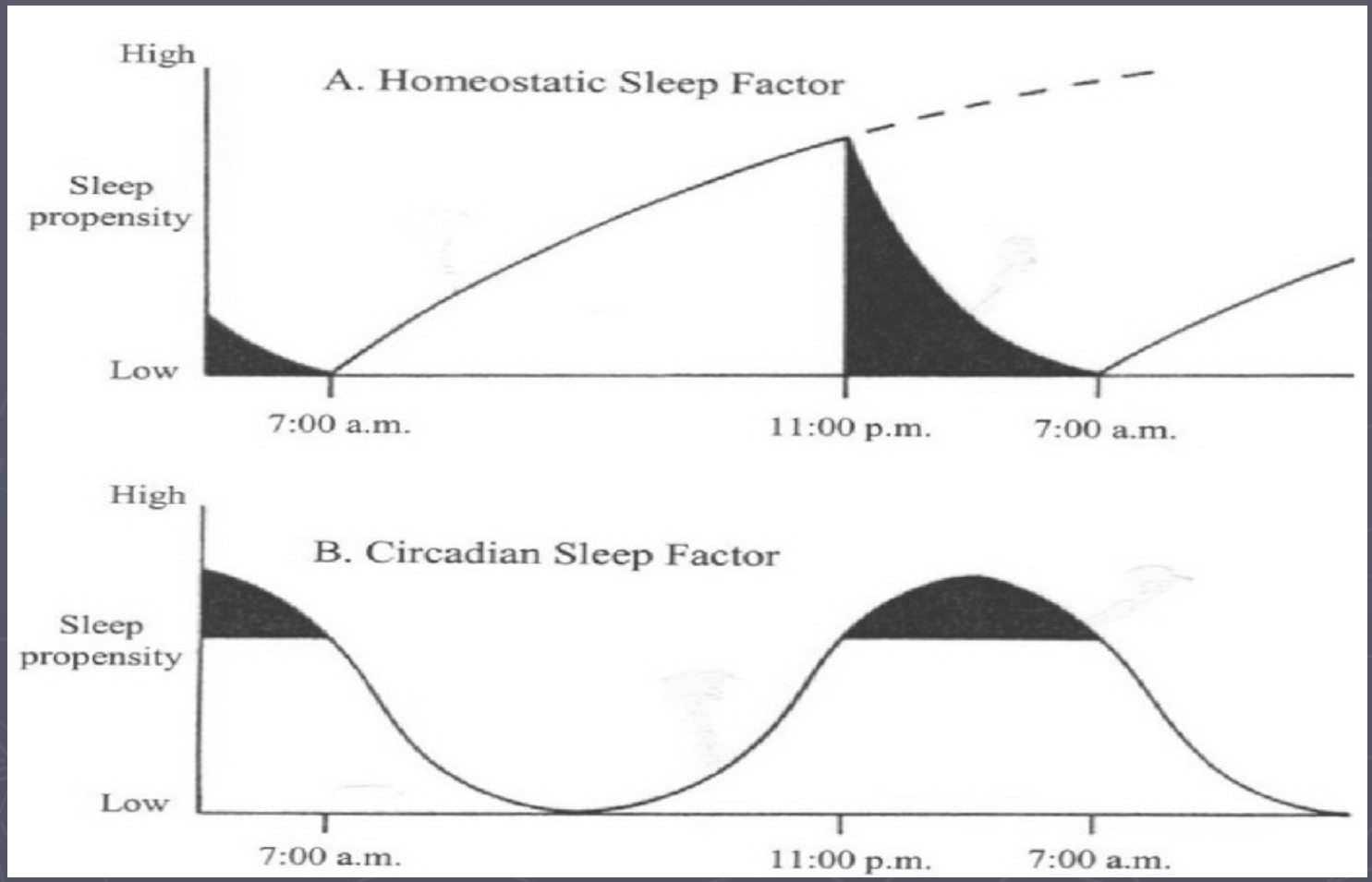
Homeostatic drive

- Has a ratio of approximately 1/3 sleep and 2/3 waking
- Sleep deprivation, acute or chronic, increases the homeostatic sleep drive and therefore sleepiness
- Hypothetically, the homeostatic sleep drive could be satisfied by sleep at any hour

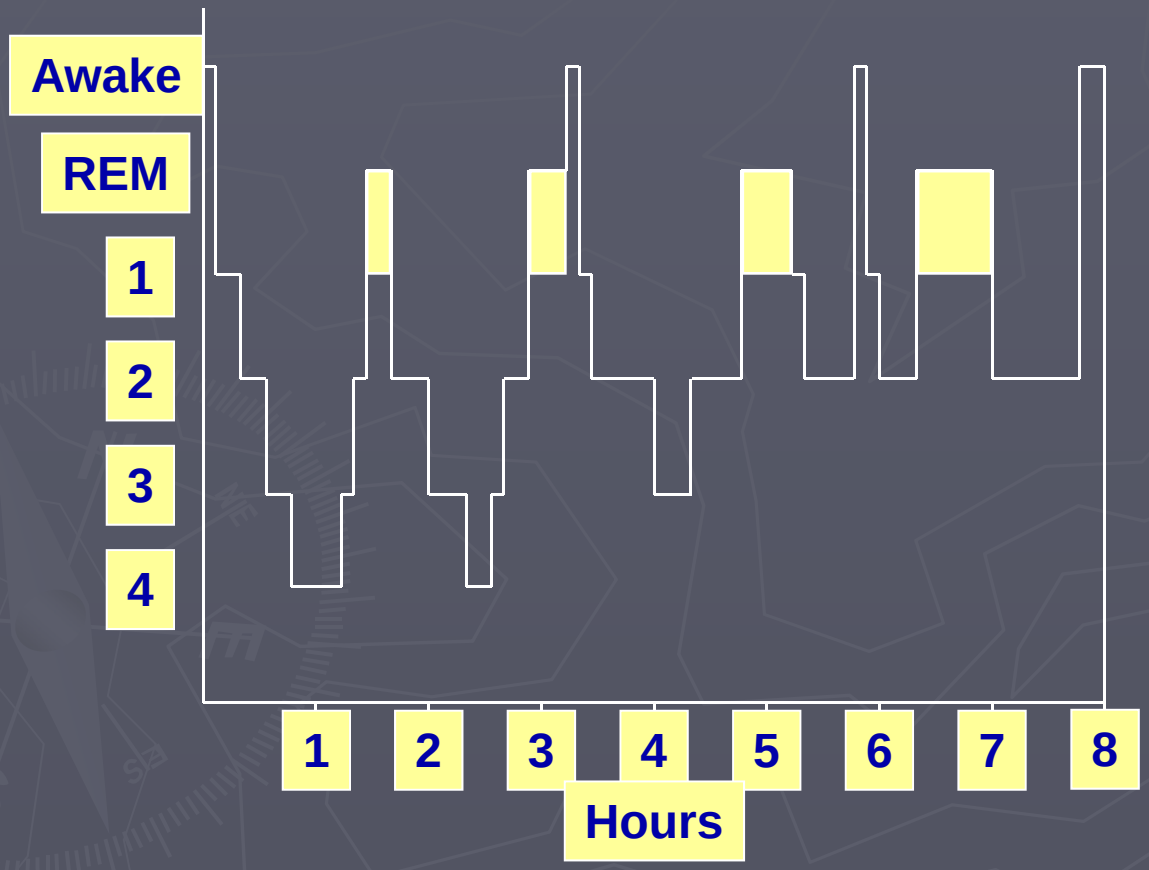
Circadian rhythm

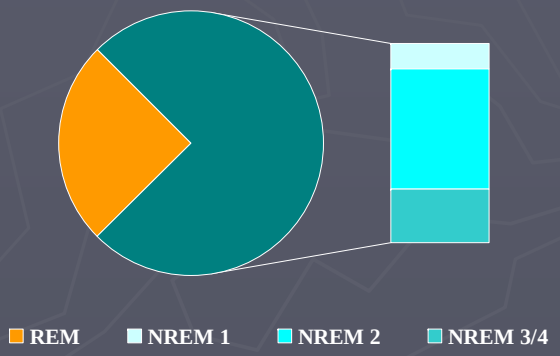
- Entrained and synchronized
- Timing of sleepiness promoted by the endogenous circadian clock
- Facilitates the rhythmic cycle of sleep at the same approximate nighttime hours (each day)
- Reinforced by the daily photoperiod, and possibly influenced by other light exposure

Sleep/Wake Cycle



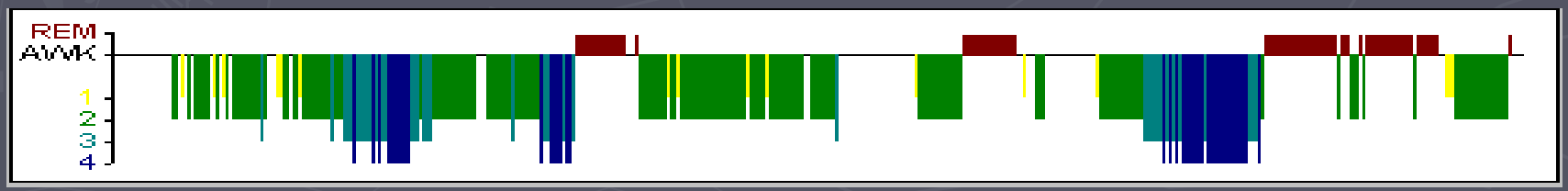
Normal Sleep





Normal Sleep Architecture

- Approximately 90 minute cycle including NREM and REM
- Slow wave dominates first third of night
- REM sleep dominates last third of night (early morning hours)
- REM sleep: 20-25% total sleep time
  - Can see REM-rebound with sleep deprivation, abrupt withdrawal of REM suppressants



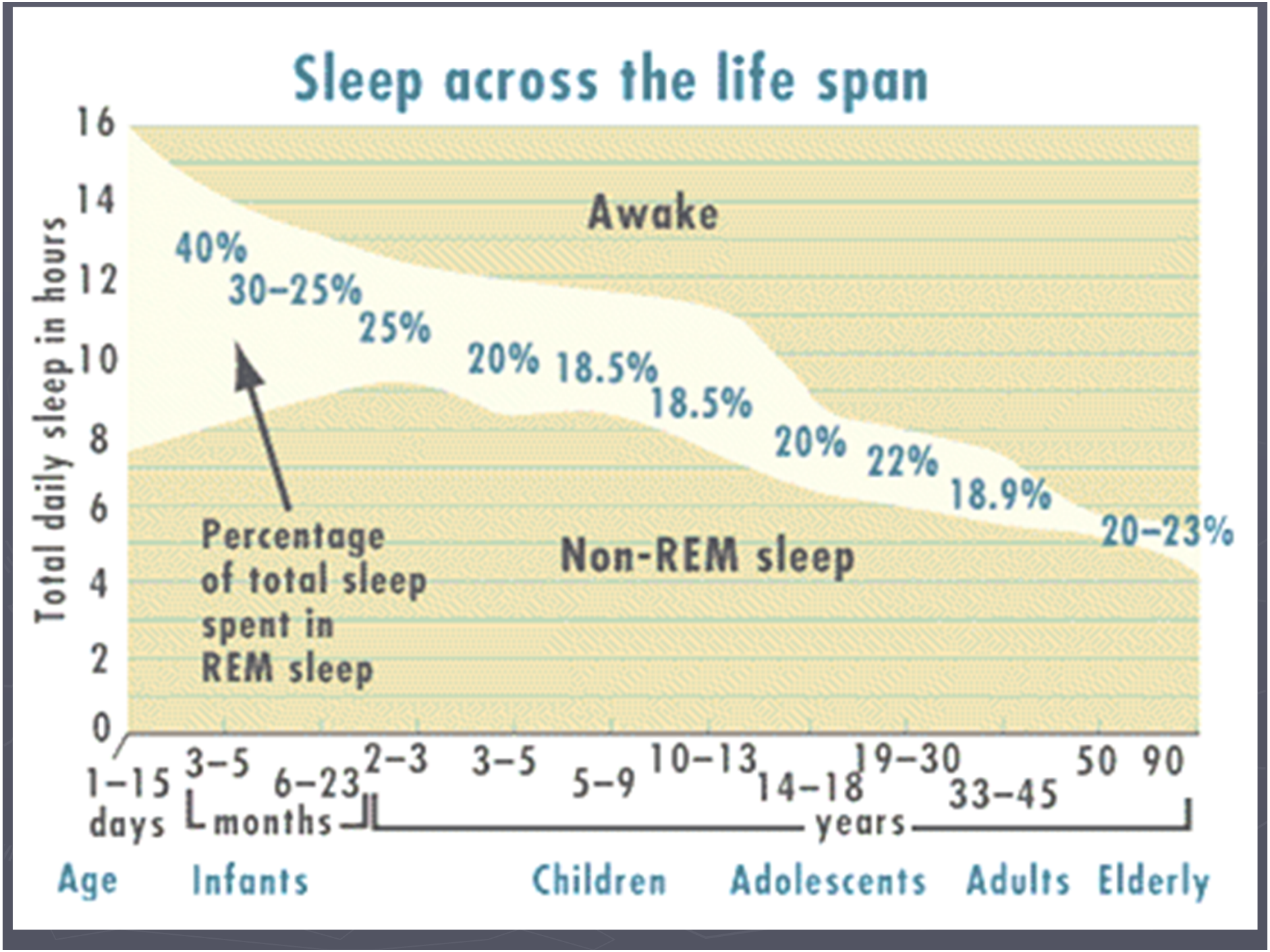

Sleep across the life span
Total daily sleep in hours
16
14
12
10
8
6
4
2
0
Awake
Non-REM sleep
40%
30–25%
25%
20%
18.5%
18.5%
20%
22%
18.9%
20–23%
Percentage of total sleep spent in REM sleep
1–15 days
3–5 months
6–23 months
2–3
3–5
5–9
10–13
14–18
19–30
33–45
50
90
years
Age
Infants
Children
Adolescents
Adults
Elderly

Table 9.1 Brain Structures for Arousal and Sleep

Structure	Neurotransmitter(s) It Releases	Effects on Behavior
Pontomesencephalon	Acetylcholine, glutamate	Increases cortical arousal
Locus coeruleus	Norepinephrine	Increases information storage during wakefulness; suppresses REM sleep
Basal forebrain		
Excitatory cells	Acetylcholine	Excites thalamus and cortex; increases learning, attention; shifts sleep from NREM to REM
Inhibitory cells	GABA	Inhibits thalamus and cortex
Hypothalamus (parts)	Histamine	Increases arousal
	Orexin	Maintains wakefulness
Dorsal raphe and pons	Serotonin	Interrupts REM sleep

Introduction to the PSG

Types of sleep studies

- **Diagnostic** – overnight study
  - In-lab (OSA, PLMD/RLS, RBD, parasomnias, sz)
  - Home sleep study (just for OSA)
- **CPAP titration** - Once a patient is identified as having sleep apnea another study is performed in which the technician adjusts the CPAP level during the test/mask fitting
- **Split Night** - Combines a diagnostic study and a CPAP titration study into one night. The patient is diagnosed during the first half of the night (AHI >40); CPAP applied the second half if required by protocol
- **MSLT** - Multiple Sleep Latency Test
- **MWT** – Maintenance of Wakefulness Test

Indications for PSG

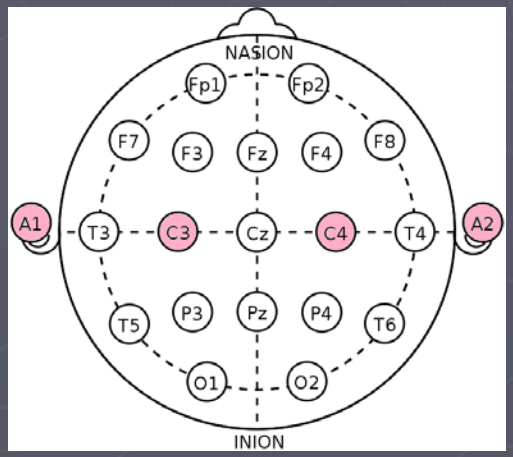
- Excessive daytime sleepiness (EDS)
- Unexplained behavioral events in sleep
- Insomnia or unexplained awakenings
- Sleep-related breathing disturbances
- Effect of treatment for sleep disorders

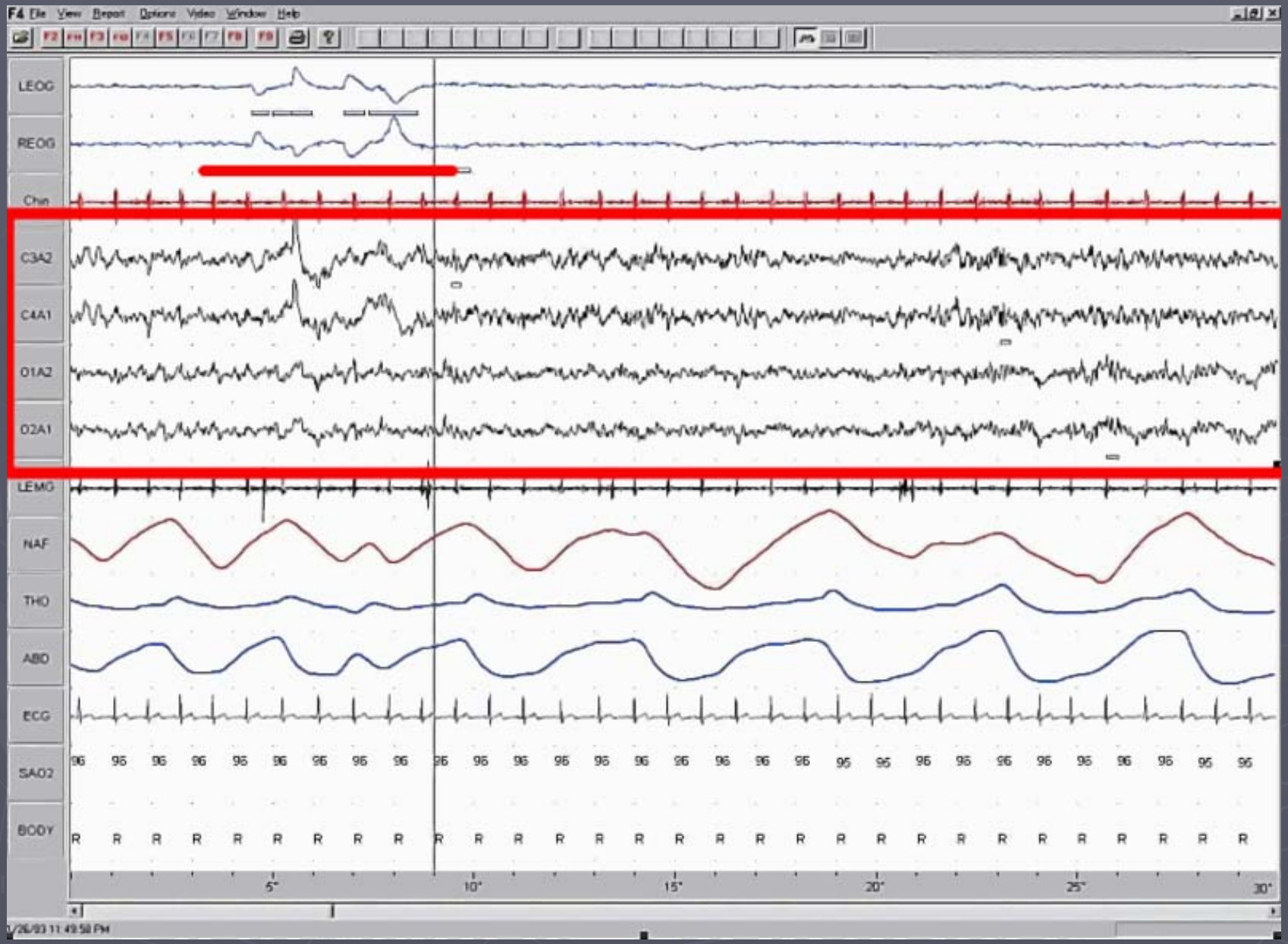
PSG Parameters

- EEG
- EOG (electro-oculogram)
- Chin EMG
- Leg EMG
- ECG
- Airflow
- Effort
- Oxygen
- Body position

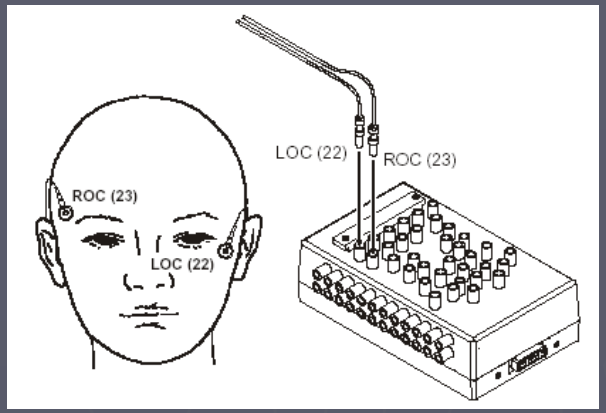
EEG

- Minimum of 3 EEG derivations required to sample from frontal, central and occipital regions
- Recommended derivations
  - F4-M1
  - C4-M1
  - O2-M1
  - F3, C3, O1 and M2 placed for backup
- Alternative derivations
  - Fz-Cz
  - Cz-Oz
  - C4-M1
  - Fpz, C3, O1 and M2 placed for backup
- Additional derivations required for evaluation of seizures
  - International 10-20 electrode placement
- Paper speed: 10 mm/sec (30 sec epochs)

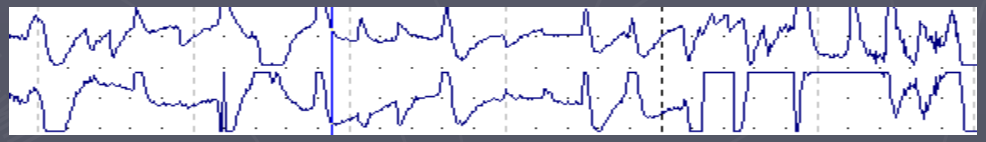



F4 File View Report Options Video Window Help
LEOG
REOG
Chin
C3A2
C4A1
O1A2
O2A1
LEMG
NAF
THO
ABD
ECG
SAO2
BODY
5'
10'
15'
20'
25'
30'

EOG

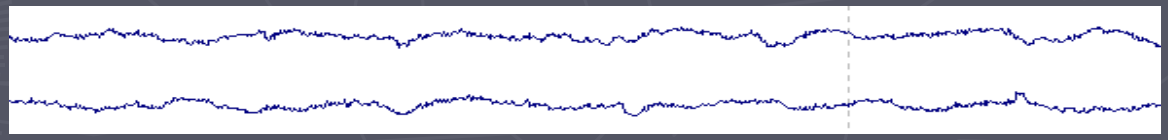


- EOG records voltage changes caused by EM
- Recommended derivations:
  - E1-M2 (E1 placed 1 cm *below* LOC)
  - E2-M2 (E2 placed 1 cm *above* ROC)
- Alternative derivations:
  - E1-FPz (E1 placed 1 cm below/lateral to LOC)
  - E2-FPz (E2 placed 1 cm above/lateral to ROC)
- Wake:



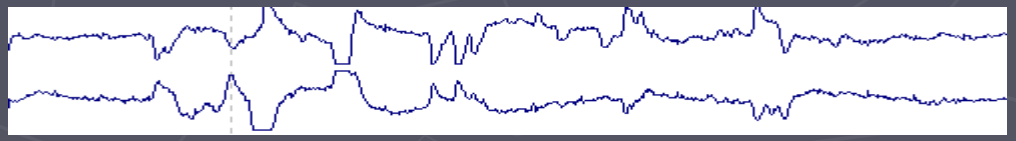
random, high amplitude

- Stage 1:



slow rolling, conjugate, regular

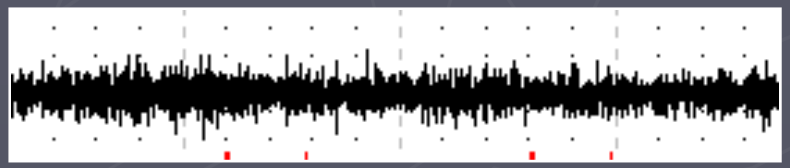
- REM:



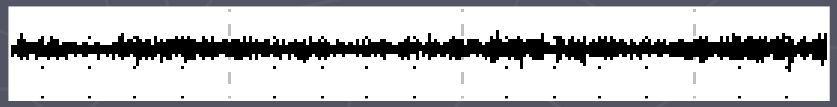
conjugate, irregular, sharply peaked EM

EMG

- Recorded as the potential between two surface electrodes placed several centimeters apart
- Typically, the chin (submental) muscle is used because it exhibits large differences during sleep, aiding in the identification of stages
- Wake - high activity



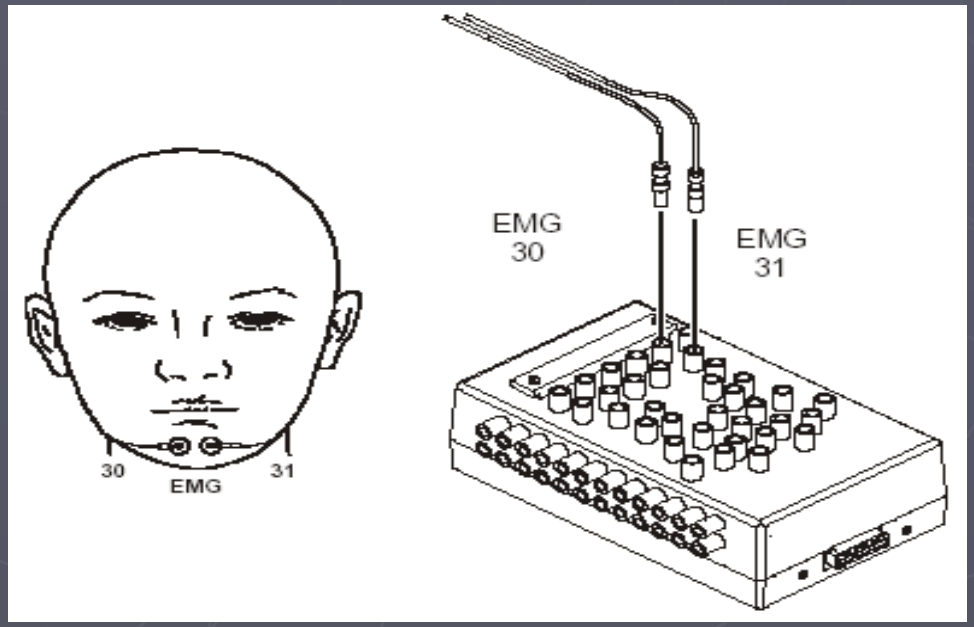
- Sleep - lower activity



- REM sleep - paralysis of skeletal muscles

EMG Placement

- Chin Electrode placement (2 required)
  - Midline 1 cm above inferior edge of mandible (optional)
  - 2 cm below inferior edge of mandible to right of midline
  - 2 cm below inferior edge of mandible to left of midline

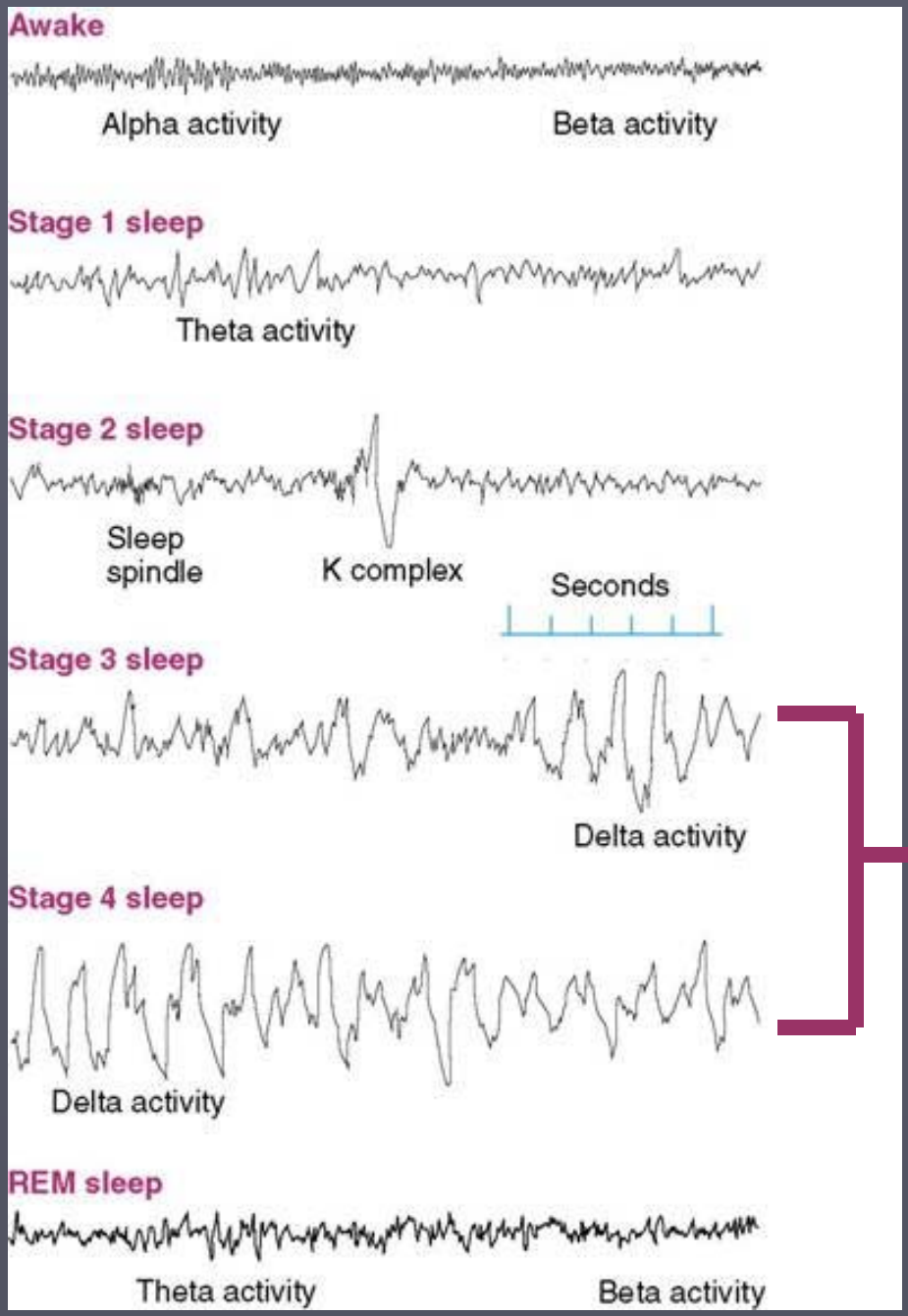


REM vs. NREM Sleep

- Non-REM
  - Physical restoration
  - Driven by homeostatic drive
  - Quiet brain, active body
- REM
  - Mental restoration/memory
  - Driven by circadian rhythm
  - Active brain, quiet body

REM vs. NREM Sleep

Physiologic Variable	NREM	REM
Heart rate	Regular	Irregular
Respiratory rate	Regular	Irregular
Blood pressure	Regular	Variable
Skeletal muscle tone	Preserved	Absent
Brain 0_2 consumption	Reduced	Increased
Ventilatory response	Normal	Reduced
Temperature	Normal	Poikilothermic

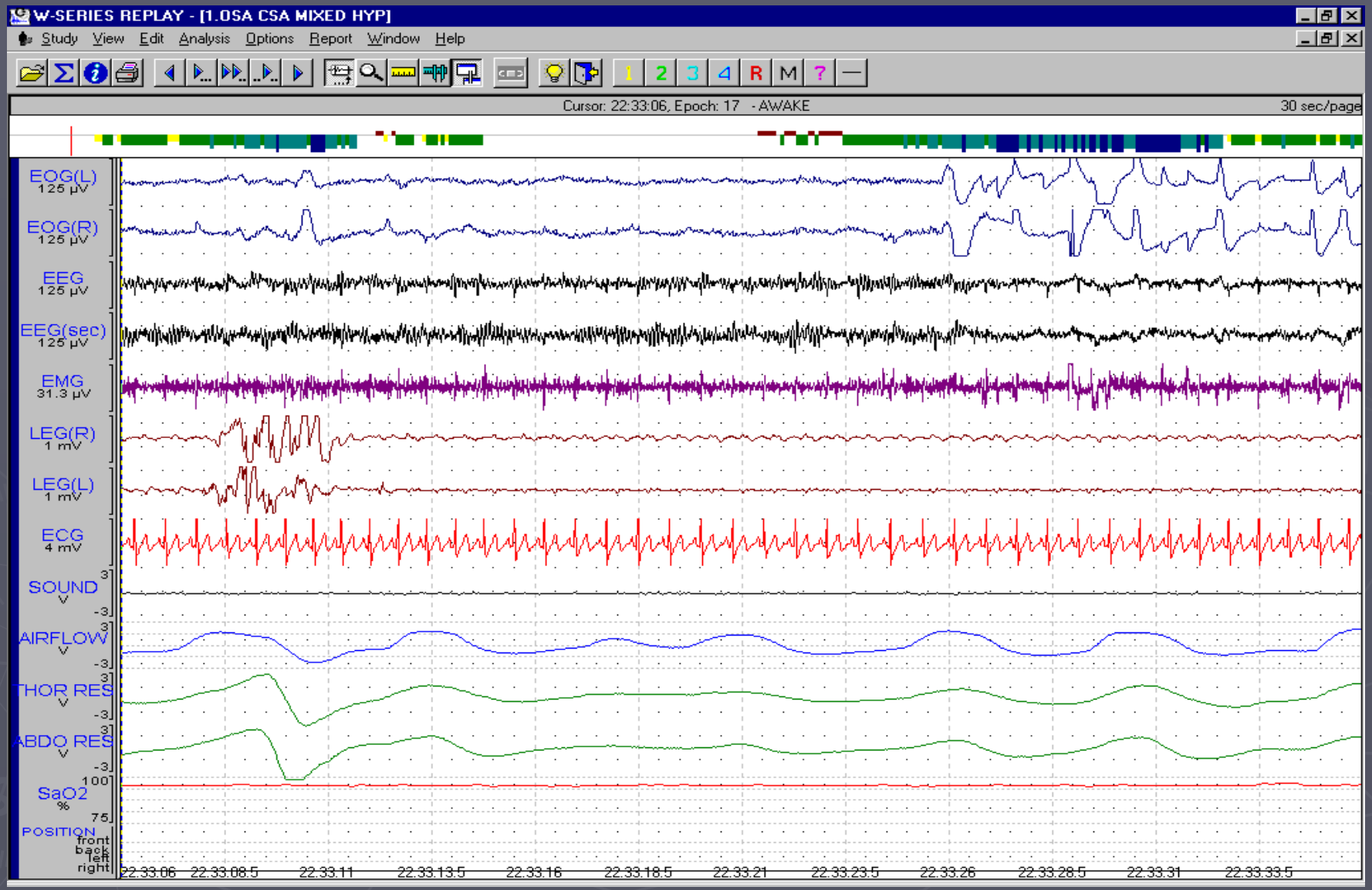


Overview of sleep stages

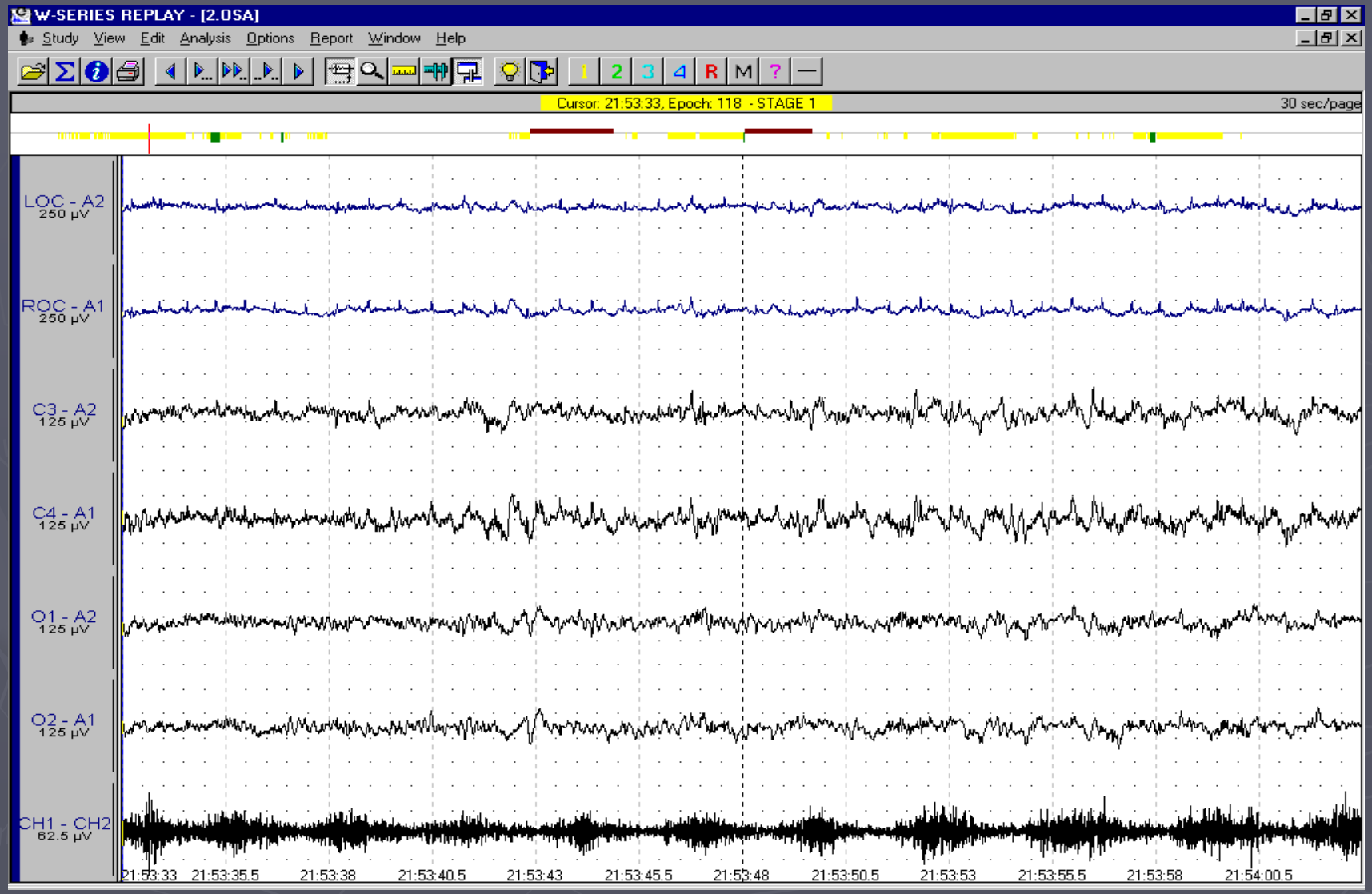
Combined to become N3

2007 AASM scoring guidelines

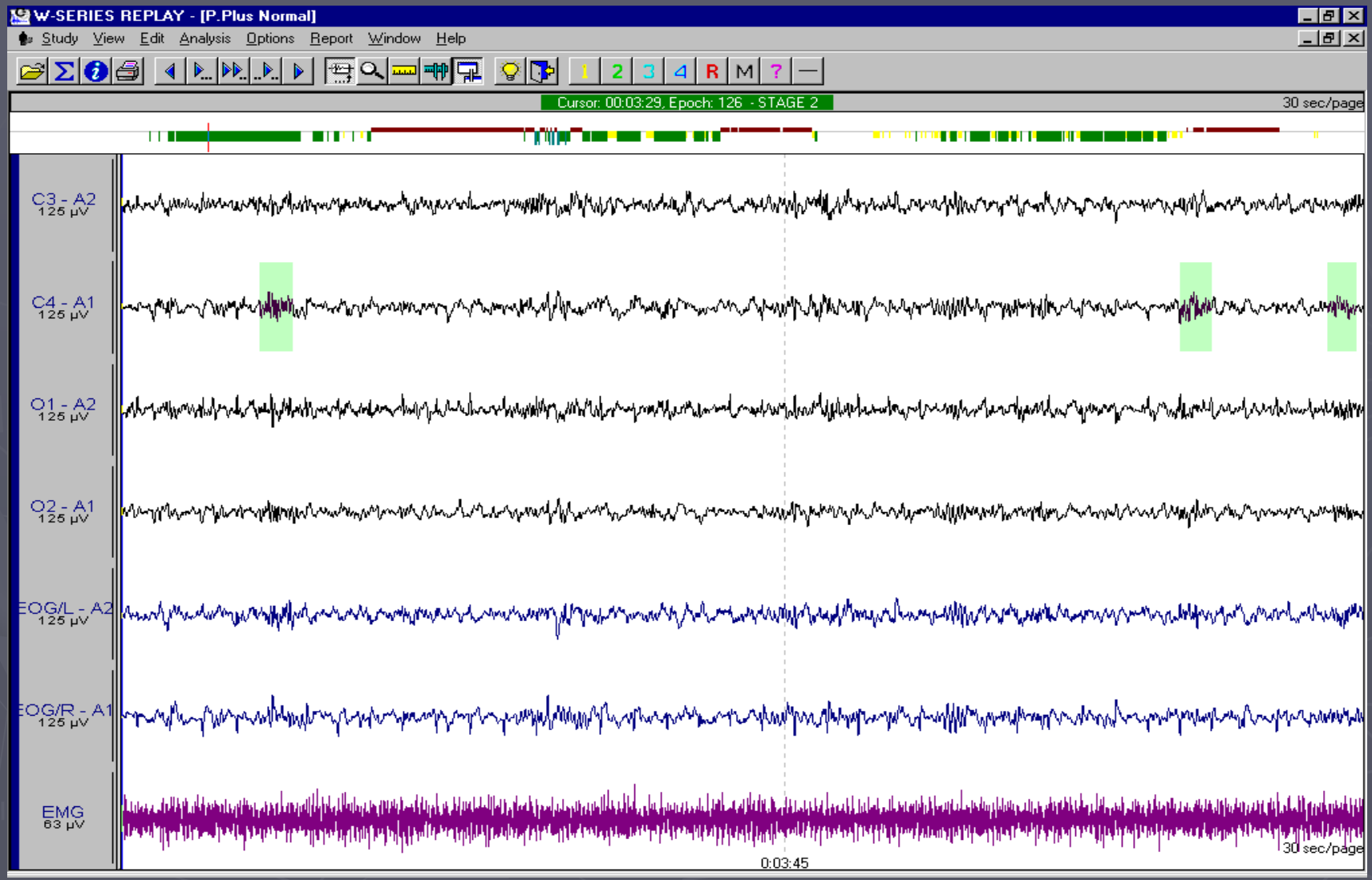
Stage W


W-SERIES REPLAY - [1.OSA CSA MIXED HYP]
Study View Edit Analysis Options Report Window Help
Cursor: 22:33:06, Epoch: 17 - AWAKE
30 sec/page
EOG(L) 125 µV
EOG(R) 125 µV
EEG 125 µV
EEG(sec) 125 µV
EMG 31.3 µV
LEG(R) 1 mV
LEG(L) 1 mV
ECG 4 mV
SOUND
AIRFLOW
THOR RES
ABDO RES
SaO2 %
POSITION front back left right
22:33:06 22:33:08.5 22:33:11 22:33:13.5 22:33:16 22:33:18.5 22:33:21 22:33:23.5 22:33:26 22:33:28.5 22:33:31 22:33:33.5

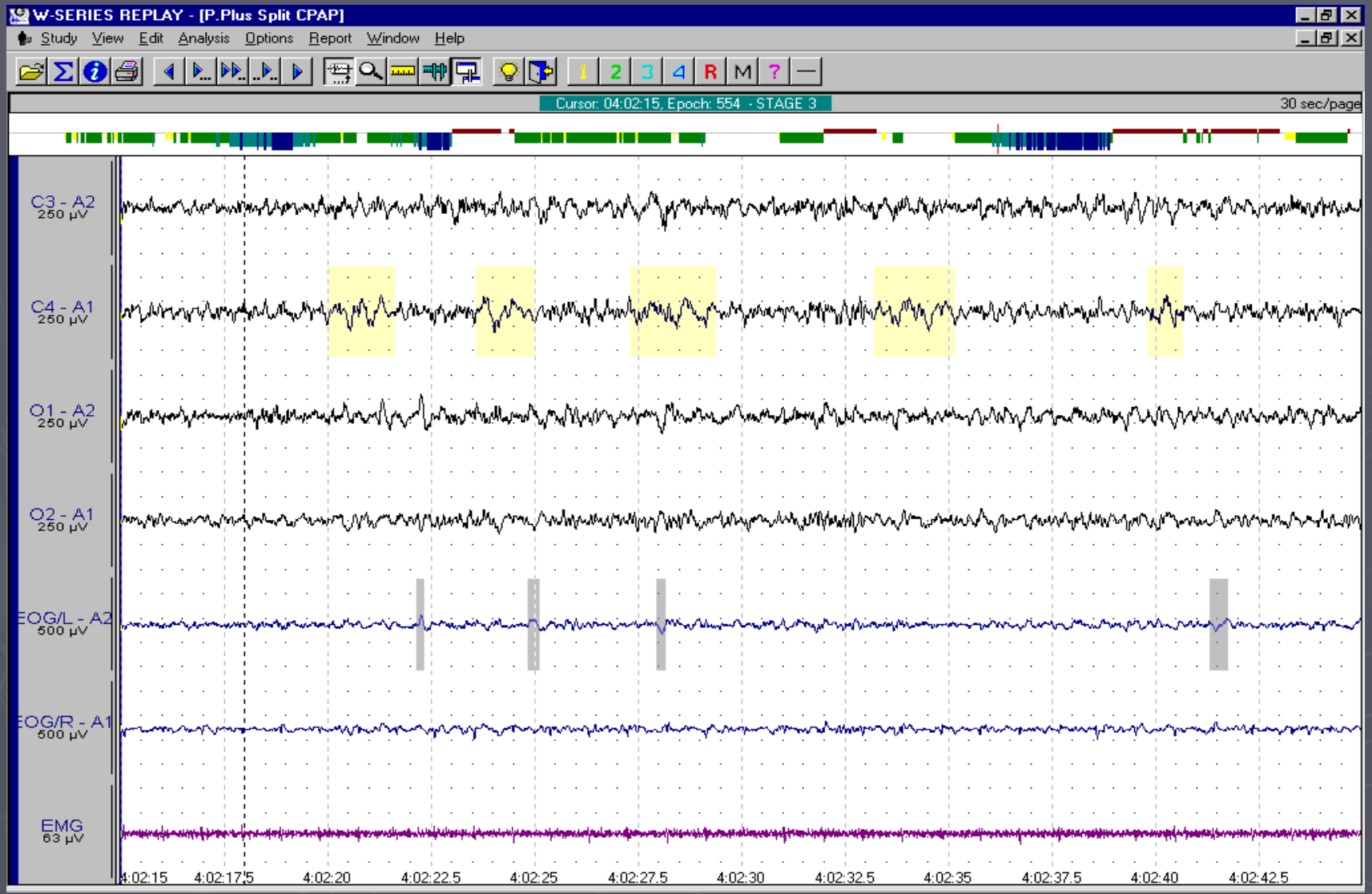
Stage 1


W-SERIES REPLAY - [2.OSA]
Study View Edit Analysis Options Report Window Help
Cursor: 21:53:33, Epoch: 118 - STAGE 1
30 sec/page
LOC - A2
250 µV
ROC - A1
250 µV
C3 - A2
125 µV
C4 - A1
125 µV
O1 - A2
125 µV
O2 - A1
125 µV
CH1 - CH2
62.5 µV
21:53:33
21:53:35.5
21:53:38
21:53:40.5
21:53:43
21:53:45.5
21:53:48
21:53:50.5
21:53:53
21:53:55.5
21:53:58
21:54:00.5

Stage 2

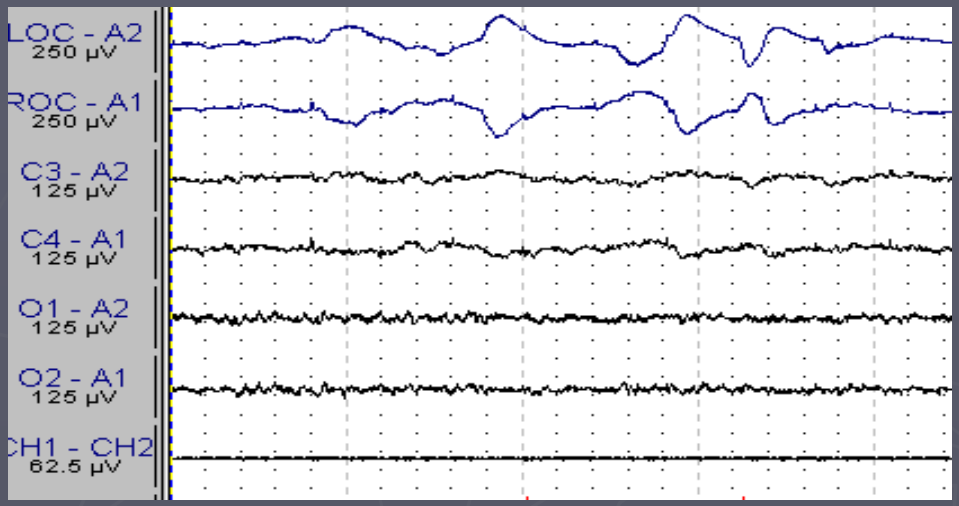

W-SERIES REPLAY - [P.Plus Normal]
Study View Edit Analysis Options Report Window Help
Cursor: 00:03:29, Epoch: 126 - STAGE 2
30 sec/page
C3 - A2
125 µV
C4 - A1
125 µV
O1 - A2
125 µV
O2 - A1
125 µV
EOG/L - A2
125 µV
EOG/R - A1
125 µV
EMG
63 µV
30 sec/page
0:03:45

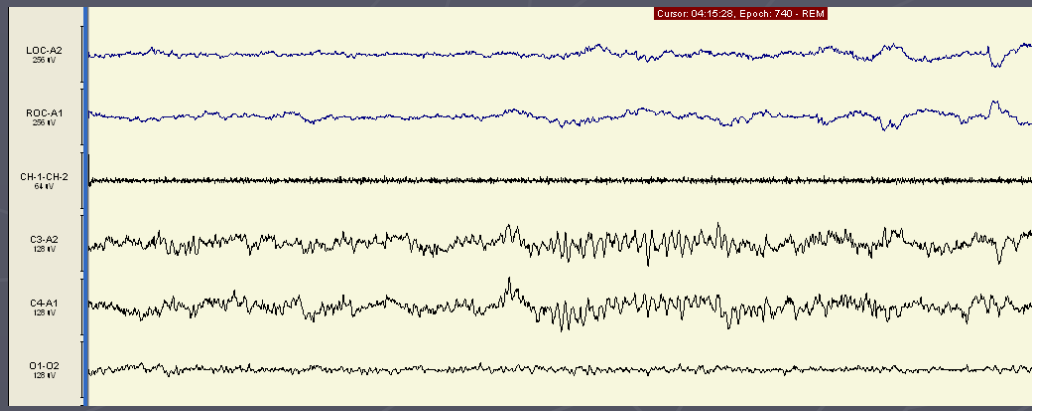
Stage 3


W-SERIES REPLAY - [P.Plus Split CPAP]
Study View Edit Analysis Options Report Window Help
Cursor: 04:02:15, Epoch: 554 - STAGE 3
30 sec/page
C3 - A2
250 µV
C4 - A1
250 µV
O1 - A2
250 µV
O2 - A1
250 µV
EOG/L - A2
500 µV
EOG/R - A1
500 µV
EMG
63 µV
4:02:15
4:02:17.5
4:02:20
4:02:22.5
4:02:25
4:02:27.5
4:02:30
4:02:32.5
4:02:35
4:02:37.5
4:02:40
4:02:42.5

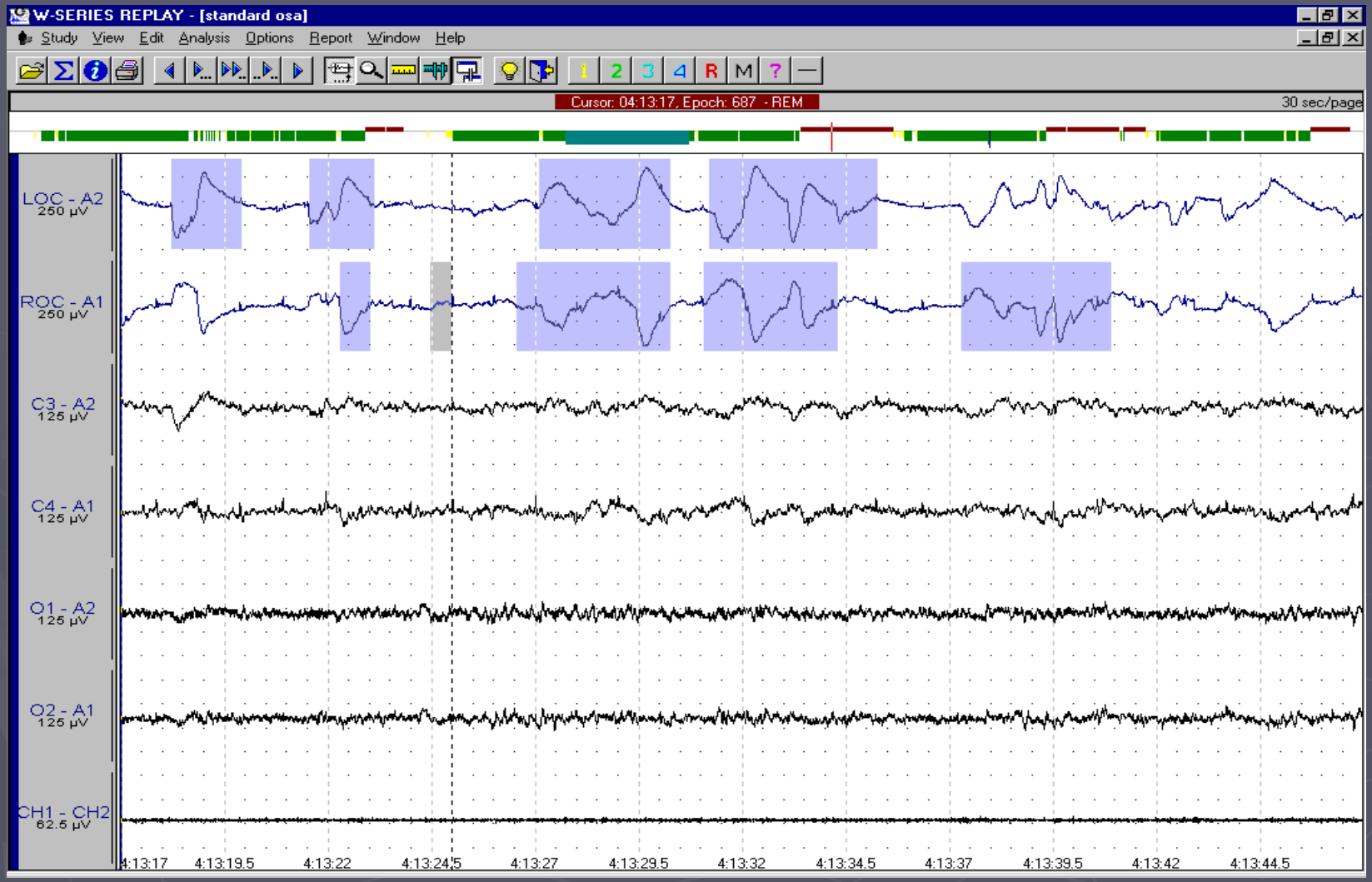
Stage R (REM)

- Low amplitude, mixed frequency EEG
- Low chin EMG tone (baseline no higher than in any other stage and usually the lowest of the recording)
- Rapid eye movements
- Sawtooth waves and transient muscle activity are strongly supportive of Stage R but not required
  - Sawtooth waves: trains of sharply contoured or triangular, often serrated, 2-6 Hz waves maximal over central regions and often preceded by burst of REMs
  - Transient muscle activity: short, irregular bursts of EMG activity usually with duration <0.25 sec, superimposed on low EMG tone in chin or anterior tibialis, EEG or EOG derivations and maximally associated with REMs





Stage REM Sleep



Respiratory Variables

- Respiratory effort (thoracic and abdominal belts)
- Airflow (thermistor, thermocouple, nasal pressure, ETCO2)
- SpO2 (pulse oximetry)
- Snoring microphone
- Optional signals
  - ETCO2
  - tcCO2

Airflow methods

- **Qualitative**
  - Thermal sensors
    - Measure temperature changes
    - Breathe in cool air, breathe out warm air; measures the difference in temperature, but can underestimate
    - Measures apneas
  - ET-CO2 detectors
    - End tidal CO2 monitor
    - Not accurate for mouth breathers, nasal congestion
  - Nasal pressure
    - More sensitive, detects hypopneas

- **Quantitative**
  - Pneumotachography
    - Gold standard
    - Place a face mask over pt's face and measure tidal volume, uncomfortable so not commonly used

Effort methods

- Qualitative
  - Piezo-electric belts (crystals embedded in belt that sense movement)
  - Intercostal EMG
- Semi-quantitative
  - Respiratory inductive plethysmography (RIP): can give tidal volume, but not very accurately
- Gold standard: Esophageal pressure (balloon inserted into lower esophagus)

Other Variables Typically Recorded

- ECG
- Leg movement: EMG
- Video
- Body position

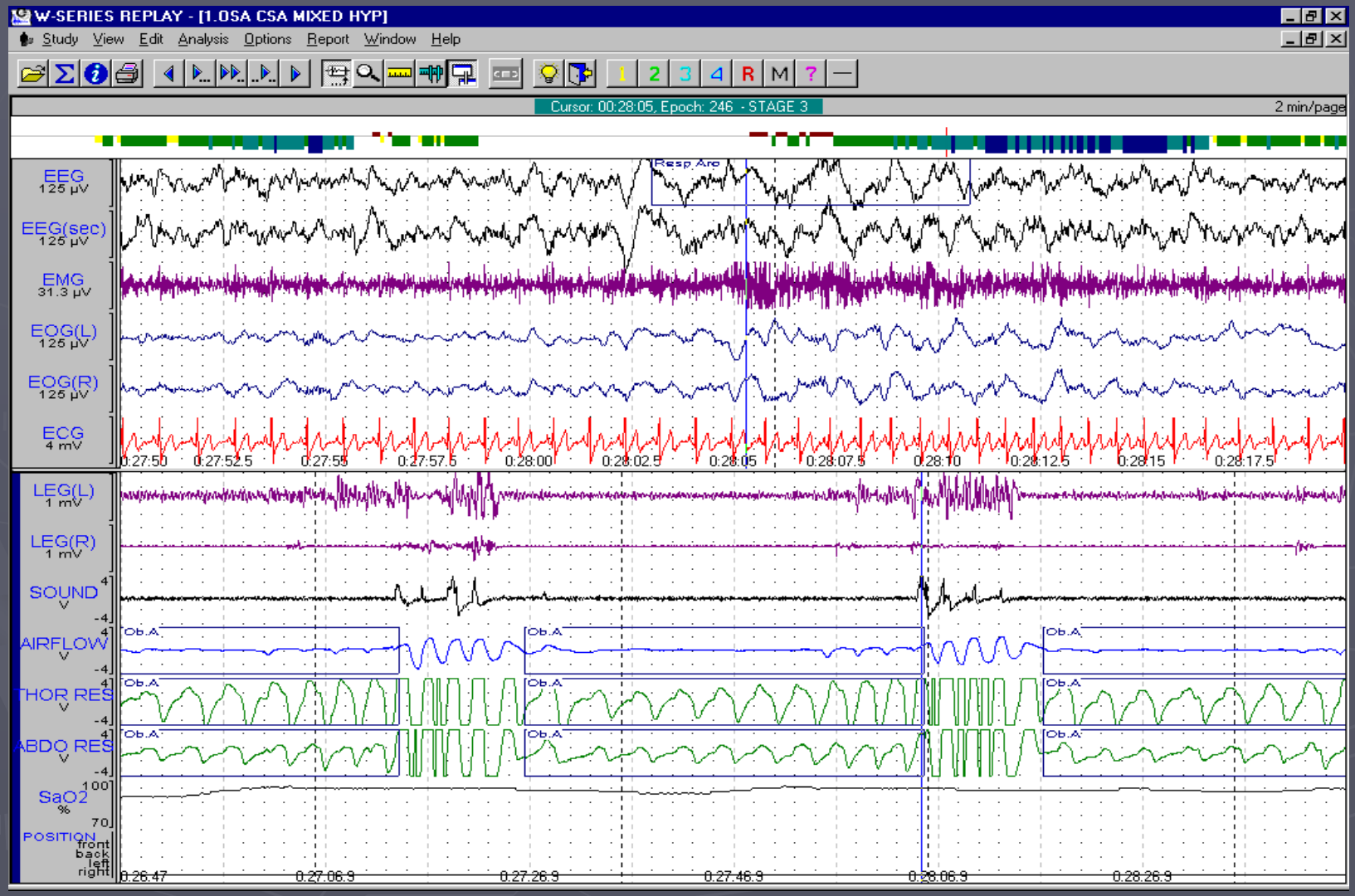
Respiratory Events

- Apneas – absence of airflow
  - Drop in peak thermal sensor excursion by >90% of baseline
  - Duration of events lasts at least 10 seconds
  - At least 90% of event's duration meets the amplitude reduction criteria for apnea
- Hypopneas – reduced airflow
- Respiratory Event Related Arousals (RERA)
  - Respiratory event does not meet the criteria for event types above
  - Causes a disruption of the sleep architecture

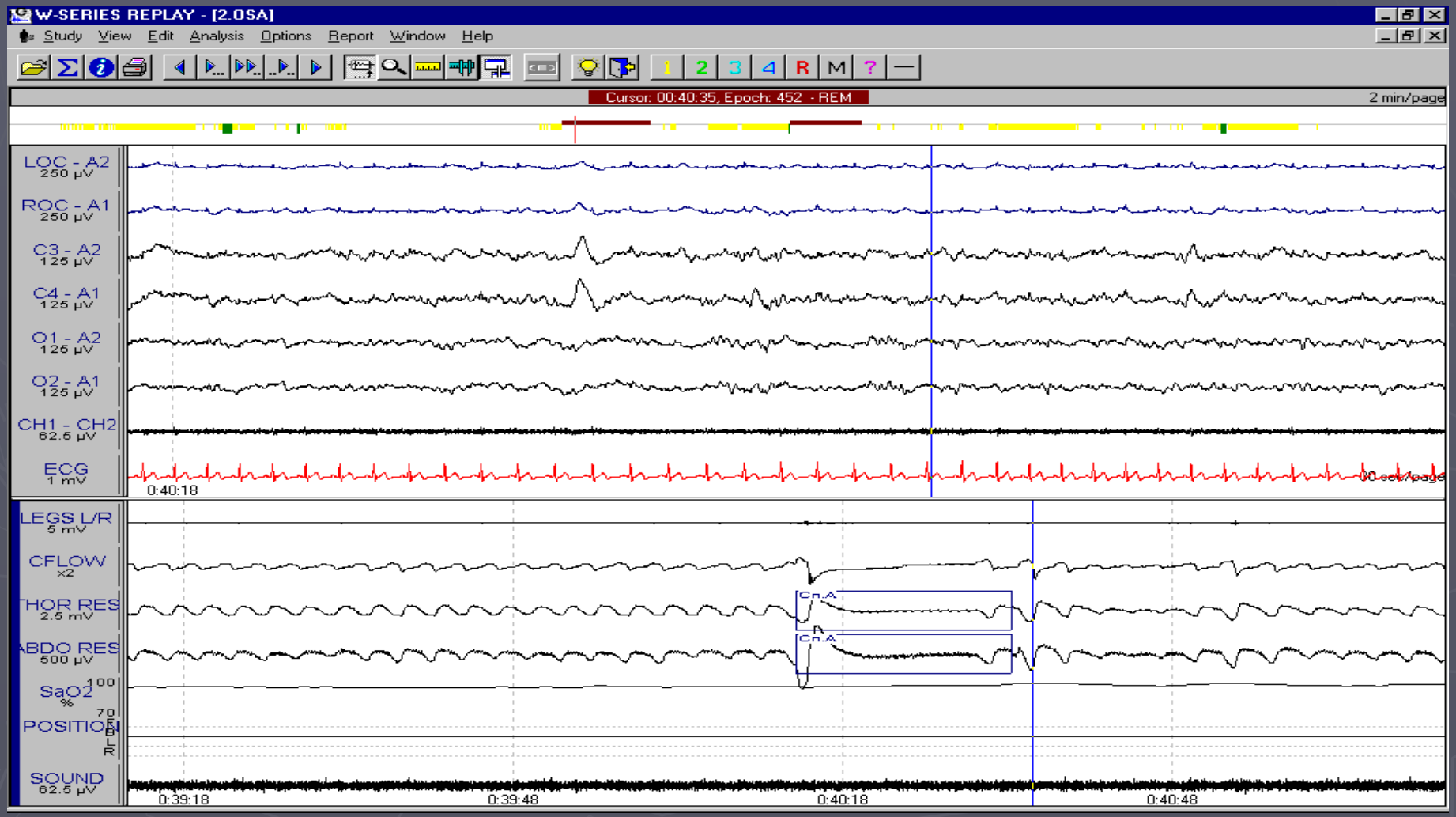
Types of Apnea

- Obstructive:
  - Associated with continued or increased inspiratory effort, but absent airflow
- Central:
  - Absent inspiratory effort and airflow
- Mixed:
  - Absent inspiratory effort initially, followed by resumption of effort in the second portion of the event

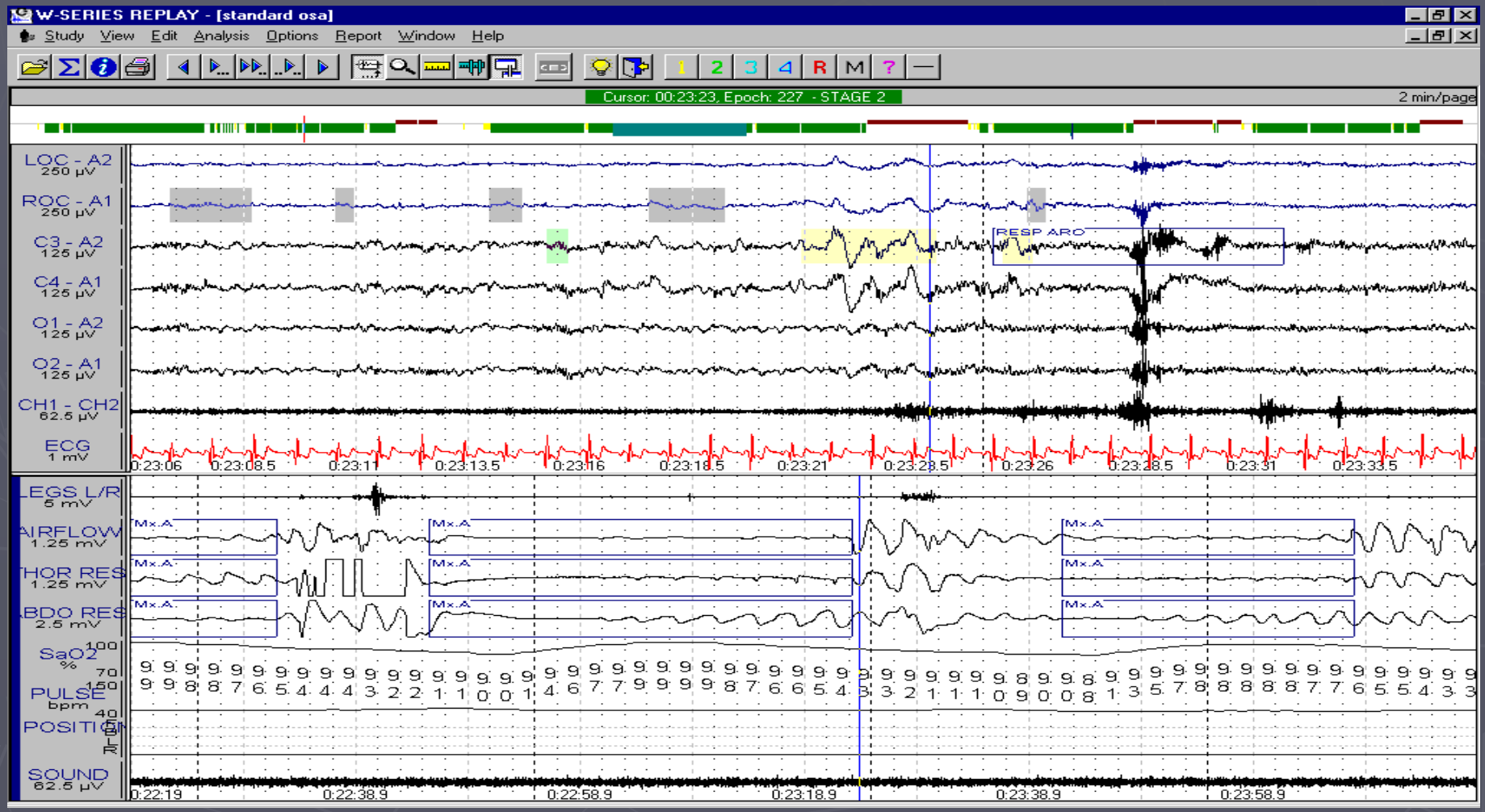
Example - Obstructive Apnea



Example - Central Apnea



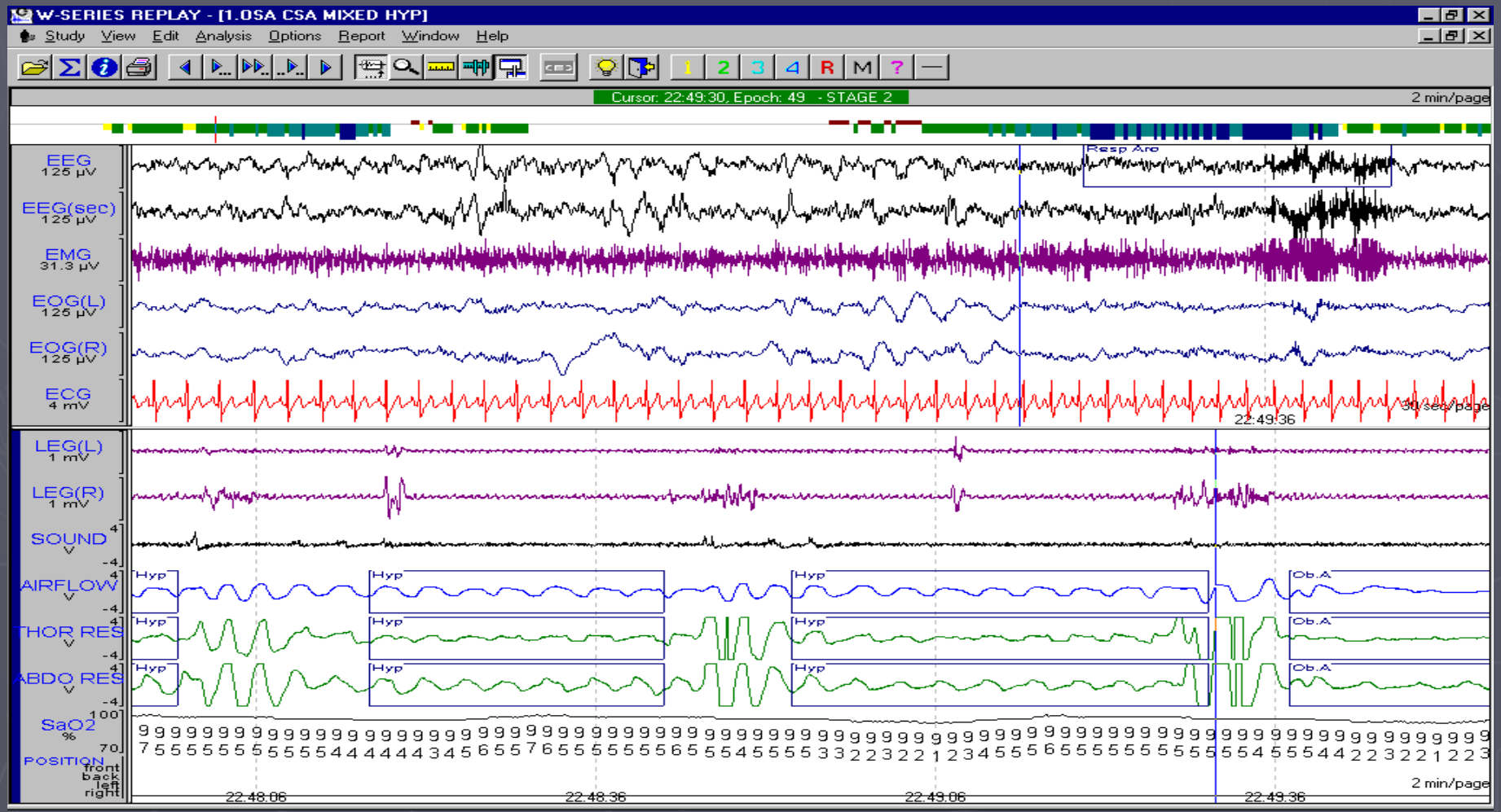
Example - Mixed Apnea



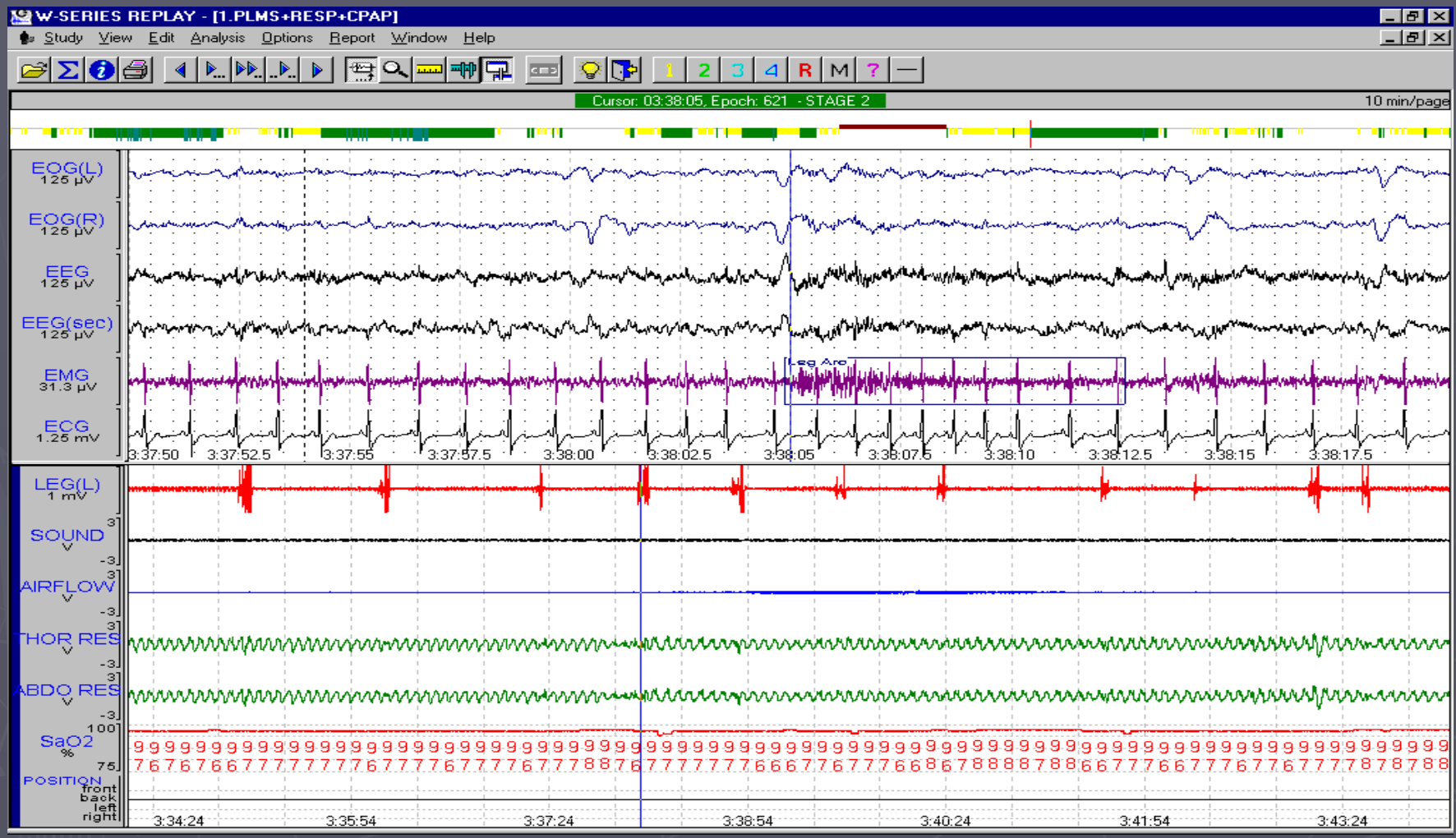
Hypopnea

- Medicare hypopnea:
  - Nasal pressure excursions drop by at least 30% from baseline
  - Duration at least 10 seconds
  - There is a ≥4% desaturation from the pre-event baseline
  - At least 90% of the event's duration must meet the amplitude reduction criteria
- Alternative rule (AASM criteria): >30% reduction in airflow + ≥3% desaturation or an arousal, 90% of event meets reduction criteria

Example - Hypopnea



Example - PLMS



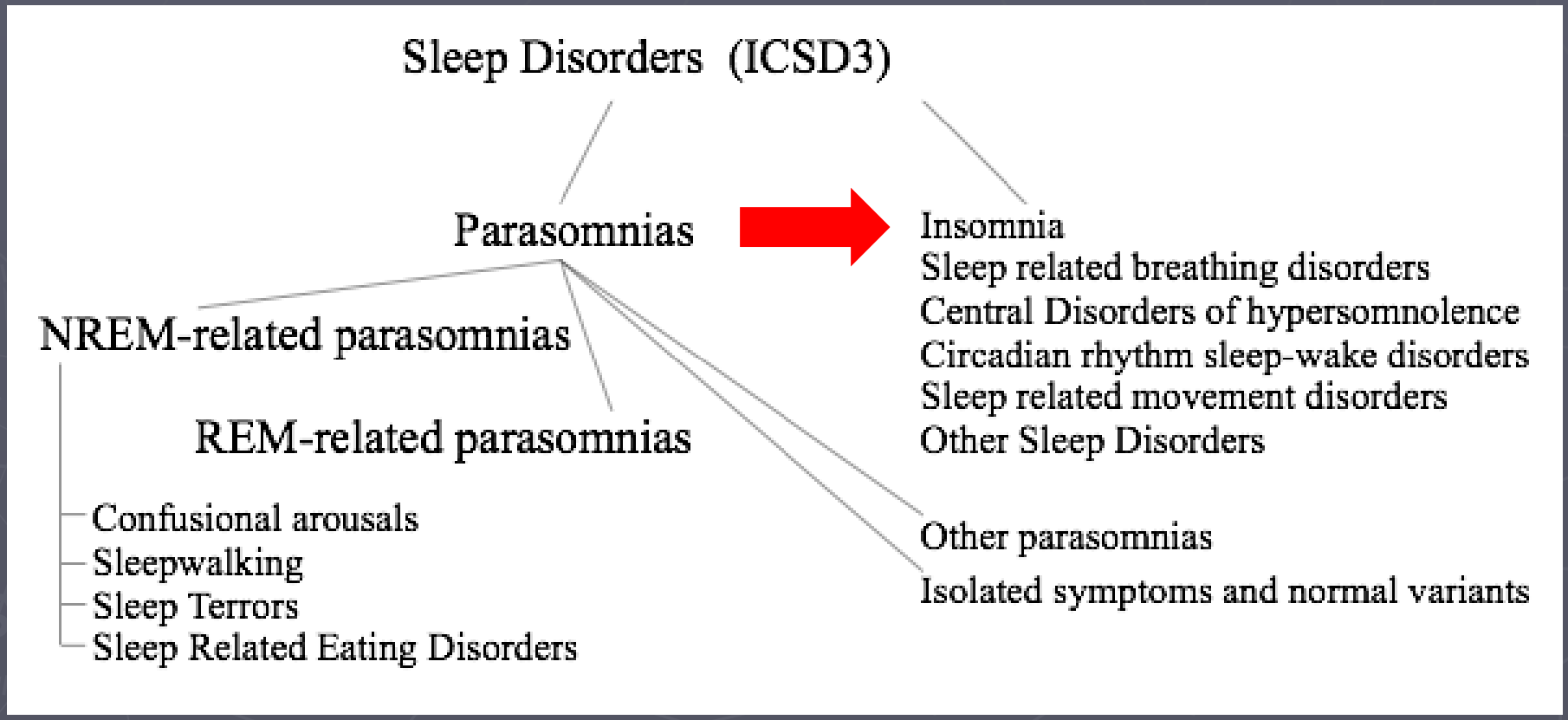
Sleep disorders: An overview

ICSD-2 (2006)

- Insomnia
- Sleep Related Breathing Disorders
- Hypersomnias of Central Origin
- Circadian Rhythm Sleep Disorders
- Parasomnias
- Sleep Related Movement Disorders
- Isolated symptoms and normal variants
- Other

70 distinct sleep disorders categorized

ICSD-3 (2014)


Sleep Disorders (ICSD3)
Parasomnias
Insomnia
Sleep related breathing disorders
Central Disorders of hypersomnolence
Circadian rhythm sleep-wake disorders
Sleep related movement disorders
Other Sleep Disorders
NREM-related parasomnias
REM-related parasomnias
Confusional arousals
Sleepwalking
Sleep Terrors
Sleep Related Eating Disorders
Other parasomnias
Isolated symptoms and normal variants

Case 1

- 69 yo F, travel agent presents with insomnia x 15+ years
- PMH: hypothyroidism, OA, MVP, irritable bowel syndrome, migraines headaches
- Rx: levothyroxine, sumatriptan
- Currently rx'd temazepam 30 mg qhs for insomnia but c/o morning grogginess
- Other tried rx:
  - lorazepam 1-2 mg, diazepam 2 mg – initially worked, lost effectiveness
  - zolpidem 10-20 mg – nocturnal eating, sleep walking
  - Trazodone, imipramine, paroxetine, seroquel – "like a zombie"

Case 1

- Sleep routine
  - BT: 22:30 (admits to reading but in lounge chair next to bed)
  - SL: 45-60 min
  - Awakenings: 1-3 x with variable SL after each (10-60 min), admits to rumination (stressors: finances, parents)
  - WT: 7 AM
  - Estimated TST: 5-6 hours (desires 7 hours)
- No symptoms to suggest OSA, RLS/PLMD, parasomnias, REM behavior disorder
- No psychiatric co-morbidities but family label her a "worry-wart"
- No drug or excessive caffeine/ETOH use, non-smoker

Case 1

- Exam
  - BMI 23.5
  - BP 126/78, pulse 72, RR 13, O2 sat 97% RA
  - Friedman tongue position 1 (Mallampati 1), no nasal obstruction
  - Rest of exam nl (cardio/lungs/neuro/affect/etc)
- Questionnaires
  - Epworth sleepiness score: 6
  - Beck Depression Inventory Score 5 (mild)
  - Pittsburgh Sleep Quality Index 9 (moderate insomnia)
- Lab work: TSH, CBC, Vit D, B12, Fe all wnl
- PSG 1 year ago, showed no OSA
  - Sleep latency 66 min, TST 246 min, SE 73%, no N3 sleep, 15% REM

Differential Diagnosis?

Case 1

- Differential Diagnosis
  - OSA? Negative PSG, no symptoms/signs
  - Insomnia due to poor sleep hygiene? Overall good (no excessive late night caffeine/tob, reads out of bed, no clockwatching
  - Insomnia due to medication effect? Levothyroxine and sumatriptan not known to cause insomnia
  - Insomnia due to a co-morbid medical condition? TSH, lab work wnl
  - Insomnia due to a co-morbid psychiatric condition? Perhaps but no clinical diagnosis of anxiety/depression, overall questionnaire values wnl
- FINAL DIAGNOSIS……

Case 1

- CHRONIC INSOMNIA
  - Sleep onset and sleep maintenance
  - Treatment:
    - Both behavioral + pharmacological treatments are reasonable
    - Behavioral:
      - Sleep restriction in bed
      - Delaying bedtime until sleepy
      - Stimulus control (getting out of bed when unable to sleep)
      - Regular BT/WT (even on weekends)
    - Pharmacological:
      - Benzodiazepines can be used for <3months (with co-morbid anxiety) but recommended as short-term therapy; >6 months → develop tolerance and dependence
      - Other anxiolytics with SE of sedation: TCA's
      - GBP (concomitant tx for migraines/OA pain), "Vitamin G"
      - Other sedative-hypnotics (next slide)

Prescription Sedative-Hypnotics

Drug	Duration	Onset of action	Hypnotic dose	Half life
Zaleplon (Sonata)	Short	15-30 min	10-20 mg	1 hr
Zolpidem (Ambien)	Short	30 min	5-10 mg	2.5 hrs
Ramelteon (Rozerem)	Short	30-45 min	8mg	1-2.6 hours
Triazolam (Halcion)	Short	15-30 min	0.125-0.25 mg	2.9 hrs
Suvorexant(Belsomnra)	**Intermediate**	**30-60 min**	**10-20 mg**	**12 hours**
Eszopiclone (Lunesta)	Intermediate	30 min	1-3 mg	6 hours
Oxazepam (Serax)	Intermediate	45-60 min	15-30 mg	8.0 hrs
Estazolam	Intermediate	15-60 min	1-2 mg	10-24 hrs
Lorazepam (Ativan)	Intermediate	30-60 min	1-2 mg	14 hrs
Temazepam (Restoril)	Intermediate	45-60 min	15-30 mg	11 hrs
Clonazepam (Klonopin)	Long	30-60 min	0.5 mg-1 mg	23 hrs
Diazepam (Valium)	Long	15-30 min	5-10 mg	43 hrs*
Flurazepam (Dalmane)	Long	30-60 min	15-30 mg	74 hrs*

Insomnia

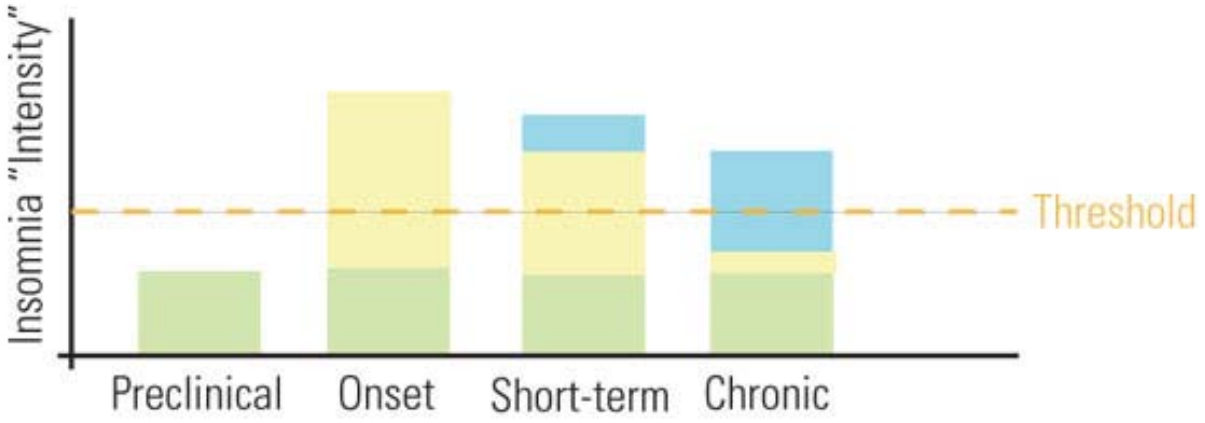
- 2012 Sleep In America Poll by NSF – 58% of American Adults experience insomnia a few nights a week or more
- Insomnia definition: sleep latency >30 min + dysfunction
- ICSD-3 recognizes 3 types:
  - Short-term – “adjustment” or “transient”, <3 mos
  - Chronic – at least 3x/week for >3 mos
  - Other – catch-all group
- 3 patterns
  - Sleep Onset Insomnia
  - Sleep Maintenance Insomnia
  - Terminal Insomnia (Early Morning Awakening)

Spielman's model for insomnia

FIGURE

A MODEL OF CHRONIC INSOMNIA[2-4]

Predisposing Factors	Precipitating Factors	Perpetuating Factors
• Biologic traits	• Medical illness	• Excessive time in bed
• Psychological traits	• Psychiatric illness	• Napping
• Social factors	• Stressful life events	• Conditioning



Erman MK. *Primary Psychiatry*. Vol 14, No 7. 2007.

Treatment of Insomnia

Depends on the Stage of Insomnia

- Treatment of Pre-Morbid Conditions
  - Sleep Hygiene
- Treatment of Precipitating Conditions
  - Psychiatric Counseling
- Treatment of Perpetuating Conditions
  - Cognitive Behavioral Therapy
    - Relaxation Techniques
    - Breathing Techniques
  - Medications – ok but SHORT TERM ONLY

Good sleep hygiene tips

Sleep Hygiene *Do's* and *Don'ts*

Do:

- Establish a regular bedtime and rise time
- Exercise in the late afternoon or early evening
- Take a hot bath a couple of hours before bedtime
- Establish a comfortable sleep environment (e.g., bed, and bedding)
- Sleep in a dark, quiet area that is temperature and humidity controlled
- Establish a relaxing pre-sleep routine that you use every night before sleep, such as washing your face, getting into pajamas, reading or listening to soft music before turning the lights out.

Don't:

- Take daytime naps
- Use stimulants such as caffeine and nicotine
- Drink alcohol before bedtime
- Go to bed too hungry or too full
- Eat offensive foods, such as spicy or acidic foods (e.g., orange juice) before bed
- Try too hard to fall asleep
- "Watch the clock"
- Take prescription and over-the-counter medications that might be stimulating (check with your doctor)

Insomnia inducing Rx

Table 2. Medications and Substances That May Contribute to Insomnia	
Analgesics	Opioids, NSAIDs
Antidepressants	SSRIs, venlafaxine, duloxetine, MAOIs
Stimulants	Caffeine, methylphenidate, amphetamines, cocaine
Decongestants	Phenylephrine, pseudoephedrine
Cardiovascular	β-blockers, diuretics
Pulmonary	Albuterol, theophylline

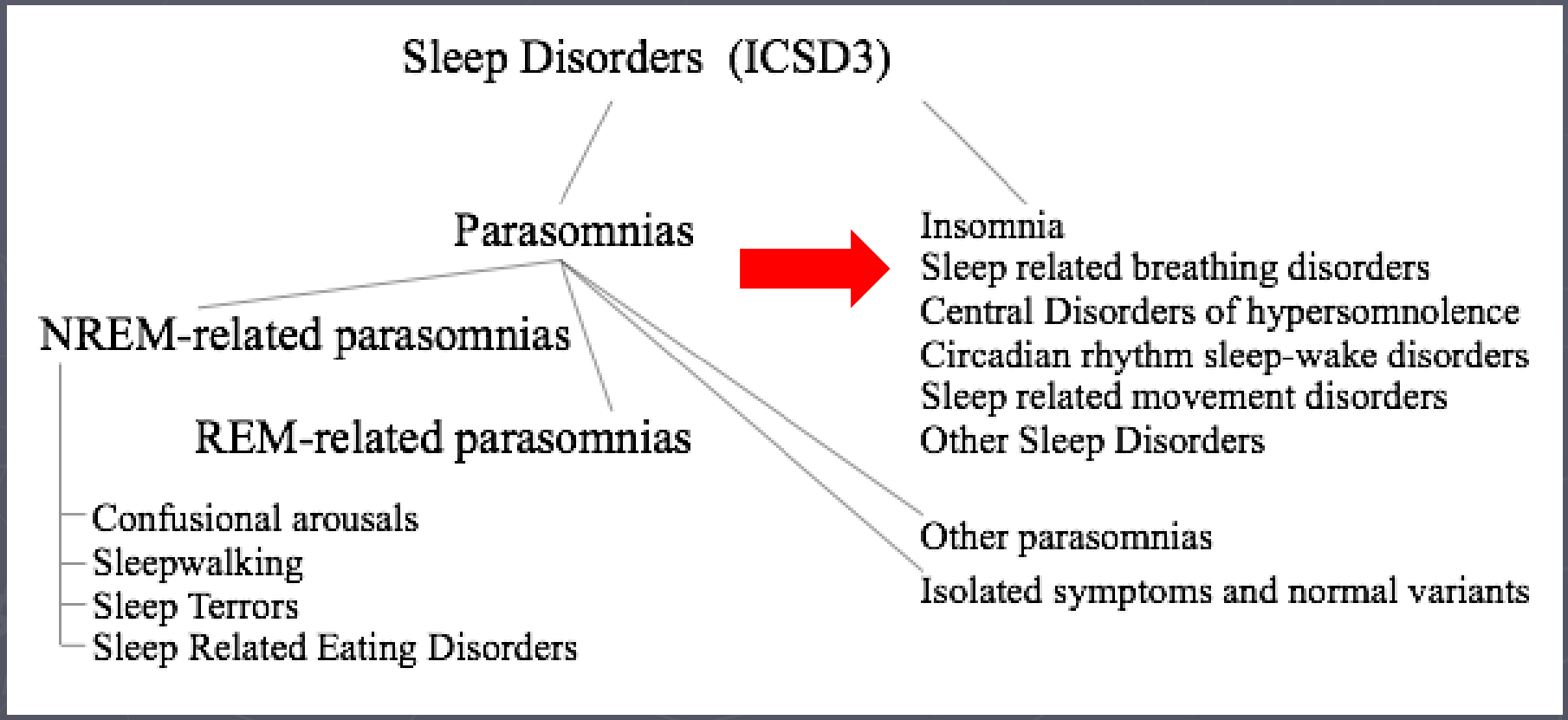
MAOI, monoamine oxidase inhibitor; **NSAID**, nonsteroidal anti-inflammatory drug; **SSRI**, selective serotonin reuptake inhibitor

Based on references 2, 7, 8, and 10.

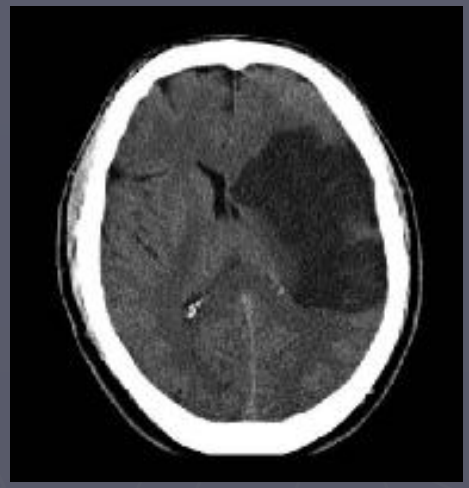
Table 1. Sleep Disorder Differential Diagnosis of Insomnia

Disease	*Characteristics*	*Notes*
Sleep-related breathing disorders		
The obstructive sleep apnea syndrome	Upper airway obstruction during inspiration in sleep.	History of snoring, witnessed pauses in respiration, and daytime sleepiness. Patients may report non-restful sleep or insomnia. Polysomnography is necessary for diagnosis.
The central sleep apnea syndrome	Repetitive pauses in breathing during sleep without upper airway occlusion.	History of congestive heart failure or central nervous system disease. Polysomnography is necessary for diagnosis.
Sleep-related movement disorders		
The restless legs syndrome	Uncomfortable or restless feeling in legs most prominent at night and at rest; alleviated by movement.	Occurs in up to 10% of the general population. Approximately 80% of patients with this syndrome also have periodic leg movement disorder on polysomnography, although polysomnography is not necessary for diagnosis.
Periodic limb movement disorder	Repetitive stereotypic leg movement in sleep and during quiet wakefulness.	Strongly associated with the restless legs syndrome. Polysomnography is necessary for diagnosis.
Nocturnal leg cramps	Pain in calf or foot resulting in awakening from sleep.	Painful cramp awaken the patient from sleep. Predisposing factors include diabetes, exercise, pregnancy, and metabolic and endocrine abnormalities.
Circadian rhythm sleep–wake disorders		
Time zone change syndrome (jet lag)	Travel leads to reports of poor sleep, daytime sleepiness, or both.	History of recent travel across multiple time zones.
Shiftwork sleep disorder	Insomnia as a consequence of shiftwork. Sleep occurs at times counter to normal circadian rhythm and social and environmental factors.	History of insomnia associated with shiftwork; this disorder also affects persons who permanently work the night shift.
The delayed sleep-phase syndrome	Delay of the major sleep phase relative to clock time.	History of sleep-onset insomnia and difficulty awakening at the desired time. Patients have no difficulty maintaining sleep once asleep. Sleep log and actigraphy can aid diagnosis.
The advanced sleep-phase syndrome	The major sleep phase is advanced relative to clock time.	Inability to stay awake until desired bedtime and early-morning awakening. Occurs most commonly in elderly. Sleep log and actigraphy can aid diagnosis.
Parasomnias related to non–rapid eye movement	Include confusional arousals, sleepwalking, sleep terrors, and sleep-related eating disorders.	Disorders of arousal that may be a cause of disrupted sleep. Sleep history and input from bed partner or family may aid in identification.

ICSD-3 (2014)


Sleep Disorders (ICSD3)
Parasomnias
NREM-related parasomnias
REM-related parasomnias
Confusional arousals
Sleepwalking
Sleep Terrors
Sleep Related Eating Disorders
Insomnia
Sleep related breathing disorders
Central Disorders of hypersomnolence
Circadian rhythm sleep-wake disorders
Sleep related movement disorders
Other Sleep Disorders
Other parasomnias
Isolated symptoms and normal variants

Case 2



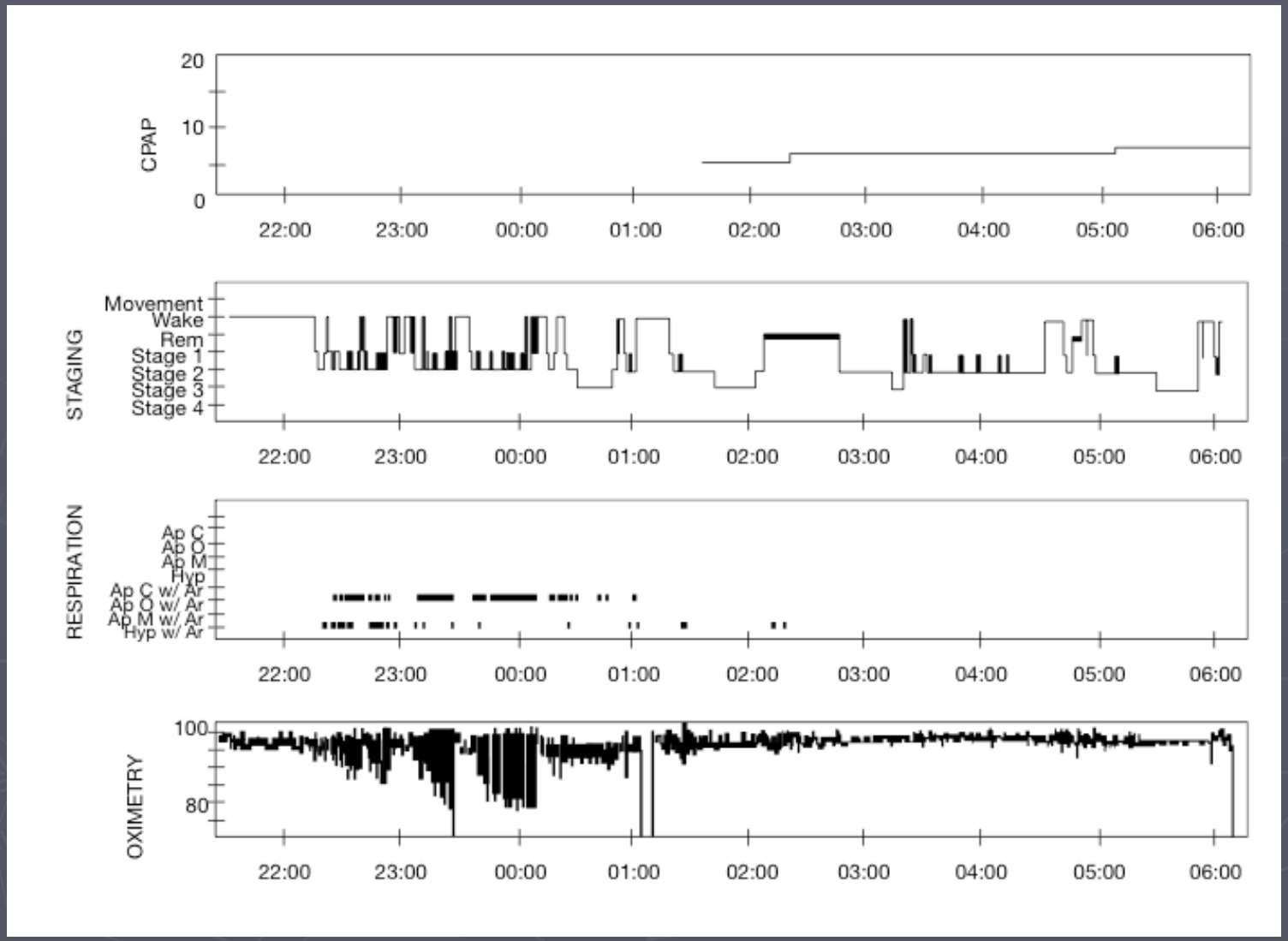
- 73 yo RH German man
- PMH: HTN, HPL, CAD, CHF (EF 30%), V-fib s/p ICD, paroxysmal AF
- Recent left MCA stroke secondary to AF-related cardiac emboli with residual right HP and expressive aphasia

Case 2

- Noted to have abnormal overnight oximetry while in stroke rehab

Evidence of periodic desaturations in saw-tooth pattern with lowest O2 saturation of 82%, a pattern suggestive of sleep apnea.

Split study


CPAP
20
10
0
22:00
23:00
00:00
01:00
02:00
03:00
04:00
05:00
06:00
STAGING
Movement
Wake
Rem
Stage 1
Stage 2
Stage 3
Stage 4
RESPIRATION
Ap C
Ap O
Ap M
Hyp
Ap C w/ Ar
Ap O w/ Ar
Ap M w/ Ar
Hyp w/ Ar
OXIMETRY
100
80

Case 2

- Pt used CPAP 8 cm H2O
- No stroke recurrence
  - Patient symptomatically improved, able to cooperate with rehabilitation
  - NIHSS 12→5
- Downloaded data showed good compliance (88%) and efficacy (AHI 45→3)

Sleep Related Breathing Disorders

- Obstructive Sleep Apnea
  - Most common cause of EDS and sleep disruption
- Central Sleep Apnea
- Hypoventilation Syndromes

What is OSA?

"… characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation…" with associated features of daytime sleepiness and snoring.

OSA Definitions

- **Obstructive Apnea** – cessation of airflow for 10 s with continued respiratory effort.
- **Central Apnea** – cessation of airflow for 10 s without respiratory effort.
- **Obstructive Hypopnea** – "some" reduction in airflow for at least 10 s.
  - 30-50% reduction in airflow
  - associated with either an arousal or desaturation (3-4%)

What is OSA Syndrome?

- Apnea – Hypopnea Index (AHI or RDI) ≥5 events/hour in conjunction with symptoms
- What is a relevant AHI?
  - Consensus Statement 1999: "RDI of 5 (or greater) accompanied by symptoms..."

    Loube et al, Chest 1999
  - Medicare 2014: AHI ≥ 5 with symptoms, or HTN, CAD or CVA

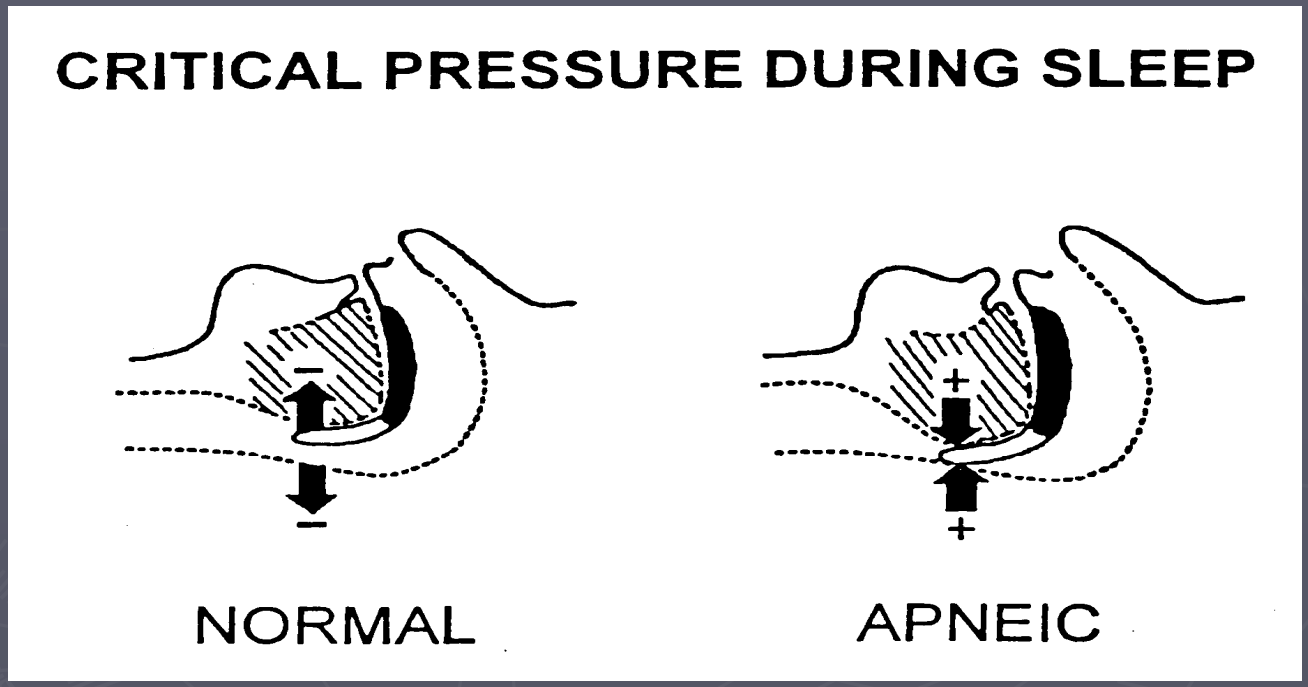
Prevalence of OSA

- Wisconsin Sleep Cohort Study
  - Population based study: 602 working subjects, aged 30-60 years studied with PSG
  - Definition OSAS: AHI ≥5 and hypersomnolence

	F	M
OSA	9%	24%
OSAS	2%	4%

Young et al, NEJM 1993

Pathophysiology of OSA



- Narrowing or collapse of the upper airway
- Decreased tidal volume → hypercapnia and hypoxia
- Increased respiratory effort
- Arousal opens airway
- Ensuing hyperpnea with hypocapnia and adequate oxygenation

Demographics of OSAS

- In younger, but not middle aged groups, OSAS has been reported to be more prevalent in AA's compared to Caucasians
- Despite lower BMI, Asians have a predisposition of OSA thought to be due to cranio-facial features
- Prevalence of OSA increases with age

Risk Factors for OSA

- Sleep Heart Health Study: male, age, BMI, neck girth, snoring, and witnessed apnea predict AHI >15

  Young et al. Arch IM.2002
- Craniofacial abnormalities - nasal obstruction, enlarged uvula/tongue/tonsils, long soft palate, retrognathia, micrognathia, brachycephaly (flat posterior head)
- Family History (increases risk of OSAS 2-4 fold)
- Co-morbid illness
  - cardiopulmonary disease (CHF, OHV)
  - metabolic disorders (hypothyroidism, acromegaly)
  - neurologic disorders (CVA, neuromuscular disorders e.g. MD)
  - Down's syndrome (macroglossia)
- Environmental Factors - tobacco use, ETOH, sedatives

Symptoms/Signs of OSA

- Snoring
- Witnessed apneas
- Daytime sleepiness
- Sleep fragmentation
- Night sweats
- Nocturia
- Dry mouth/sore throat
- Leg kicking while sleeping
- Morning headaches
- Mood changes
- Decreased libido
- Memory problems

- Obesity
- Associated diseases
  - Hypertension
  - Cardiac disease
  - Stroke
  - Glucose intolerance
  - Hypothyroidism
  - Acromegaly

STOP-BANG Questionnaire

TABLE 2. STOP-BANG Questionnaire for identifying patients with obstructive sleep apnea (OSA)

SNORE	Do you snore loudly? (Snoring can be heard through closed door)
TIRED	Do you feel tired, sleepy, fatigued, during daytime?
OBSERVED	Has anyone seen you stop breathing during sleep?
BLOOD PRESSURE	Do you have or are you being treated for high blood pressure?
BMI	Is your BMI > 35kg/m2?
AGE	Are you older than 50?
NECK CIRCUMFERENCE	Is your neck circumference greater than 40 cm?
GENDER	Are you a male?

If the answer to three or more of these questions is "yes," a presumptive diagnosis of OSA can be made.

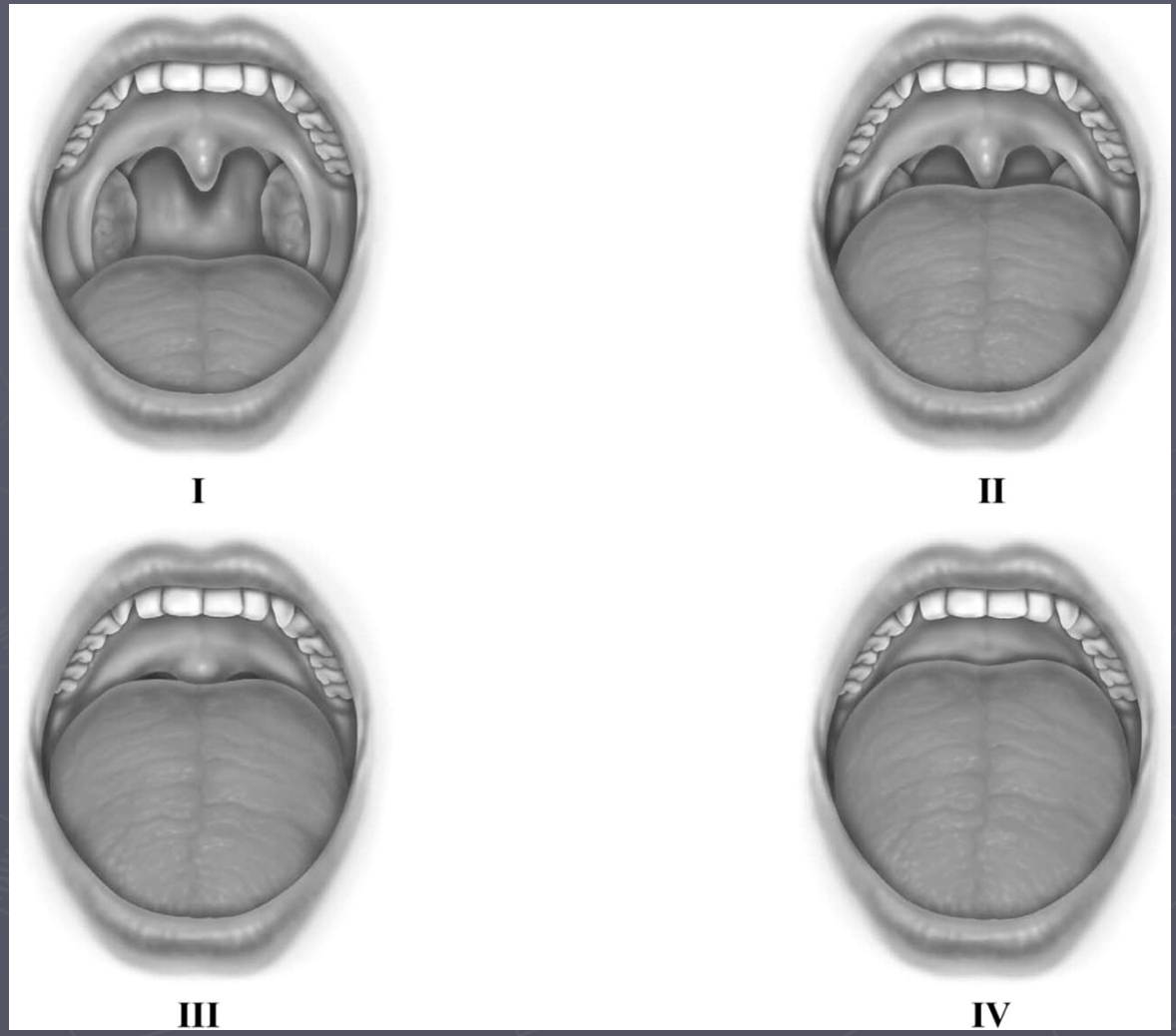
Modified from: Chung F, Elsaid H. Screening for obstructive sleep apnea before surgery: why is it important? *Current Op Anaesthesiol.* 2009;22: 405–411.

Clinical Examination

- Vital signs (hypertensive, arrhythmias)
- Obese (BMI >30)
  - 40% of those with BMI >40 have OSAS and 50% of those with BMI >50 have OSAS

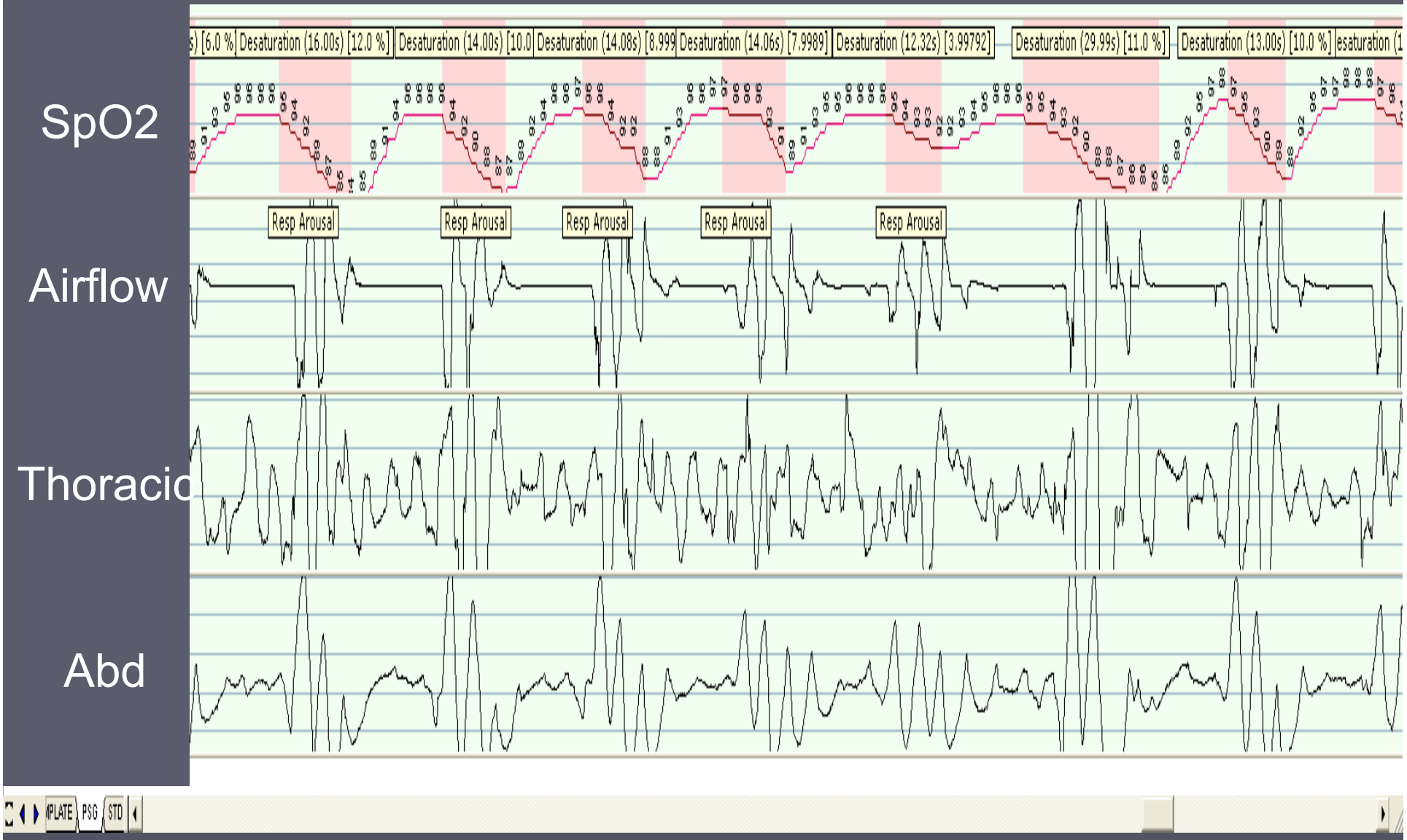
    Kripke et al. Sleep 1997.
- Neck circumference
  - ≥40 cm associated with sensitivity of 61% and specificity of 93% for OSAS
  - Men >17 inches, women >16 inches
- Oral airway
  - Retrognathia (narrows the upper airway behind the base of the tongue)
  - Dental malocclusion and overlapping teeth (indicated small oral cavity)
  - Macroglossia
  - Edema and erythema of the uvula
  - Elongated soft palate
  - Narrow high arched palate
  - Tonsillar hypertrophy
  - Lateral airway narrowing
- Nasal airway
  - Nasal valve collapse with sniff test
  - Nare size and asymmetry
  - Septal deviation
  - Enlarged inferior turbinates

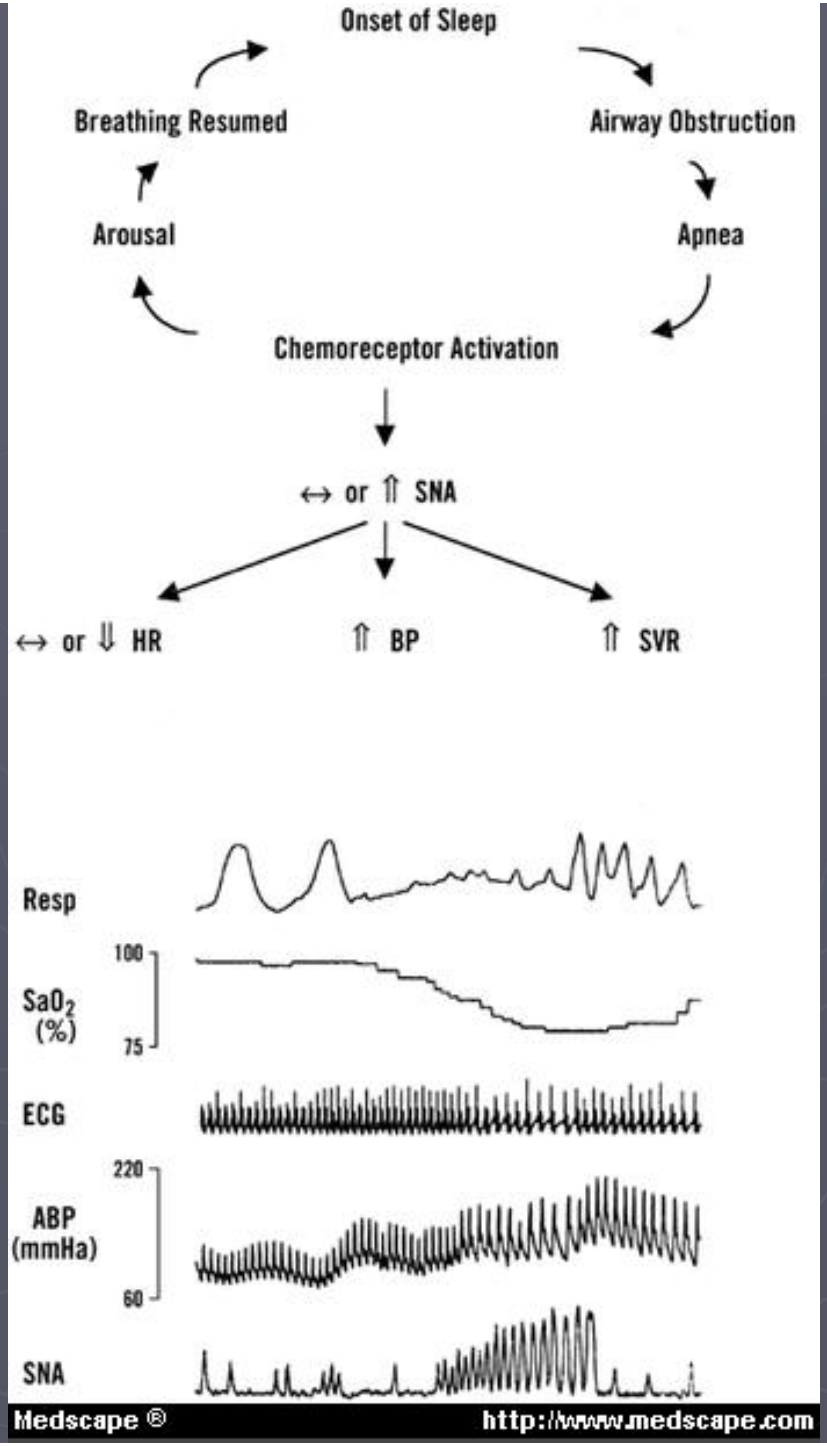
Friedman tongue position (FTP) is based on visualization of structures with the mouth opened widely without protruding the tongue.



Friedman M et al. Otolaryngology -- Head and Neck Surgery 2006;134:187-196

OSA – Example of a PSG




Onset of Sleep
Airway Obstruction
Apnea
Chemoreceptor Activation
↔ or ⇑ SNA
↔ or ⇓ HR
⇑ BP
⇑ SVR
Breathing Resumed
Arousal
Resp
100
SaO2 (%)
75
ECG
220
ABP (mmHa)
60
SNA
Medscape ®
http://www.medscape.com

Consequences of OSA

- Coronary artery disease
- Heart failure
- Stroke
- Sleep Heart Health Study: cross-sectional association between OSA and self-reported CVD:

	CAD	CHF	CVA
AR	1.27	2.38	1.58

Shahar et al, AJRCCM 2001

OSA related to stroke and death

- Conducted at Yale Medical Center
- 1022 participants enrolled but only 898 completed
  - 573 (68%) with OSA (AHI >5, mean AHI 35±29)
  - 325 w/o OSA (AHI<5, mean AHI 2±1.5)
- Mean age 60 yrs
- Follow up of 2-4yrs
- Adjusted for age/sex/race, smoking, alcohol intake, BMI, DM, HTN, AF, high cholesterol

Yaggi et al, NEJM 2005; 353: 2034-2041.

Results

- OSA group - 22 strokes, 50 deaths
  [3.48 events per 100 person-years]
- Control group – 2 strokes, 16 deaths
  [1.60 events per 100 person-years]
- After adjustment for age, sex, race, tobacco use, ETOH, BMI, DM, HTN, AF, HPL, OSA retained a statistically significant association with stroke or death
  [Hazard ratio 1.97; 95% CI 1.12-3.48, P=0.01]

Yaggi et al, NEJM 2005; 353: 2034-2041.

Table 3. Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).*

Severity of Syndrome	Stroke or Death		Mean Follow-up Period	Hazard Ratio (95% CI)
	No. of Events	No. of Patients		
			yr	
AHI ≤3 (reference score)	13	271	3.08	1.00
AHI 4–12	21	258	3.06	1.75 (0.88–3.49)
AHI 13–36	20	243	3.09	1.74 (0.87–3.51)
AHI >36	34	250	2.78	3.30 (1.74–6.26)

- Trend analysis showed a step-wise increase in the risk of stroke/death as a function of increased severity of OSA (p=0.005)
- The risk of stroke/death in pts in the most severe quartile of OSA was 3 x that in the controls

Yaggi et al, NEJM 2005; 353: 2034-2041.

Other Consequences of OSA

- Pulmonary HTN
- Cor Pulmonale
- Cardiac Arrhythmias (atrial fibrillation)
- GERD
- Increased frequency of seizures in epileptics
- Increased headache syndromes (migraines)

Consequences of OSA

- Psychiatric/mood - depression, anxiety, irritability
- Social and sexual dysfunction
- Neurocognitive impairment – general intellectual ability, learning and memory, attention, information processing efficiency, visual and psychomotor performance

Consequences of OSA

- Increased traffic accidents - case-controlled study found those with AHI > 10 had OR of 6.3 for MVA

  Teran-Santos et al, NEJM 1999

- Increased utilization of Health Care Services
- Increased mortality - relative risk 2.7-3.3
- All of these adverse outcomes can be improved by treatment

Treatment of OSA: Conservative Measures

- Weight loss
  - 10% weight loss leads to 26-50% decrease in AHI
  - pharyngeal function improves as weight decreases
  - extensive weight loss (i.e. following gastric bypass surgery) may resolve OSA
  - almost always should be combined with other therapies

Treatment of OSA: Conservative Measures

- Lateral positioning
- Elevating the head of the bed
- Avoiding upper airway irritants - tobacco
- Minimizing sedating agents - alcohol, sedatives

Treatment of OSA: CPAP

- First-line therapy for OSA
- Can eliminate sleep disordered breathing in most patients
- Produces a “pressurized” upper airway to maintain airway patency
- PAP titration study vs autoPAP

Treatment of OSA: CPAP

- Benefits
  - decreases sleep-disordered breathing and EDS
  - improves oxygenation, exercise function
  - improves neuropsychiatric measures
  - decreases MVAs and hospitalizations
  - appears to decrease mortality
- Problems
  - acceptance suboptimal
  - compliance poor at times but can overcome

Alternative treatment for OSA: Oral Appliances

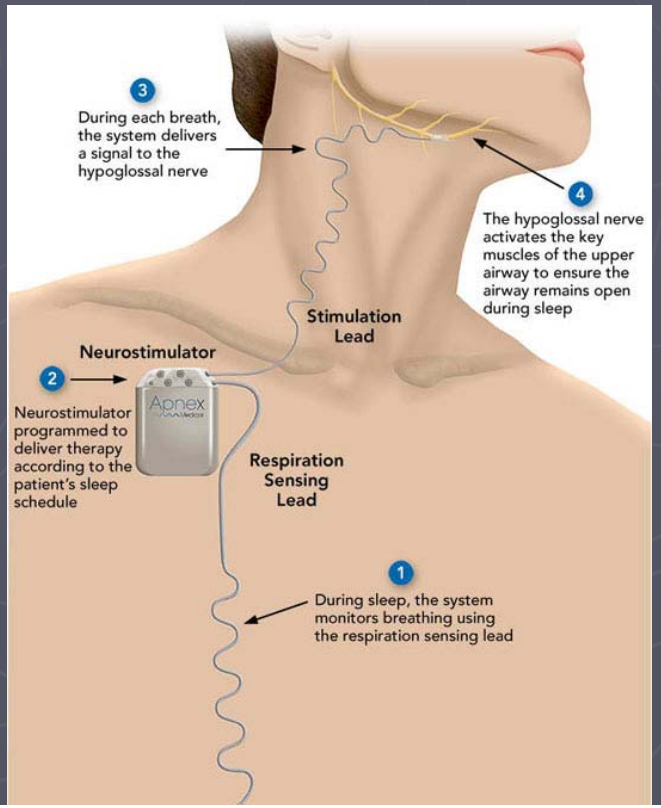
- Relatively new therapy for OSA
- Two categories:
  - Mandibular Advancing Devices
  - Tongue Retaining Devices
- Work by enlarging the pharyngeal cross-sectional area
- Consider in patients with mild/moderate OSA
- RCT suggest about equal efficacy to CPAP with better tolerance

Alternative treatment of OSA

- Provent nasal strips

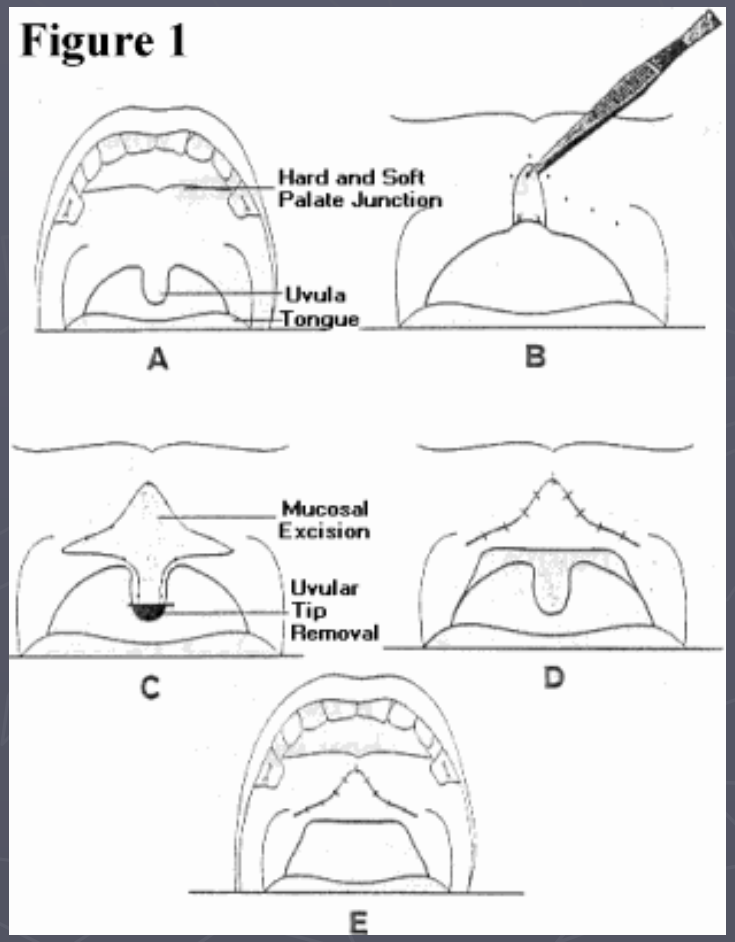
- Positional therapy

- Hypoglossal nerve stimulator



Treatment of OSA: Surgery

- Numerous approaches have been tried
- Surgical data limited
- Procedures in general use:
  - Nasal surgery
  - Tonsillectomy +/- adenoidectomy
  - UPPP
  - Genioglossus advancement
  - Maxillomandibular Advancement (MMA)
  - Tracheotomy

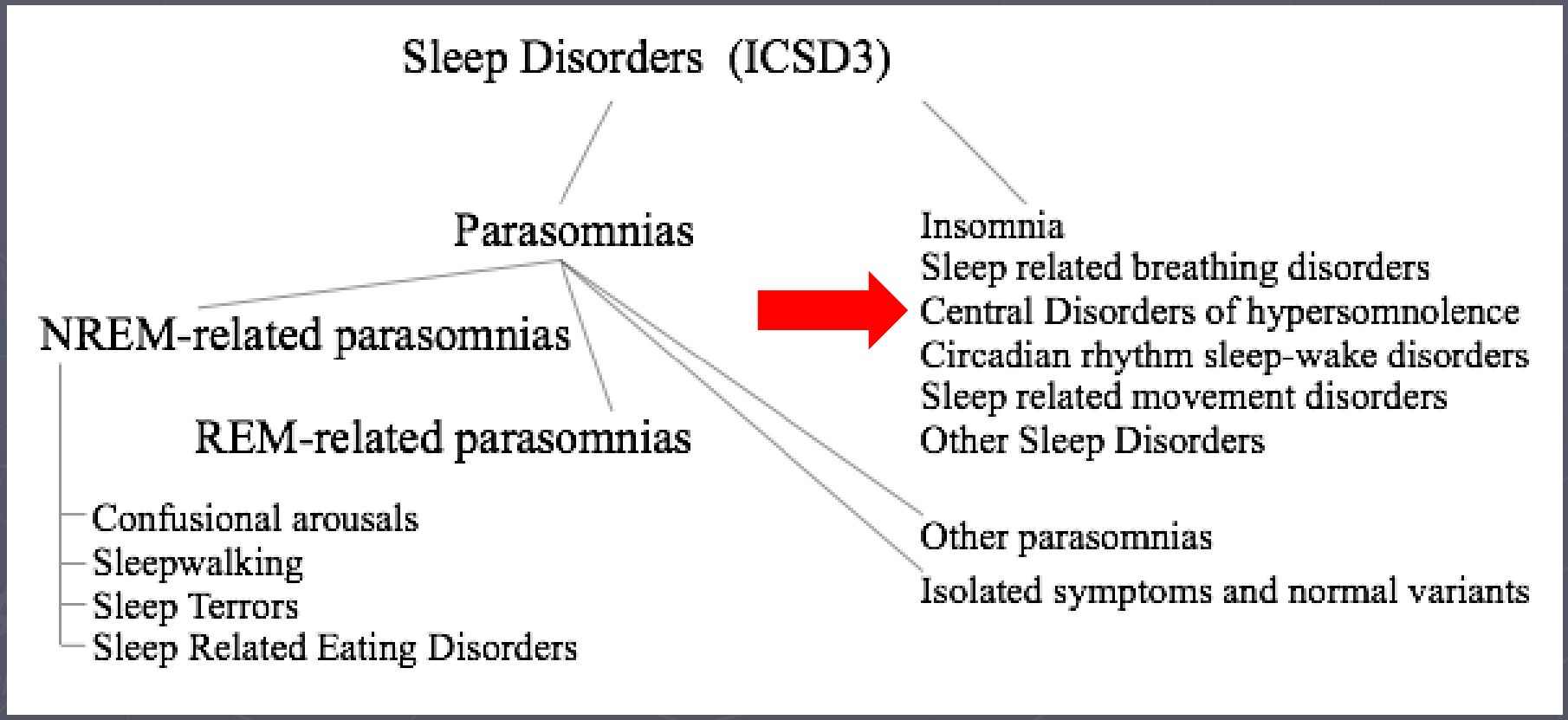


Treatment of OSA: Pharmacotherapy

- Little successes at this point in time
- "Some" efficacy may be present in the following situations:

Condition	Medication
OHV	Medroxyprogesterone
REM OSA	SSRIs, TCAs
CHF	Theophylline

ICSD-3 (2014)


Sleep Disorders (ICSD3)
Parasomnias
NREM-related parasomnias
REM-related parasomnias
Confusional arousals
Sleepwalking
Sleep Terrors
Sleep Related Eating Disorders
Other parasomnias
Isolated symptoms and normal variants
Insomnia
Sleep related breathing disorders
Central Disorders of hypersomnolence
Circadian rhythm sleep-wake disorders
Sleep related movement disorders
Other Sleep Disorders

Case 3

- 17 yo M presents with EDS x 2 years
- C/o decline in academic performance due to falling asleep in classes
- Dx'd with ADD by PCP, rx'd Adderall 40 mg → palipitations, HA
- Since age 12, he's had multiple episodes of knees bucking and facial twitching with laughter
- When he woke up, he felt paralyzed for 30 seconds, couldn't speak

Case 3

- He reported seeing little minions running around his room right before falling asleep
- He would finish chores without recollection of doing them
- He would nap throughout the day (10-20 min each) and noted vivid dreams with all naps
- No recent head injury, no drug/substance abuse

Case 3

- Bedtime routine:
  - BT: 23:00
  - SL: minutes
  - Awakenings: 2-5 times, unclear reasons
  - WT: 6:30, snoozes alarm multiple times
- Exam: normal but you crack a joke and he slumps over for 15 secs (no LOC, no DTR's)
- MRI negative for hypothalamic lesions

Case 3

- PSG: SL 5 min, normal AHI, fragmented sleep
- MSLT
  - Napped during 5 nap trials
  - Mean sleep latency: 4.5 minutes
  - + SOREMP in 3 (REM <15 min)
  - Reported vivid dreams in 3 naps
- Negative urine drug screen prior to MSLT (off stimulants x 2 weeks)
- CSF hypocretin-1 assay 90 pg/ML
- + HLP DQB1*0602
  - +90% of narcolepsy 1 pts, 25% general population

Differential Diagnosis?

Case 3

- Narcolepsy type 1
  - EDS >3 months
  - Cataplexy
  - Sleep paralysis
  - Hypnagogic hallucinations
  - Automatic behavior
  - Vivid dreams shortly after sleep onset
- + MSLT with negative drug screen, low hypocretin-1 assay levels, + HLA haplotype

Case 3

- Pt was started on Provigil 200 mg qAM, with extra 200 mg at noon prn with drop in is ESS from 18 to 9
- Started on Effexor for cataplexy (down from 5 episodes a week to 0-1, could attend comedy shows now)
- Grades improved, feeling better

Narcolepsy

A central nervous system disorder that is an important cause of persistent sleepiness.

The second most common cause of disabling daytime sleepiness after sleep apnea.

*Should be on differential for syncope!

Epidemiology/Prevalance

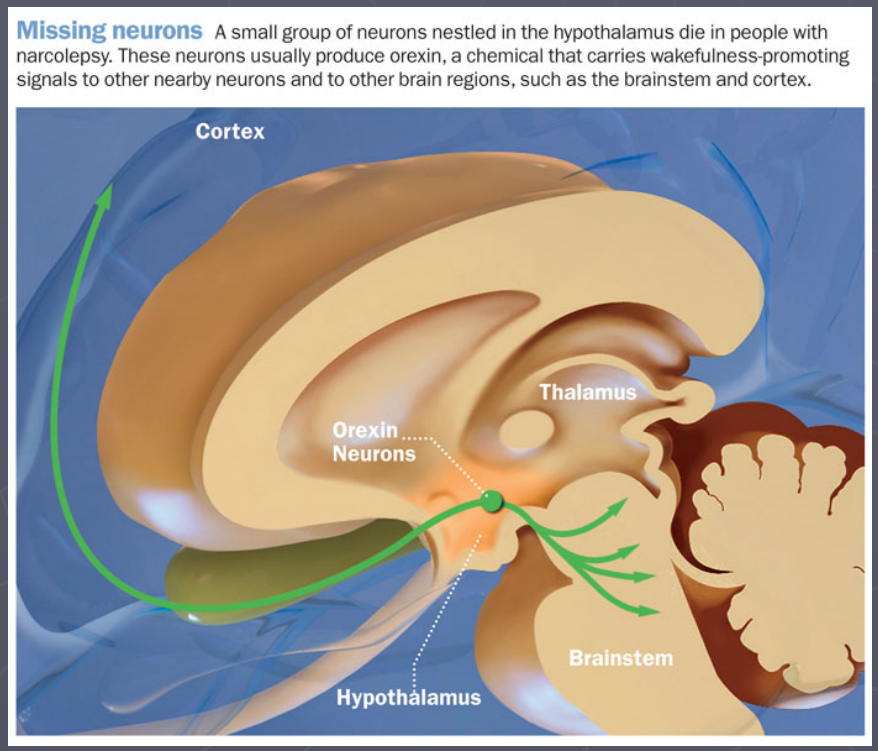
- Affects 1 in 200 people in Western Europe and North America
- Prevalence men = women
- Typically begins in the teens and early 20's, but can occur as early as age 5 or age 40
- Symptoms may worsen over the first few years and then persist for life
- Half of patients report that symptoms interfere with job, marriage or social life

Gelineau (1862) applied the term "narcolepsy" to a clinical syndrome of daytime sleepiness with…

- Hypnagogic hallucinations (vivid, often frightening hallucinations that occur just as the patient is falling asleep)
- Sleep paralysis (complete inability to move for 1-2 minutes after awakening)
- Cataplexy (sudden episodes of bilateral muscle weakness leading to partial or complete collapse; often triggered by strong emotions, last 1-2 minutes with preserved LOC)

Neurobiology

- Loss of function of the neuropeptide orexin (hypocretin)
- Made by neurons in the lateral hypothalamus
- Excitatory effects on postsynaptic neurons through the ox1 and ox2 receptors



Genetic factors

- Usually sporadic, but genetic factors play important role
- Most narcoleptics (50-90 percent) have HLA DR2 and DQ1
- Environmental factors appear to be even more important: only about 25 percent of affected monozygotic twins are concordant for narcolepsy
- On rare occasions, narcolepsy runs in families.

Narcolepsy +/- Cataplexy

- ICSD-2 diagnostic criteria
  - Complaint of EDS almost daily for >3 months
  - +/- cataplexy
    - Sudden transient weakness of muscles during periods of stress, great emotion (buckling of knees, facial weakness, drop attacks)
  - Diagnosis confirmed by noctural PSG followed by MSLT
    - MSL is ≤ 8 minutes
    - 2 or more SOREM
  - Alternatively, CSF hypocretin-1 levels ≤110 can be used to confirm diagnosis

ICSD-3: Narcolepsy, type 1 and 2

- Narcolepsy type 1 (with hypocretin deficiency)
  - Both criteria must be met:
    - Daily periods of irrepressible need to sleep or daytime lapses into sleep, occurring for at least 3 months
    - Presence of one or both:
      - Cataplexy and a MSL of up to 8 min or 2+ SOREMP (15 min) on MSLT (1 SOREMP on preceding PSG can count as one)
      - CSF hypocretin-1 concentration is either up to 110 picograms/ml measured by immunoreactivity or <1/3 of mean values obtained in normal subjects with the standardized assay

ICSD-3: Narcolepsy, type 1 and 2

- Narcolepsy type 2 (without hypocretin deficiency)
  - All 5 of the following must be met:
    - Daily pds of irrepressible need to sleep or EDS >3 mos
    - MSL ≤8 min or 2 or more SOREMP (15 min) on MSLT (1 SOREMP on preceding PSG can count)
    - Cataplexy is absent
    - CSF hypocretin-1 concentration is >110 picograms/ml measured by immunoreactivity or >1/3 of mean values obtained in normal subjects with the standardized assay
    - No other causes (OSA,DSPS, rx/substance)

MSLT

- Full night PSG is performed prior
- A patient is given four or five opportunities to nap every two hours
- On average, healthy subjects fall asleep in about 10-15 minutes
- People with narcolepsy often fall asleep in less than five minutes
- The naps of narcoleptics often include REM sleep
- Occurrence of sleep onset REM periods (SOREMs) in two or more naps is an essential feature in establishing the diagnosis of narcolepsy

Drug Effects…

- REM sleep-suppressing medications (TCAs, SSRIs) or withdrawal from these drugs also can produce SOREMs ("rebound" phenomenon)
- Stimulants obscure results
- These drugs should be discontinued at least three weeks before the MSLT if possible

DIFFERENTIAL DIAGNOSIS

- With Cataplexy:
  - Hypothalamic lesions
  - Prader-Willi syndrome
  - Niemann-Pick disease type C
  - Norrie disease

- Without Cataplexy:
  - OSA
  - PLMD
  - Idiopathic hypersomnia

TREATMENT

- Mainstays of therapy are
  - -Stimulants for the treatment of sleepiness
  - -REM sleep-suppressing medications for the treatment of cataplexy
- Napping and sleep hygiene
- Psychosocial support

Medication

- Amphetamines (methylphenidate, dextroamphetamine)
  - Oldest, used since 1930's
- Modafinil (200-400 mg qAM)
  - SE: HA, n/v, dry mouth, anorexia, diarrhea
  - Lack of sympathomimetic effects makes it ideal for older pts with HTN, CAD
- Gamma hydroxybutyrate (Xyrem)
  - 2002 –approved by FDA for treatment of cataplexy
  - Metabolite of GABA, mechanism unknown
  - Can also improve EDS
  - SE: 14% UT, somnambulism, n/v
  - Potential for abuse, overdose can be fatal

Table 2. Medications Used for the Treatment of Narcolepsy

Drug (Brand)	Adult Daily Dose	Class	Indication	Patient Education
Sodium oxybate (Xyrem)	4.5-9.0 g per night	GHB	Cataplexy and EDS	Take 2 doses each night on an empty stomach. The 2nd dose should be given 2.5-4 h after the 1st dose. Avoid alcohol. Avoid driving for at least 6 h after taking
Modafinil (Provigil)	200-400 mg	Non-sympathomimetic wake-promoting agent	EDS	Take medicine in the morning with or without food. May decrease effectiveness of OC; recommend additional form of birth control
Armodafinil (Nuvigil)	150-250 mg			
Dextroamphetamine/ amphetamine salts (Adderall)	5-60 mg	Stimulant	EDS	Take medicine in the morning. Avoid sudden drug discontinuation
Dextroamphetamine (Dexedrine)	5-60 mg			
Methylphenidate (Ritalin)	10-60 mg			
Methamphetamine (Desoxyn)	5-15 mg			
Imipramine (Tofranil)[a]	50-250 mg	TCA	Cataplexy	Take medicine with or without food. If medicine causes sleepiness, take it at bedtime. Avoid sudden drug discontinuation
Nortriptyline (Aventyl, Pamelor)[a]	50-150 mg			
Protriptyline (Vivactil)[a]	2.5-10 mg			
Clomipramine (Anafranil)[a]	10-200 mg			
Fluoxetine (Prozac)[a]	20-80 mg	SSRI	Cataplexy	Take medicine in the morning with or without food. Avoid sudden drug discontinuation
Venlafaxine (Effexor)[a]	75-375 mg	SNRI	Cataplexy	Take medicine with food. Avoid sudden drug discontinuation
Atomoxetine (Strattera)[a]	18-100 mg	SNRI	Cataplexy and EDS	Take medicine early in the day with or without food
Selegiline (Eldepryl)[a]	5-10 mg	MAO-B inhibitor	Cataplexy and EDS	Take capsule or tablet early in the day with food. Avoid sudden drug discontinuation

[a] Off-label use; not FDA approved for the treatment of narcolepsy.
EDS: excessive daytime sleepiness; GHB: gamma-hydroxybutyrate; MAO-B: monoamine oxidase type B; OC: oral contraceptives; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.
Source: References 1, 3, 23, 31, 36.

BUMC-P Sleep

- Clinic – Neuroscience clinic in Rehab building
- Sleep lab – West tower, 1st floor
- We see everything – insomnia, OSA, CSA, narcolepsy, RBD, nocturnal epilepsy, etc
- Office number: 602-351-2200
- Cyrus Guevarra (sleep lab manager)
- Crystal McDonald (field representative)
- Email me: joyce.lee-iannotti@bannerhealth.com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Summary

- Sleep Medicine is a relatively new field
- Normal Sleep is dictated by homeostatic pressure and circadian rhythms
- PSG is the gold standard for diagnosis of most sleep disorders
- Insomnia is the most common sleep disorder, but OSA is the most common cause of EDS
- Narcolepsy is not common, but can be debilitating

Sleep is cool, dude~

We welcome rotators all the time ☺

QUESTIONS??


GLASBERGEN
7-5
"It was the most dynamic presentation I ever gave. One person stayed awake for almost seven minutes!"