Basics of Sleep Medicine: From A to ZZZZZ’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

A. Homeostatic Sleep Factor

Sleep propensity

High

Low

7:00 a.m. 11:00 p.m. 7:00 a.m.

B. Circadian Sleep Factor

Sleep propensity

High

Low

7:00 a.m. 11:00 p.m. 7:00 a.m.
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
<table>
<thead>
<tr>
<th>Structure</th>
<th>Neurotransmitter(s) it Releases</th>
<th>Effects on Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontomesencephalon</td>
<td>Acetylcholine, glutamate</td>
<td>Increases cortical arousal</td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td>Norepinephrine</td>
<td>Increases information storage during wakefulness; suppresses REM sleep</td>
</tr>
<tr>
<td>Basal forebrain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitatory cells</td>
<td>Acetylcholine</td>
<td>Excites thalamus and cortex; increases learning, attention; shifts sleep from NREM to REM</td>
</tr>
<tr>
<td>Inhibitory cells</td>
<td>GABA</td>
<td>Inhibits thalamus and cortex</td>
</tr>
<tr>
<td>Hypothalamus (parts)</td>
<td>Histamine, Orexin</td>
<td>Increases arousal</td>
</tr>
<tr>
<td>Dorsal raphe and pons</td>
<td>Serotonin</td>
<td>Maintains wakefulness</td>
</tr>
</tbody>
</table>

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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
Minimum of 3 EEG derivations required to sample from frontal, central and occipital regions

- 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)
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

<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Regular</td>
<td>Variable</td>
</tr>
<tr>
<td>Skeletal muscle tone</td>
<td>Preserved</td>
<td>Absent</td>
</tr>
<tr>
<td>Brain $O_2$ consumption</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Ventilatory response</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Temperature</td>
<td>Normal</td>
<td>Poikilothermic</td>
</tr>
</tbody>
</table>
Overview of sleep stages

Combined to become N3

2007 AASM scoring guidelines
Stage W
Stage 1
Stage 2
Stage 3
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
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 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 <3 months (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)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Onset of action</th>
<th>Hypnotic dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon (Sonata)</td>
<td>Short</td>
<td>15-30 min</td>
<td>10-20 mg</td>
<td>1 hr</td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>Short</td>
<td>30 min</td>
<td>5-10 mg</td>
<td>2.5 hrs</td>
</tr>
<tr>
<td>Ramelteon (Rozerem)</td>
<td>Short</td>
<td>30-45 min</td>
<td>8 mg</td>
<td>1-2.6 hours</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>Short</td>
<td>15-30 min</td>
<td>0.125-0.25 mg</td>
<td>2.9 hrs</td>
</tr>
<tr>
<td>Suvorexant (Belsomnra)</td>
<td>Intermediate</td>
<td>30-60 min</td>
<td>10-20 mg</td>
<td>12 hours</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>Intermediate</td>
<td>30 min</td>
<td>1-3 mg</td>
<td>6 hours</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>Intermediate</td>
<td>45-60 min</td>
<td>15-30 mg</td>
<td>8.0 hrs</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Intermediate</td>
<td>15-60 min</td>
<td>1-2 mg</td>
<td>10-24 hrs</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>Intermediate</td>
<td>30-60 min</td>
<td>1-2 mg</td>
<td>14 hrs</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>Intermediate</td>
<td>45-60 min</td>
<td>15-30 mg</td>
<td>11 hrs</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>Long</td>
<td>30-60 min</td>
<td>0.5 mg-1 mg</td>
<td>23 hrs</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>Long</td>
<td>15-30 min</td>
<td>5-10 mg</td>
<td>43 hrs*</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>Long</td>
<td>30-60 min</td>
<td>15-30 mg</td>
<td>74 hrs*</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Predisposing Factors</th>
<th>Precipitating Factors</th>
<th>Perpetuating Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Biologic traits</td>
<td>- Medical illness</td>
<td>- Excessive time in bed</td>
</tr>
<tr>
<td>- Psychological traits</td>
<td>- Psychiatric illness</td>
<td>- Napping</td>
</tr>
<tr>
<td>- Social factors</td>
<td>- Stressful life events</td>
<td>- Conditioning</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Opioids, NSAIDs</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>SSRIs, venlafaxine, duloxetine, MAOIs</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Caffeine, methylphenidate, amphetamines, cocaine</td>
</tr>
<tr>
<td>Decongestants</td>
<td>Phenylephrine, pseudoephedrine</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>β-blockers, diuretics</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Albuterol, theophylline</td>
</tr>
</tbody>
</table>

*MAOIs, monoamine oxidase inhibitor; NSAIDs, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor. Based on references 2, 7, 8, and 10.*
<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-related breathing disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The obstructive sleep apnea syndrome</td>
<td>Upper airway obstruction during inspiration in sleep.</td>
<td>History of snoring, witnessed pauses in respiration, and daytime sleepiness. Patients may report nonrestful sleep or insomnia. Polysomnography is necessary for diagnosis.</td>
</tr>
<tr>
<td>The central sleep apnea syndrome</td>
<td>Repetitive pauses in breathing during sleep without upper airway occlusion.</td>
<td>History of congestive heart failure or central nervous system disease. Polysomnography is necessary for diagnosis.</td>
</tr>
<tr>
<td>Sleep-related movement disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The restless legs syndrome</td>
<td>Uncomfortable or restless feeling in legs most prominent at night and at rest; alleviated by movement.</td>
<td>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.</td>
</tr>
<tr>
<td>Periodic limb movement disorder</td>
<td>Repetitive stereotypic leg movement in sleep and during quiet wakefulness.</td>
<td>Strongly associated with the restless legs syndrome. Polysomnography is necessary for diagnosis.</td>
</tr>
<tr>
<td>Nocturnal leg cramps</td>
<td>Pain in calf or foot resulting in awakening from sleep.</td>
<td>Painful cramp awaken the patient from sleep. Predisposing factors include diabetes, exercise, pregnancy, and metabolic and endocrine abnormalities.</td>
</tr>
<tr>
<td>Circadian rhythm sleep–wake disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time zone change syndrome (jet lag)</td>
<td>Travel leads to reports of poor sleep, daytime sleepiness, or both.</td>
<td>History of recent travel across multiple time zones.</td>
</tr>
<tr>
<td>Shiftwork sleep disorder</td>
<td>Insomnia as a consequence of shiftwork. Sleep occurs at times counter to normal circadian rhythm and social and environmental factors.</td>
<td>History of insomnia associated with shiftwork; this disorder also affects persons who permanently work the night shift.</td>
</tr>
<tr>
<td>The delayed sleep-phase syndrome</td>
<td>Delay of the major sleep phase relative to clock time.</td>
<td>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.</td>
</tr>
<tr>
<td>The advanced sleep-phase syndrome</td>
<td>The major sleep phase is advanced relative to clock time.</td>
<td>Inability to stay awake until desired bedtime and early-morning awakening. Occurs most commonly in elderly. Sleep log and actigraphy can aid diagnosis.</td>
</tr>
<tr>
<td>Parasomnias related to non–rapid eye movement</td>
<td>Include confusional arousals, sleepwalking, sleep terrors, and sleep-related eating disorders.</td>
<td>Disorders of arousal that may be a cause of disrupted sleep. Sleep history and input from bed partner or family may aid in identification.</td>
</tr>
</tbody>
</table>
ICSD-3 (2014)

Sleep Disorders (ICSD3)

Parasomnias
  - NREM-related parasomnias
    - Confusional arousals
    - Sleepwalking
    - Sleep Terrors
    - Sleep Related Eating Disorders
  - REM-related parasomnias
    - Insomnia
    - Sleep related breathing disorders
    - Central Disorders of hypersonolence
    - 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
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) $\geq 5$ 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 $\geq 5$ 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

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>9%</td>
<td>24%</td>
</tr>
<tr>
<td>OSAS</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

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

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

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.

<table>
<thead>
<tr>
<th>SpO2</th>
<th>Airflow</th>
<th>Thoracic</th>
<th>Abd</th>
</tr>
</thead>
</table>

**OSA – Example of a PSG**

[Graph showing SpO2, Airflow, Thoracic, and Abd scales with specific markers for desaturations and arousals.]
Consequences of OSA

- Coronary artery disease
- Heart failure
- Stroke
- Sleep Heart Health Study: cross-sectional association between OSA and self-reported CVD:
  - CAD: AR 1.27
  - CHF: CVA 2.38
  - CVA: AR 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 2-4 yrs
- Adjusted for age/sex/race, smoking, alcohol intake, BMI, DM, HTN, AF, high cholesterol

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]

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

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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:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHV</td>
<td>Medroxyprogesterone</td>
</tr>
<tr>
<td>REM OSA</td>
<td>SSRIs, TCAs</td>
</tr>
<tr>
<td>CHF</td>
<td>Theophylline</td>
</tr>
</tbody>
</table>
Sleep Disorders (ICSD3)

- Parasomnias
  - NREM-related parasomnias
    - Confusional arousals
    - Sleepwalking
    - Sleep Terrors
    - Sleep Related Eating Disorders
  - REM-related parasomnias
- 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

ICSD-3 (2014)
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 → palpitations, 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.
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 nocturnal 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)
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>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>Adult Daily Dose</th>
<th>Class</th>
<th>Indication</th>
<th>Patient Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium oxybate (Xyrem)</td>
<td>4.5-9.0 g per night</td>
<td>GHB</td>
<td>Cataplexy and EDS</td>
<td>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</td>
</tr>
<tr>
<td>Modafinil (Provigil)</td>
<td>200-400 mg</td>
<td>Non-sympathomimetic wake-promoting agent</td>
<td>EDS</td>
<td>Take medicine in the morning with or without food. May decrease effectiveness of OC; recommend additional form of birth control</td>
</tr>
<tr>
<td>Armodafinil (Nuvigil)</td>
<td>150-250 mg</td>
<td></td>
<td>EDS</td>
<td>Take medicine in the morning. Avoid sudden drug discontinuation</td>
</tr>
<tr>
<td>Dextroamphetamine/amphetamine salts (Adderall)</td>
<td>5-60 mg</td>
<td>Stimulant</td>
<td>EDS</td>
<td>Take medicine in the morning. Avoid sudden drug discontinuation</td>
</tr>
<tr>
<td>Dextroamphetamine (Dexedrine)</td>
<td>5-60 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate (Ritalin)</td>
<td>10-60 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methamphetamine (Desoxyn)</td>
<td>5-15 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
<td>50-250 mg</td>
<td>TCA</td>
<td>Cataplexy</td>
<td>Take medicine with or without food. If medicine causes sleepiness, take it at bedtime. Avoid sudden drug discontinuation</td>
</tr>
<tr>
<td>Nortriptyline (Aventyl, Pamelor)</td>
<td>50-150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protriptyline (Vivactil)</td>
<td>2.5-10 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>10-200 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>20-80 mg</td>
<td>SSRI</td>
<td>Cataplexy</td>
<td>Take medicine in the morning with or without food. Avoid sudden drug discontinuation</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>75-375 mg</td>
<td>SNRI</td>
<td>Cataplexy</td>
<td>Take medicine with food. Avoid sudden drug discontinuation</td>
</tr>
<tr>
<td>Atomoxetine (Strattera)</td>
<td>18-100 mg</td>
<td>SNRI</td>
<td>Cataplexy and EDS</td>
<td>Take medicine early in the day with or without food</td>
</tr>
<tr>
<td>Selegiline (Eldepryl)</td>
<td>5-10 mg</td>
<td>MAO-B inhibitor</td>
<td>Cataplexy and EDS</td>
<td>Take capsule or tablet early in the day with food. Avoid sudden drug discontinuation</td>
</tr>
</tbody>
</table>

* 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
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??

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