10:45 – 11:30 am

Tackling Sleep Disorders

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- James K. Wyatt, PhD, FAASM: Consultant for Philips Respironics.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

SLEEP DISORDERS

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LEARNING OBJECTIVES

By the end of this educational activity, learners will be able to:

1. Recognize signs and symptoms of common sleep disorders
2. Understand known or presumed pathophysiology of common sleep disorders
3. Initiate diagnostic workup procedures for common sleep disorders
4. Discuss treatment options with their patients
5. Appreciate clinical situations when collaborative care is required with a sleep disorders specialist

WHY SLEEP MATTERS FOR HEALTH

DURING SLEEP:
- Development and restoration (growth hormone)
- Nervous system restoration (axonal transport)
- Dedicated memory processing (cortex, hippocampus)
- Gastrointestinal function (parasympathetic)
- Immune system (ties to slow wave sleep)
- Preparation for the day (circadian release of cortisol)

DURING WAKEFULNESS:
- Optimal alertness and performance
- Avoidance of accidents, dangers

SLEEP AND DISEASE: BIDIRECTIONAL CAUSALITY

- Congestive Heart Failure → Central Sleep Apnea
- Stroke → Obstructive and/or Central Sleep Apnea
- Obstructive Sleep Apnea → MI and stroke

- Infection → excessive sleepiness and/or insomnia
- Sleep deprivation → weakened immune function

- Sleep deprivation → lowers pain threshold
- Pain condition → sleep fragmentation

ENDOGENOUS MODULATION OF SLEEP AND WAKEFULNESS

Sleep Homeostasis vs. Circadian Timekeeping System

STRAW POLL

- How much did you sleep last night?
  - At least 4 hours?
  - At least 6 hours?
  - At least 8 hours?
  - At least 8.3 hours?
- ~8.3 hours is the mean sleep need for the human adult

"NORMAL" SLEEP

- Total sleep time (TST)
  - Greater than 6.5 hours
- Sleep latency (SL or SOL)
  - 30 minutes or less
- Wake after sleep onset (WASO)
  - 30 minutes or less

SLEEP ARCHITECTURE

- Enter through NREM sleep
  - Except infants, narcoleptics, acute phase reversal (e.g., severe jet lag)
- NREM-REM cycle: every 90-110 minutes
- Slow wave sleep (stage N3): most in first 1-2 cycles
- REM: episodes lengthen with each cycle
- REM sleep: most in 2nd half of the night
- Awakenings vs. EEG- or other- arousals

CAUSES OF EXCESSIVE DAYTIME SLEEPINESS (EDS)

1. Sleep Deprivation (voluntary, environment)
2. Sleep Fragmentation (environement, OSA)
3. Circadian Phase (shift work, let jag)
4. Medication Effect (hypnotics, antihistamines)
5. CNS Pathology (infections, neuro disease)

6. Sleep Disorders (cause or involve 1-5)

MEASUREMENT OF SLEEP AND DAYTIME SLEEPINESS

POLYSOMNOGRAPHY (PSG)

- The "gold standard" for measuring sleep
- Overnight PSG
  - Sleep duration, SL, WASO, TST, SE%
  - Sleep stage percentages, arousal index
  - 2-lead ECG for basic rhythm changes
  - Respiratory measures
  - Leg movement measures
  - Lab vs. home (limited measures)

LEVELS OF SLEEP TESTING

LAB SLEEP TESTING

- **Type 1: full attended polysomnography (≥ 7 channels) in a laboratory setting**

HOME SLEEP TESTING

- Type 2: full unattended polysomnography (≥ 7 channels)
- **Type 3: limited channel devices (usually using 4–7 channels)**
- Type 4: 1 or 2 channels usually using oximetry as 1 of the parameters

EPWORTH SLEEPINESS SCALE (average daytime sleepiness)

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze

1 = *slight* chance of dozing

2 = *moderate* chance of dozing

3 = *high* chance of dozing

Situation	Chance of Dozing
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g., theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when the circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a minute in traffic	_____

ESS SCORING

- Normal / average: 0-10
- Excessive daytime sleepiness: 11-24

- OSA 13.0
- Narcolepsy + cataplexy: 18.6

Johns, Sleep 1991, 1992; Johns, Chest, 1993

OBJECTIVE MEASUREMENT OF EXCESSIVE DAYTIME SLEEPINESS

- Multiple Sleep Latency Test (MSLT)
  - 4-6 naps in bed, 2hr apart, after full sleep
  - Optimal sleep conditions, speed to fall sleep
  - "What is your **worst sleepiness**?"
- Maintenance of Wakefulness Test (MWT)
  - 4-6 tests, 2hr apart, after full sleep
  - Dim light, chair reclined, speed to fall asleep
  - "How well can you **avoid falling asleep**?

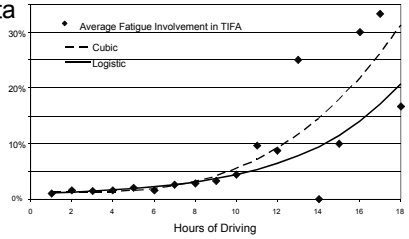
Littner et al., Sleep, 2005

MULTIPLE SLEEP LATENCY TEST

- Midafternoon dip
- Dose-response relationship (TST to EDS)
- "Twilight Zone" of pathologic daytime sleepiness

Separate "Time on Task" Adder for 2005 and After

- Allowed for an independent effect beyond effect of excessive time awake
- Fit a polynomial, then a logistic, to TIFA data



mcsac.fmcsa.dot.gov/.../Analysis_of_Hours_of_Service_Regulation.ppt

RISKS TO SELF AND OTHERS

Ayas et al., *JAMA,* 2006

- **Needlesticks and lacerations (n = 2,737)**
- **1.61 OR (1.46-1.78) from extended hours**
- **2.04 OR (1.98-2.11) from night work**

Barger et al., *NEJM,* 2005

- **"Extended shift" ~ 32 hours**
- **Near Miss: odds ratio of 5.9 (5.4-6.3)**
- **MVA: odds ratio of 2.3 (1.6-3.3)**

PART 2: SLEEP DISORDERS

MAKING THE DIAGNOSIS

- Sleep Sxs and daytime functioning history
  - Onset, variation over time, current state
  - Daytime symptoms
  - Prior treatment attempts
  - Sleep habits (e.g., naps, sleep schedule)
  - Sleep environment (e.g., noise, TV, snoring)
- Medical history
  - Medications, injuries, diseases, pain conditions
- Psychiatric history
  - Mood or anxiety disorders, medications
- Family History (Med, sleep)
- Sleep diary & wrist actigraphy
- Polysomnography
  - Checking for primary sleep disorders

Wyatt et al., in Oxford Handbook of Sleep Disorders, 2012

HIGH YIELD QUESTIONS

- Do you snore?
- Are you sleepy during the day?
- Do you have trouble falling asleep or staying asleep at night?
- Do you need to take something in order to sleep? Or to stay awake during the day?
- How many hours are you sleeping on the typical night?

INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS – 3ND EDITION

1. Insomnia (3)
2. Sleep Related Breathing Disorders (17)
3. Central Disorders of Hypersomnolence (8)
4. Circadian Rhythm Sleep-Wake Disorders (7)
5. Parasomnias (13)
6. Sleep Related Movement Disorders(10)

- 58 disorders of sleep + isolated symptoms and normal variants
- ICSD-3 just released mid-2014

ICSD-3, *AASM*, 2014

1. CHRONIC INSOMNIA DISORDER

- Difficulty initiating sleep, or
- Difficulty maintaining sleep, or
- Waking up too early, or
- Resisting going to bed on schedule, or
- Difficulty sleeping w/o parent/caregiver

- Adequate opportunity and circumstances for sleep
- At least 1 daytime consequence
- At least 3 nights per week
- At least 3 months (Acute insomnia: < 3 months)

- At least 1 month = chronic insomnia
- 30M in U.S. with chronic insomnia !

ICSD-3, *AASM*, 2014

DAYTIME COMPLAINTS IN INSOMNIA

- Fatigue or malaise
- Attention, concentration, or memory impairment
- Social, family, occupational, or academic impairment
- Mood disturbance or irritability
- Daytime sleepiness
- Behavioral problems (e.g., hyperactivity, impulsivity, aggression)
- Motivation, energy, or initiative reduction
- Proneness for errors or accidents
- Concerns about or dissatisfaction with sleep

ICSD-3, *AASM*, 2014

TREATMENT OPTIONS: "The 30,000 foot view"

- (possibly) no treatment
  - Acute insomnia
- Hypnotic administration
  - Acute insomnia
  - Initial treatment, severe chronic insomnia
- Cognitive-Behavioral Treatment for insomnia
  - Chronic insomnia, sometimes in acute insomnia
- Hypnotic tapering and discontinuation
  - Chronic insomnia, along with CBT for insomnia

SPIELMAN'S "3-P MODEL"

- Predisposing factors
  - Physiological hyperarousal
  - Lower sleep homeostatic drive
- Precipitating events
  - Stressful life event (74%; Healy et al., 1981)
  - Good or bad stressors
- Perpetuating factors

Spielman, Clinical Psychology Review, 1986
Wyatt & Crisostomo, in Sleep Medicine, 2008

PERPETUATING FACTORS: after insomnia onset, patient begins to…

- too much time in bed
  - "catch sleep if it occurs"
- sleep later when possible
- nap after poor night's sleep

Behavioral

- caffeine & stimulants for EDS
- alcohol self-medicating for sleep
- random use of hypnotics

Pharmacologic

- expectations of poor sleep
- unreasonable concerns over next-day consequences

Cognitive

Spielman, Clinical Psychology Review, 1986
Wyatt & Crisostomo, in Sleep Medicine, 2008

SHORT-TERM INSOMNIA DISORDER

- Same major criteria as chronic insomnia disorder
- Acute onset
- < 3 months in duration
- Look for stressors, medications, medical conditions
- 15-20% prevalence per YEAR

STRAW POLL:

- Midterms, final exams
- Waiting for acceptance to Rush

ICSD-3, *AASM*, 2014

COMORBIDITY OF INSOMNIA

- Moving away from various insomnia diagnoses
- Comorbidity concept

- Insomnia due to a mental disorder
- Insomnia due to a medical disorder
- Insomnia secondary to substance
- Psychophysiological (conditioned) insomnia
- Idiopathic (life-long) insomnia
- Inadequate sleep hygiene

ICSD-2; *AASM*, 2005
Edinger, Wyatt, et al, Arch Gen Psychiatry, 2011

STIMULUS CONTROL

- Go to bed only when sleepy
- Bed for sleep (and sex) only
- If not asleep in 15-20 minutes, leave the bed and engage in calming activity elsewhere
  - Return to bed when sleepy
  - Repeat as needed
- Fixed wake time
- No napping
- [The gold standard]

Bootzin RR et al., in Case Studies in Insomnia, 1991
Bootzin RR. Proceedings of the American Psychological Association 1972
Morin et al., Sleep, 2006

HYPNOTICS: RULES OF THUMB

- Lowest effective dose, elderly & women
- Match ½-life to sleep complaint
- 2-4 weeks is standard, then re-evaluation of need for continued use
  - Chronic for Tx of PLMD, parasomnias, idiopathic insomnia, other chronic conditions
- Warn against concurrent alcohol use
- Warn about sedation, memory impairment, imbalance, increased MVAs
- Not recommended in (un)treated OSA

"OLD SCHOOL" HYPNOTICS

Ambien (zolpidem)

- BZRA
- 5, 10 mg dosing
- T_{max} =1.6 hr, $T_{½}$ = 2.5 hr
- No active metabolites
- Does not suppress SWS
- Does suppress SWA
- "Recent" data on sleepwalking risk
- Schedule IV / Pregnancy category C (used to be category B)

Restoril (temazepam)

- Benzodiazepine
- 15, 30 mg typical
- 7.5, 22.5 mg – new doses
- $T_{½}$ = 8.8 hr
- Reasonable for sleep maintenance
- Morning hangover possible
- Good for parasomnias (e.g., sleepwalking)
- Schedule IV/ Pregnancy category X

NEWER HYPNOTICS

Sonata (zaleplon)

- Non-benzodiazepine
- 5, 10 mg dosing
- T_{max} =1 hr, $T_{½}$ = 1 hr
- Approved for middle-of-night dosing
- ≥ 4 hr time for sleep must follow
- q hs not for sleep maintenance insomnia
- Schedule IV / Pregnancy category C

Lunesta (eszopiclone)

- Non-benzodiazepine
- 1, 2, 3 mg dosing
- T_{max} ≈ 1 hr $T_{½}$ ≈ 6 hr
- 6 month + 6 month open label data
- Maintains efficacy: SOL, WASO
- Schedule IV/ Pregnancy category C

Other "Newer" Hypnotics

- Rozerem (ramelteon, melatonin receptor agonist)
- Ambien CR (2-layer pill of zolpidem, a BZRA)
- Silenor (low-dose doxepin, a sedating antidepressant)
- Belsomra (suvorexant, orexin receptor antagonist)

OFF-LABEL USE OF OTHER MEDS

- Trazodone
  - **Most commonly prescribed med for insomnia**
  - Scarcity of data in non-depressed insomnia
  - No effect on SE% (Roth et al., JSR 2011 20(4) in primary insomnia
  - No increase in TST
- Low-dose tricyclics
  - Anticholinergic and other side effects
  - Cardiac safety concerns
  - Daytime hangover

2. SLEEP RELATED BREATHING DISORDERS

- Obstructive sleep apnea disorders (OSA)
  - Adult and pediatric OSA
- Central sleep apnea syndromes (CSA)
  - E.g., central sleep apnea with Cheyne-Stokes breating
- Sleep related hypoventilation disorders
  - e.g., obesity hypoventilation syndrome
- Sleep related hypoxemia disorder

ICSD-3, *AASM*, 2014

OSA PATHOPHYSIOLOGY

- Upper airway crowding (obesity or other), occasionally nasal obstruction
- Pharyngeal dilator fatigue during wake
- Upper airway narrowing or collapse
- >10 second airflow reduction or cessation
- ↑ C02 detected -> CNS "alarm", arousal, hyperpnea, rapid return to sleep, repeat

AASM Manual for Scoring Sleep, 2007; Dempsey et al., Physiol Rev, 2010

"STOP-BANG"

- S: snoring
- T: tired
- O: observed apneas, pauses in breathing
- P: (blood) pressure
- B: BMI (over 35)
- A: Age (over 50)
- N: neck (over 40cm)
- G: gender (male)
- 3+ items = increased risk for OSA

RESPIRATORY MEASURES

- Nasal/oral <u>airflow</u>
  - Nasal/oral thermistor (temperature sensor) &
  - Nasal pressure transducer
- Respiratory <u>effort</u>
  - inductance plethysmography
- Oxygen <u>saturation</u>
  - earlobe or finger pulse oximetry
- Snoring microphone
- End-tidal CO2 (mandatory for children)

SEVERITY OF OSA

- AHI = # of apneas + hypopneas per hour of recorded sleep
- RDI = respiratory disturbance index (when sleep is not measured)
  - AHI 5-15 = mild OSA
  - AHI 15-30 = moderate OSA
  - AHI 30+ = severe OSA
- Consider also:
  - Medical comorbidities, risks
  - Alertness-sensitive occupations
  - Degree of oxygen desaturation
  - Degree of daytime symptoms

RISK FACTORS

- Obesity (70% of OSA patients)
- Neck circumference: ≥17" M, ≥ 16" F
- Women partially "protected" until menopause
- Aging, even healthy aging
- 4% men, 2% of women have symptomatic OSA (OSA + EDS)
- **23% men, 9% of women have AHI ≥5**
- HIGHER NOW – obesity epidemic

Dancey et al., Chest, 2003; Young et al., NEJM, 1993

CARDIOPULMONARY SEQUELAE

- Cardiac arrhythmias (n-sVT, a fib, PAC, PVC)
- Systemic HTN
- MI, CVA
- Changes in inflammatory markers (e.g., CRP)
- Higher GLU and insulin levels
- worsening LVEF
- (not to mention EDS, accidents, mood & cognitive problems)

Mehra et al., Arch Int Med, 2009; Pack & Gislason, Prog Cardiovasc Dis, 2009

TREATMENT OPTIONS

- PAP (CPAP, bilevel PAP, autoPAP)
- Weight loss
- ENT Surgery
  - Uvulopalatopharyngoplasty (UPPP)
  - Genioglossus advancement w/ hyoid suspension
  - Maxillary-mandibular advancement
- Oral Appliances
  - Mandibular repositioning devices
  - Tongue retaining devices
- Body position training
- Adjuvant treatments (e.g., nasal steroids)
- Tracheostomy

ADJUVANT TREATMENTS

- Decrease ETOH
  - Lowers upper airway muscle tone
  - Suppression of early REM sleep, rebound later
  - Higher fragmentation of sleep
  - Diuresis, nocturia
- Stop smoking
- Increase nasal patency
- Treat nasal allergies
- Avoid sleep deprivation

3. CENTRAL DISORDERS OF HYPERSOMNOLENCE

- Insufficient Sleep Syndrome
- Narcolepsy Type 1, Type 2
  - Severe EDS + REM phenomena
- Idiopathic Hypersomnia
  - Severe EDS, chronic
- Recurrent hypersomnia / Klein-Levin Syndrome
  - Intermittent severe EDS

ICSD-3, *AASM*, 2014

EDS or not EDS

- Sleepy
- Fatigued
- Tired
- Exhausted
- Wiped out
- Low energy
- Nodding
- Dozing
- Drowsy
- Sluggish
- Bushed
- Dragging
- All tuckered out
- Beat
- Lethargic
- Somnolent
- Resting my eyes
- Slumberous
- Yawning
- …

SLEEPINESS vs. FATIGUE

- Sleepiness
  - Desire to fall asleep / inability to stay awake
- Cognitive Fatigue
  - Slowed mental performance, often from sustained mental effort
- Physical Fatigue
  - Low physical energy, muscle weakness

INSUFFICIENT SLEEP SYNDROME

- Voluntary restriction of time for sleep
- Short sleep = daytime complaints
  - EDS and/or fatigue
  - cognitive problems
  - lability or moodiness
- Sxs clear on rebound
  - Vacation, weekends
- EPIDEMIC IN U.S. per the CDC
- Longer sleep, recovery sleep, napping, caffeine

ICSD-3, *AASM*, 2014

If you do not have time for sufficient nighttime sleep (and you don't have insomnia), an intentional nap is the best countermeasure you can take.

An unintentional nap means it's too late.

4. CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

- Shift work sleep disorder (SWSD)
  - Voluntary change of sleep/wake timing
- Jet lag
  - Voluntary change of S/W and light/dark cycle
- Delayed and advanced sleep phase types
  - Wrong timing of circadian phase
- Irregular and free-running S/W types
  - Malfunctioning SCN

Wyatt, in Sleep Medicine Clinics 2, 2007

Shift Work Disorder

- There is a report of **insomnia and/or excessive sleepiness**, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
- The symptoms have been present and associated with the shift work schedule for **at least three months**.
- **Sleep log and actigraphy monitoring** (whenever possible and preferably with concurrent light exposure measurement) for at least **14 days** (work and free days) demonstrates disturbed sleep and wake pattern.
- The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder.

ICSD-3

SHIFT WORK

- Nap before or during night or extended shifts [indicated: standard]
- Hypnotic for day sleep [indicated: guideline]
- Melatonin for day sleep (guideline)
- Caffeine (option)
- Modafinil (guideline)

- Recovery sleep
  - rebound sleep, telephone & doorbell off, protected sleep time (kids, pets)
  - catch up prior to next night shift
- Light exposure at work for stimulatory effect
- Don't work shifts
  - some individuals are more intolerant of shift work

Because sleep taken at night during the WOCL is more restful than sleep taken during the day,[63] flightcrew members who begin their FDP in the morning will be better rested than flightcrew members who begin their FDP later in the day or at night. Accordingly, Table C sets higher FDP limits for augmented FDPs that begin in the morning and lower FDP limits for augmented FDPs that begin later in the day or at night.

63 See, e.g., James K. Wyatt, et. al., Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day, Am. J. Physiol. 277 (4), at R1160–62 (1999); Torbjorn Akerstedt & Mats Gillberg, The Circadian Variation of Experimentally Displaced Sleep, Sleep, Vol. 4, No. 2, at 159-69 (1981).

CAFFEINE

[1] Wyatt, et al, *Sleep,* 2004
[2] Landolt, et al, *Neuropsychopharmacology,* 1995
[3] Landolt, et al, *Brain Res*., 1995

THE GOOD:

- 3-7 hr half life
- 100mg coffee, 45mg soda, 200mg No-Doz
- Adenosine receptor antagonist
- **Attenuates the expression of sleep homeostatic drive**
- Beneficial effect on homeostatic-related (not circadian) cognitive deficits with extended wakefulness[1]

THE BAD:

- Increases sleep latency[2]
- Suppresses slow wave activity (deep sleep) [3]
- "sensitivity": insomnia, nervousness, irritability, tachycardia

5.PARASOMNIAS

- NREM parasomnias
  - Sleepwalking (somnambulism)
  - Sleep Terrors (pavor nocturnus)
  - Confusional Arousals
  - Sleep Related Eating Disorder
- REM parasomnias
  - REM Sleep Behavior Disorder (RBD)
  - Recurrent Isolated Sleep Paralysis
  - Nightmare Disorder
- Other parasomnias (6)

ICSD-3, *AASM*, 2014

6. SLEEP RELATED MOVEMENT DISORDERS

- Restless Legs Syndrome (RLS)
- Periodic Limb Movement Disorder (PLMD)
- 8 others

ICSD-3, *AASM*, 2014

RESTLESS LEGS SYNDROME

- "Ekbom's Disease/Syndrome" – 1944
- Being renamed: "Willis-Ekbom Disease"

Clinical diagnosis: must include:

1. Irresistible urge to move legs accompanied by sensory complaints ("creepy-crawly")
2. Motor restlessness
3. Sxs worse at rest; movement or walking relieves Sxs
4. Onset in presleep or evening hours

- Idiopathic vs. secondary (anemia, pregnancy, ESRD, neuropathy)
- **5-10% prevalence**

ICSD-3; IRLSSG, *Mov Disord*, 10, 1995

RLS / PLMD TREATMENTS

- Iron supplement: if ferritin < 50 µg/L
- DA agonists (low dose, vs. for PD)
  - Requip / ropinirole
  - Mirapex / pramipexole
- Hypnotics
- Anticonvulsants
- Opiates

- Antidepressants typically worsen symptoms

Littner et al., Sleep, 2004