Inaugural Yale Sleep Symposium: Advances in the Treatment of Common Sleep Disorders

September 18, 2015
Inaugural Yale Sleep Symposium:
Advances in the Treatment of Common Sleep Disorders

Friday, September 18, 2015

LEARNING OBJECTIVES
This course will enable participants to:

- Identify patients at high risk for sleep disorders and those appropriate for sleep evaluation
- Review health risks related to untreated sleep disorders
- Examine advances in treatments for various sleep disorders such as sleep disordered breathing, sleep related movement disorders, circadian rhythm disorders, and parasomnias
- Recognize barriers to effective diagnosis, treatment, and management of sleep disorders in various populations including women, children, and the elderly

ACCREDITATION STATEMENT
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DESIGNATION STATEMENT
The Yale School of Medicine designates this live activity for a maximum of 5.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
## Schedule

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<tr>
<td>8:00 AM</td>
<td>Registration and Continental Breakfast</td>
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<tr>
<td>8:55 AM</td>
<td>Welcome and Introductions</td>
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<tr>
<td></td>
<td><em>Christine Won MD, MS</em></td>
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<tr>
<td>9:00 AM</td>
<td>Chronic Insomnia: Implications on Medical and Psychological Health</td>
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<td></td>
<td><em>Nancy Redecker PhD, RN, FAHA, FAAN</em></td>
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<tr>
<td>9:30 AM</td>
<td>Pharmacologic and Behavioral Therapies for Chronic Insomnia</td>
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<td><em>Lynelle Schneeberg PsyD</em></td>
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<tr>
<td>10:00 AM</td>
<td>Treating Sleep Health in the Shift Worker</td>
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<td><em>Christine Won MD, MS</em></td>
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<tr>
<td>10:30 AM</td>
<td>Circadian Disorders: Re-setting the Clock</td>
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<td><em>Melissa Knauert MD, PhD</em></td>
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<tr>
<td>11:00 AM</td>
<td>Refreshment Break</td>
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<tr>
<td>11:15 AM</td>
<td>Hypersomnia: Pathophysiology, Clinical Features and Diagnosis</td>
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<td></td>
<td><em>Meir Kryger MD</em></td>
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<tr>
<td>11:45 AM</td>
<td>Management of Patients with Narcolepsy</td>
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<td><em>Vahid Mohsenin MD</em></td>
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<td>12:15 PM</td>
<td>Lunch</td>
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<tr>
<td>1:15 PM</td>
<td>Things That Go Bump in the Night: Parasomnias and Sleep-Related</td>
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<td>Movement Disorders</td>
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<td><em>Brian Koo MD</em></td>
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<tr>
<td>1:45 PM</td>
<td>Multidisciplinary Treatment Approach for Obstructive Sleep Apnea</td>
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<td></td>
<td><em>Lauren Tobias MD</em></td>
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<tr>
<td>2:15 PM</td>
<td>A Novel Therapy for Obstructive Sleep Apnea: Upper Airway Stimulator</td>
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<td><em>H. Klar Yaggi MD, MPH</em></td>
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<tr>
<td>2:45 PM</td>
<td>Innovative, Patient-Centered Care for Common Sleep Disorders</td>
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<td></td>
<td><em>Janet Hilbert MD</em></td>
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<td>3:15 PM</td>
<td>Adjourn</td>
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Faculty

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Medical Director, Yale Centers for Sleep Medicine
Yale School of Medicine

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The following indicates participants’ responses to disclosure policy:

<table>
<thead>
<tr>
<th>Name</th>
<th>Nothing to Disclose</th>
<th>Speaker (and/or spouse/partner) has significant corporate relationship(s) with:</th>
<th>Role of service/financial relationship</th>
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<tr>
<td>Janet Hilbert MD</td>
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<td>Melissa Krauer MD, PhD</td>
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<td>Brian Koo MD</td>
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<td>Meir Kryger MD</td>
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<td>Vahid Mohsenin MD</td>
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<td>Teva Pharmaceuticals</td>
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<td>Jazz Pharmaceuticals</td>
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<td>Nancy Redeker PhD, RN, FAHA, FAAN</td>
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<td>Lauren Tobias MD</td>
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<td>Anne Stark</td>
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<td>Christine Won MD, MS</td>
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<td>H. Klar Yaggi MD, MPH</td>
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After review by the Course Director, it has been determined there are no conflicts of interest.
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Recording of this session by attendees is strictly prohibited
Chronic Insomnia: Implications for Medical & Psychological Health

Nancy S. Redeker, PhD, RN, FAHA FAAN
Beatrice Renfield Term Professor of Nursing

Disclosures

• I have nothing to disclose
Objectives

At the conclusion of this session, participants will be able to:

- Describe the epidemiology of chronic insomnia
- Explain the contributions of chronic insomnia to health and function

ICSD-3 Chronic Insomnia Disorder
(ICD-9-CM 307.42; ICD-10-CM F51.01)

One or more (patient or parent report):
- Difficulty initiating sleep
- Difficulty maintaining sleep
- Waking up earlier than desired
- Resistance to going to bed on appropriate schedule
- Difficulty sleeping without parent or caregiver intervention

Chronic Insomnia Disorder (cont.)

One or more:
- Fatigue/malaise
- Attention, concentration or memory impairment
- Impaired performance
- Mood disturbance/irritability
- Daytime sleepiness
- Behavioral problems
- Reduced motivation
- Proneness for errors/accidents
- Dissatisfaction with sleep

Chronic Insomnia Disorder (cont.)

- At least 3 time per week
- At least 3 months
- Not better explained by another sleep disorder or comorbid condition
Sub-types of Insomnia

- Duration
  - Acute
  - Intermittent
  - Chronic
- Etiology: primary; comorbid (90%)
- Type
  - Sleep onset: SOL > 31 min > 3 nights/week
  - Sleep maintenance: WASO > 31 mins/ > 3 nights/week
  - Mixed: 1 or 2 nights of either SOL or WASO
  - Combined: meets both of first 2 criteria

(Lichstein et al. in Kryger et al. 2011)

Short-Term Insomnia Disorder
(ICD-9-CM 307.41; ICD-10-CM F51.02)

Criteria as for Chronic Insomnia disorder, but sleep disturbance and associated symptoms are present for less than three months.

Epidemiology of Insomnia

- Estimates: 4-48%
- Studies/surveys different criteria may explain wide variability
- ~10% of the adult population experience chronic insomnia
- ~30% of adult primary care population
- Rates higher among those with comorbid medical and/or psychiatric disorders

Explanatory Models of Insomnia

Perlis et al., in Kryger, Roth, Dement, 2011

- Stimulus control model - physical alteration of sleep environment
- Spielman “3 P” model – predisposing, precipitating and perpetuating factors
- Neurocognitive model – disorder of retrograde amnesia of sleep
- Psychobiological inhibition model – failure to inhibit wakefulness
- Drosophila model – genetic basis
- Cage exchange model – insomnia a hybrid state: wake and sleep
Factors that contribute to insomnia and its consequences

The 3-P Model - updated
Harvey & Spielman in Kryger et al., 2011
Predisposing Factors

• Personality
• Sleep-wake cycle
• Circadian mechanisms
• Coping mechanisms
• Age

Precipitating Factors

• Situational
• Environmental
• Medical
• Psychiatric
• Prescription medications
Perpetuating Factors

- Conditioning
- Substance Abuse
- Performance anxiety
- Poor sleep hygiene
- Cognitions
- Hyperarousal
  - Cognitive
  - Cortical
- Sleep-related behavior

Consequences of Insomnia

- Health-related quality of life
- Symptoms: fatigue, sleepiness, anxiety, depression, pain
- Medical Conditions
- Psychiatric Conditions
- Performance
- Injury
**Insomnia, Symptoms & Daytime Function**

Redeker et al., Sleep 2010; 33; 551-560

<table>
<thead>
<tr>
<th>Insomnia Symptoms (DIMS)</th>
<th>Yes</th>
<th>Mean (95% CI)</th>
<th>No</th>
<th>Mean (95% CI)</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
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<tr>
<td>Sensory Fatigue</td>
<td>6.10</td>
<td>(5.59, 6.61)</td>
<td>4.88</td>
<td>(4.33, 5.43)</td>
</tr>
<tr>
<td>Depression</td>
<td>20.66</td>
<td>(18.45, 22.87)</td>
<td>13.84</td>
<td>(11.47, 16.21)</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>9.55</td>
<td>(8.60, 10.51)</td>
<td>7.72</td>
<td>(6.68, 8.75)</td>
</tr>
<tr>
<td>Functional Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>17.10</td>
<td>(16.16, 18.04)</td>
<td>18.60</td>
<td>(17.60, 19.60)</td>
</tr>
<tr>
<td>Six minute walk (feet)</td>
<td>875.3</td>
<td>(791.0, 959.6)</td>
<td>976.8</td>
<td>(882.9, 1070.7)</td>
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</table>

**Consequences: Hypertension**

- Central PA cohort/cross sectional (Vgontzas et al., Sleep 2009)
  - Insomnia + < 5 hours sleep: HTN (OR [95% CI] 5.1 (2.2,11.8)
  - Insomnia + 5-6 hours sleep: HTN (OR [95% CI] 3.5 (1.6,7.9)
- Active duty services members (Lewis et al., MSMR 2014)
  - Insomnia (HR [95% CI] 2.0 (1.85-2.16).
- Norway/prospective (Haaromo et al., J Sleep Res 2015)
  - Insomnia: use of HTN and dyslipidemia medications
- Insomnia + hyperarousal/normal (Li et al., Hypertension, 2015)
  - Insomnia + MSLT > 14 (OR [95% CI] 3.27 (1.20,8.96)
  - Insomnia + MSLT > 17 (OR [95% CI] 4.33 (1.48,12.68)
Consequences: CHD

- Women’s health initiative: 10 year f/u (Sands-Lincoln et al. J Women’s Health 2013)
  - Elevated risk of CHD (38%) and CVD events (27%) after adjustment for age and race, and in fully adjusted models (HR [95% CI] 1.19, 95% (1.09-1.30); HR [95% CI] 1.11 (1.03-2.00)
- Prospective study: 11 year follow-up to AMI (Laugsand, Circulation, 2011)
  - Difficulty initiating sleep: HR [95% CI] 1.45 (1.18-1.80)
  - Difficulties maintaining sleep HR 1.27 (1.03-1.57)
  - Combined insomnia symptoms - dose-dependent association between # insomnia symptoms and AMI risk (P for trend 0.003).

Consequences: Heart Failure

- Population based study/Norway: 11 year f/u (Laugsand et al., Eur Heart J 2014)
  - One insomnia symptom: Adjusted HR [CI 95%] 0.96 (0.57–1.61)
  - Two symptoms HR 1.35 (0.72–2.50)
  - Three symptoms HR 4.53 (1.99–10.31) for
  - (P for trend 0.021
Consequences: Diabetes

• Active duty services members (Lewis et al., MSMR 2014)
  — Adjusted HR [95% CI] 2.17 (1.75-2.690)
• Hispanic Community Health Study; Cross-sectional (Cespedes et al. J Diabetes 2015)
  — short sleep and insomnia: OR [95% CI] 1.46; 95% confidence interval [CI] 1.02, 2.11).
  - Insomnia + avg sleep dur: OR 1.28 (1.02, 1.61)
  - Long sleep/no insomnia OR 1.33 (1.07, 1.65) Further adjustment for body mass index attenuated associations, except with long sleep without insomnia.

Consequences: Mental Health

• Insomnia predicts depression: Meta-analysis (Baglioni, J Affective Disorders 2011)
  — Overall OR [CI 95%] 260 (1.98–3.42).
  — Fixed effects model showed an overall OR 2.10 (CI: 1.86–2.38).
• Insomnia predicts PTSD (Wright et al., J Clin Psychology 2011)
• Failure to treat insomnia leads to relapse from alcohol recovery
Physiological Parameters Implicated in Insomnia

(Bonnet et al., Sleep Med Rev 2014; 18; 111-122)

- Increased Beta EEG
- Cortisol
- Heart rate/sympathetic activity
- MSLT (lengthened: arousal?)
- Blood pressure (increased)

- Metabolic rate (increased)
- Inflammation (increased)
- Immunity (decreased)
- Ghrelin (decreased)
- Gaba (decreased)

Evidence of Physiological Improvements with Insomnia Treatment

RCT: CBT for Insomnia vs. Tai Ch; N = 109 Adults > 55 y/o; 95% had CVD

CBT-I improved

- composite metabolic/CVD risk factors (high density lipoprotein, low-density lipoprotein, triglycerides, hemoglobin A1c, glucose, insulin, C-reactive protein, and fibrinogen (Carroll et al., Psychoneuroendocrinology 2015)
- CRP, monocyte proinflammatory cytokines, proinflammatory gene expression (Irwin et al., Biological Psychiatry, 2015)
- reduced risk of high CRP (> 3.0 mg/L) (odds ratio [OR], 0.26 [95% CI, 0.07-0.97] P < 0.05) (Irwin et al., Sleep 2014)
Costs of insomnia to the Individual & Society

- Health care services - nursing home (91%), psychologists, physician visits, hospital care, sleep specialists, mental health organizations - $13.9 billion

- Substance to promote sleep (prescription, non-prescription, alcohol) - $1.63 billion (Walsh, 1999)

- Cost of testing for sleep apnea: $17.5 billion, $3 billion to treat sleep apnea (Sassani, 2004)

Indirect costs of sleep disorders

- Workplace productivity ~$200 billion
- Medical Errors
- Motor vehicle and other accidents ~ $40 billion
Accidents vs. Time of Day

Research & Clinical Challenges

- Health care providers often do not assess for sleep/insomnia in routine clinical practice
- Hypnotic medications often have daytime effects
- Behavioral treatment is available, but access is limited
- Insomnia is often comorbid with other sleep disorders
- Various criteria use for insomnia/sleep disturbance
Summary & Implications

• Chronic insomnia is common.
• Common insomnia contributes to poor quality of life, symptoms, and injury risk
• Growing evidence suggests that chronic insomnia contributes to metabolic, CVD and psychiatric outcomes
• Assessment and management of insomnia may reduce these risks
• Future research is needed
Pharmacological and Behavioral Therapies for Chronic Insomnia

Lynelle Schneeberg, PsyD
Diplomate, American Board of Sleep Medicine
Clinician, Yale Centers for Sleep Medicine
Yale University School of Medicine

Disclosure and Conflicts of Interest

Confirmation is made that this presentation and the faculty disclosure form have been reviewed and that there are no conflicts of interest.
Topics to be discussed

- Insomnia Basics
- Pharmacological Treatments
- The Case for Using CBT
- Insomnia Evaluation
- Insomnia Treatment
- Relapse Prevention
- New Therapies
- Questions and Resources

Insomnia

- Insomnia is defined as an inability to get the amount of sleep you need to wake up feeling rested and this is accompanied by distress or daytime consequences.
- About 30-40% of adults say that they have symptoms of insomnia within a given year.
- Approximately 5-15% say they have chronic insomnia. (Roth T, et al, Biol Psychiatry, 2011)
Types of Insomnia

- Sleep onset insomnia
- Sleep maintenance insomnia
- Early morning awakening

The Three Ps of Insomnia (Diathesis-Stress Model)

- **Predisposing factors** (genetics, “wiring”)
- **Precipitating factor** (stressful event)
- **Perpetuating factors** (behaviors that cause insomnia to persist after the precipitating event has resolved)

How Chronic Insomnia Evolves

- In an attempt to cope, a person often does all the wrong things with all the right intentions:
  - Goes to bed earlier and sleeps later on weekends
  - Tries to “force” sleep ("If I lie here, sleep is bound to come") and therefore increases wake time in bed
  - Clock watches and calculates time left in the night for sleep
  - Stays in bed watching TV or working
  - Takes long naps or uses meds or alcohol to get to sleep
  - Reduces physical activity to “save energy”
  - Avoids evening social engagements to “prepare for sleep”

Insomnia Case Example

- **Amy:** 62 year old woman with multi-decade hx of insomnia. She has no SOI but struggles with SMI and EMA. She ruminates at night. She has a very complicated Rx regimen: At 10pm, she takes 1mg of diazepam, OTC valerian & 20 mg of melatonin. She usually awakens around 1am, takes 5mg of zaleplon to return to sleep and moves to another bedroom. She awakens again around 4am and takes another 1/2mg of diazepam. If unable to return to sleep, she goes downstairs to meditate or read. If she becomes sleepy after this, she returns to the second bedroom and rises by 7am. She is a clockwatcher at night and does lie in bed awake when unable to sleep. She wants to learn how to be a good sleeper and taper her use of medications but also asked about trying an additional medication at our first visit (Gravol).
Most Common Pharmacologic Treatments for Insomnia

- **Selective GABA agents:** Ambien, Ambien CR, Intermezzo, Edluar, Zolpidem, Lunesta, Sonata
- **Orexin receptor antagonists:** Belsomra (suvorexant). Best results with 30-40 mg doses but these were associated with risks of next-day drowsiness too dangerous to approve, 5-20 mg approved
- **Sleep/wake cycle modifiers:** Rozerem (ramelteon)
- **Benzodiazepines:** Ativan (lorazepam), Restoril (temazepam), Xanax (alprazolam)
- **Antidepressants:** Elavil (amitriptyline), Remeron (mirtazapine), Pamelor (nortriptyline), Trazodone (desyrel), Silenor/Adapin (doxepin)
- **OTCs:** Benedryl (diphenhydramine), melatonin (chronobiotic v. hypnotic), Zzzquil, PM pain medications

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Pharmacologic Treatment for Insomnia

- In 2007, makers of Lunesta, Ambien and Rozerem spent $600 million on ads; Lunesta ads alone have totaled a **million dollars/day**. Sleep meds are a multi-billion dollar market.
- These meds are a poor solution: EDS, cognitive/memory issues, bizarre behaviors (sleepwalking/eating/driving), dizziness, dependence, tolerance, abuse potential, etoh interactions, rebound insomnia. They do not treat the cause.
- Patients often use larger doses or several types of medications at different times of night (the “Sleep Med Algorithm”).
- Ambien compared to placebo reduced SOL by only 20 minutes
- Even OTCs have unwanted side effects and foster belief that cure is external resulting in dependency and helplessness
CBTi as an Ideal Approach

- About 70-80% of patients with even very long term poor sleep benefit from cognitive-behavioral therapy for insomnia (CBTi) and this therapy is reliable and durable. More than 100 RCTs over more than 30 years.
- CBTi also leads to better long term outcomes (about 80% of patients maintain their gains and results are better than in programs for weight loss and smoking cessation).
- 85% of long term nightly Rx users (average was a 19 year use hx) were able to eliminate Rx altogether using CBTi combined with gradual tapering protocols (Morin, et al, Am J of Psychiatry, 2004).

Sleep Medication Tapering

- A gradual tapering protocol minimizes tolerance and psychological issues as well as the side effects associated with discontinuing meds too quickly
- Safe tapering protocol (Jacobs): 7 or 14 week plan. Patients must track this carefully and will taper one med at a time all while learning and practicing good sleep skills.
- Final goal is the “rescue” protocol (use sleeping Rx only after two poor nights of sleep in a row)
Insomnia Evaluation

- Assessment of how the patient’s medical, psychological and sleep history may be contributing to insomnia
- Assessment of the patient’s ability to relax and “turn off the mind” at night
- Assessment of habits that cause and/or perpetuate insomnia and assessment of sleep hygiene
- Assessment of environmental issues
- Assessment of sleeping medication use and/or desire to taper these after good sleep skills are built

Assessment Checklist, Part 1

- I have negative thoughts about my sleep (or my ability to fall sleep or stay asleep).
- I am not good at “turning my mind off” at bedtime.
- I lie in bed when unable to sleep.
- I am in bed awake more than 10-20% of the night.
- I do not have a good bedtime routine (or buffer zone) between work and sleep.
- I ignore my drowsy feelings at bedtime and try to accomplish a few more things.
Assessment Checklist, Part 2

- My bedtimes and arise times vary from weekdays to weekends by more than two hours.
- My arise time is not 16 hours before my bedtime. (I spend too much time “trying to sleep.”)
- I nap at odd times of day (in the morning or evening) and for too long (more than one hour).

Assessment Checklist, Part 3

- My bedroom is not quiet, cool and dark.
- My partner, children or pets disturb my sleep.
- I watch the clock at night when I cannot sleep.
- I use the computer or smartphone or play video games just before bed or when I cannot sleep.
- I watch television in my bedroom to try to help me fall asleep.
Assessment Checklist, Part 4

- I do not exercise.
- I have more than 16 ounces of caffeinated beverages per day and I have these after noon.
- I have more than 1-2 alcoholic drinks per day and I drink after 7pm.
- I smoke (nicotine or marijuana)
- I have a large late dinner.

Assessment Checklist, Part 5

- I use sleeping medications.
- I would like to taper my use of sleeping medications.
Components of CBT for Insomnia

- Sleep Education
- Cognitive Restructuring
- Sleep Scheduling/Sleep Restriction
- Stimulus Control
- Sleep Hygiene
- Relaxation Response
- Sleep Medications/Tapering Protocols

Reference book: *Say Goodnight to Insomnia* / Dr. Gregg Jacobs

Sleep Education

- Sleep system v. wake system
- Sleep debt/sleep drive (8 hours sleep/16 hours of wake)
- Insomnia is a disorder of hyperarousal
- Some personality characteristics are useful in the daytime but not at night
- Information is also provided about basic sleep architecture and sleep myths; typical hypnograms may be reviewed
Cognitive Restructuring: Core Sleep

- Research shows that daytime performance will not significantly suffer if one obtains about 5 ½ hours of sleep because the first few hours of sleep each night contain most of a person’s deep sleep plus a cycle or two of REM.
- Core sleep does NOT need to be uninterrupted to “count.” Sample hypnograms help convince patients of this.
- One way to understand core sleep is to think about it the way we think about calories. We could get by on fewer calories but most of us want more!

Cognitive Restructuring: Core Sleep

- Core sleep concept helps patients relax a bit about their sleep. The effect of sleep loss is mainly on mood not on health or daytime functioning.
- Core sleep concept examples: solo sailors, students, doctors in training
Cognitive Restructuring: NSTs and PSTs

- Negative Sleep Thoughts:
  - I can’t sleep without pills.
  - This is going to be another terrible night.

- Positive Sleep Thoughts:
  - I will be sleeping better as I learn new techniques.
  - My performance will be ok if I obtain my “core sleep.”
  - These techniques have worked for others and they will work for me.

Sleep Scheduling (Sleep Restriction)

- Spend less time in bed until the sleep efficiency is 85% (time asleep divided by time allotted for sleep)
  - Example: 6 hrs of sleep/8 hrs in bed = 75%
- Minimum time allotted would be six hours and this is increased as efficiency improves
- Bedtimes and rise times must be consistent (within a 1-2 hour window) no matter how much sleep is obtained
- Nap between noon and 4pm and for less than 1 hour
- Submarine “hot bunk” example
Sleep Diaries

- Useful to track patterns and problems
- Log bedtime, amount of time it took to fall asleep, number of awakenings and approximate length of each, wake-up time, arise time, naps, medications

Sample Sleep Diary
**Stimulus Control**

- Limit activities in the bedroom
- Limit “trying to sleep” or “time awake in the dark” (cash prize study, conditioning)
- Go to bed only when drowsy but don’t delay (avoid a second wind)
- Get out of bed after 20 minutes if unable to sleep
- Have a pleasant place prepared to spend time in until drowsiness returns. (“Spa Chair” with footrest, soft lighting, blankets, basket of different reading materials, carafe of tea and so on)

**Sleep Hygiene Don’ts:**

**Avoid:**
- Alcohol
- Nicotine
- Caffeine
- Fatty, spicy, sugary foods
- MSG
- Late dinner
- Noise
- Bright light exposure in pm
- Problems with bed partner's movements or snoring (larger or separate beds)
Sleep Hygiene Do’s:

- Cool room temperature
- Exercise (but not in the 2-3 hours before bed)
- Baths (if taken, try one that is 20-25 minutes long about two hours before bedtime)
- Ideal snack at bedtime – anything with complex carbs, calcium & protein
- Comfortable but firm bed and pillow
- Design a multi-step relaxing bedtime routine to cue sleep

Relaxation Response

- Stress response: “fight or flight”
- Anticipatory anxiety about sleep
- Countering these with the “relaxation response”
- Trying the “thinking time” or “worry time” technique
Relaxation Response

- Use body scan, diaphragmatic breathing and, very importantly, one-pointed attention techniques (meditation, phrase, mental focus point)
- Practice RR for two weeks before trying to use at bedtime or during nighttime awakenings
- Use mini-relaxations during the day
  - Example: sitting at desk during lunchtime
  - At traffic lights

Insomnia Case Example

- **Amy:** CBTi for this patient involved weekly sleep diaries, stimulus control, avoidance of clockwatching, gradual tapering of post-bedtime meds, gradual taper of sleep meds one by one with monthly calendars to track, sleep education and review of the changes in sleep associated with being a woman in her seventh decade, avoidance of new med trials and mental quieting and relaxation techniques.
- Amy did very well and was able to discontinue all use of meds after bedtime and to simplify her bedtime medications to one. She made a “master list” of CBTi techniques that worked for her for home reference in addition to reading the insomnia text.
New Insomnia Therapies?

Is there anything new on the horizon?

- **Frontal Cerebral Hypothermia (cooling cap):** Reduction in metabolism in the brain’s frontal cortex occurs while falling asleep and is associated with restorative sleep. Insomnia is associated with increased metabolism in this same brain region.

- One way to reduce cerebral metabolic activity is to use frontal cerebral thermal transfer to cool the brain, a process known as “cerebral hypothermia.”

- In a trial, 12 subjects with insomnia fell asleep in 13 minutes v. 16 minutes in 12 healthy controls and both had sleep efficiencies of 89%. (Nofzinger & Buysse, 2011)

New Insomnia Therapies:
25 Hour Intensive Sleep Retraining (ISR)

- Patients slept 5 hours on prior night then reported to sleep lab at bedtime.

- The 25 hours were divided into 50 thirty-minute sessions: patients fall asleep if possible and are awakened after three minutes.

- Four randomized groups: one session of ISR + SH, one session of ISR plus five weeks of SC + SH, five weeks of SC alone + SH, and SH alone.

  (Harris J, et al, SLEEP, 2012)
Intensive Sleep Retraining, cont.

- Even the most hard-core insomniacs were able to feel what it’s like to fall asleep quickly and had opportunity for “massed practice.”
- Best results: intensive sleep retraining plus SC (61% reached “good sleeper” status).
- However, lab/staff time is expensive. The possibility of self-administered ISR is on the horizon, using portable EEG headsets, actigraphs and alarms (and, surely, extreme fortitude).
- “Adding ISR to traditional interventions seems to result in a superior treatment response.”

(Harris J, et al, SLEEP, 2012)

**Figure 6**—Mean sleep diary sleep efficiency (SE) prior to, during and following treatment. *Mean values are significantly different (P < 0.01) from control. †Mean values are significantly different (P < 0.05) from ISR. ‡Mean values are significantly different (P < 0.05) from SCT.
Implications of Chronotype for CBTi

Chronotype Predicts Depressive Sx Reduction after CBTi

- SE and depressive symptoms improved significantly after 4-6 sessions of CBTi. However, those with evening chronotypes (“owls”) showed less improvement in depressive symptoms. Evening preference may have a distinct relationship with mood so effect of CBT-I on depressive symptoms could be enhanced by thoroughly assessing/addressing circadian factors.

(Bei, et al, JCSM, 2015)

- Social Rhythm Therapy (Ellen Frank, PhD, University of Pittsburgh) is used to treat circadian rhythm disruption related to depression. SRT postulates that maintaining regular daily rhythms in sleeping, waking, working, eating, and exercise can increase QOL and reduce depressive symptoms.

Resources

The Yale Centers for Sleep Medicine are located in North Haven and Madison

- (203) 287-3550
TREATING SLEEP HEALTH IN THE SHIFT WORKER

Christine Won, MD MS
Yale Centers for Sleep Medicine
YNHH Sleep Center at North Haven and Madison
VA Connecticut Healthcare System

Faculty Disclosures

Relevant financial relationships with a commercial interest:

No relevant commercial interests.
Objectives

• Shift Work Disorder
• Circadian rhythm
• Consequences of night shift work
• Treating Shift Work Disorder

Shift work disorder is considered a “circadian rhythm sleep disorder” by the International Classifications of Sleep Disorders—meaning there is a misalignment or desynchronization in sleep patterns and biological rhythms. With shift work disorder, you have a hard time sleeping when sleep is desired, needed, or expected.
## Symptoms

- Excessive sleepiness when you need to be awake and productive.
- Insomnia, or the inability to sleep when you need to. Sleep that feels unrefreshing or insufficient.
- Difficulty concentrating.
- Lack of energy.
- Irritability or depression.
- Difficulty with personal relationships.

*“Night shift is like jet lag, without the luxury of travelling to another time zone”*  
—sleepwriter

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>15% of the U.S. workforce</td>
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<tr>
<td>10% of night and rotating shift workers have shift work disorder</td>
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</tr>
<tr>
<td>25-30% of shift workers experience symptoms of excessive sleepiness or insomnia</td>
<td></td>
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</table>
Interaction of Circadian Rhythms and Sleep

TSH

Melatonin

Cortisol
Consequences of Shift Work

![Bar chart showing the number of crashes at different times of day with peak occurrences around 15:00 (3:00 PM) and 18:00 (6:00 PM).]

Pack 1995

Epworth Sleepiness Scale

![Bar chart showing the mean sleepiness scores for Normal, Insomnia, Sleep Apnea, Residents, and Narcolepsy.]

Sleepiness in residents is equivalent to that found in patients with serious sleep disorders. Mustafa and Strohl, unpublished data. Papp, 2002

© American Academy of Sleep Medicine
Consequences of workplace fatigue

**Short-term:**
- Job error
- Accident, catastrophes
- Diarrhea, constipation
- Headache

**Mid-term:**
- Bad planning
- Poor strategizing
- Poor decisions
- Labile mood

**Long-term:**
- Cardiovascular disease
- Infections
- Cancer
- Depression
- Overweight
- DM2
- Substance abuse
Consequences of workplace fatigue

- Fatigue contributes to 20-40% of all commercial vehicle crashes
- Loss of more than 15,000 lives per year
- Increased absenteeism, sick leave
- Cost $12 billion per year in lost productivity and property damage
Homeostatic and circadian influences on performance
Serious Medical Error Rates of Interns Working in Intensive Care Units

- Traditional Shift (>24h)
- Scheduled Shift (≤16h)

Consequences of workplace fatigue

- Chernobyl 1986
- Exxon Valdez oil spillage 1989
- Challenger Space Shuttle 1986
- Metro-North Railroad derailment 2013
Consequences of Shift Work

- International Agency for Research on Cancer (IARC) 2007 – “shift work involving circadian disruption is probably carcinogenic to humans”

- Hypotheses: desynchronization of biological rhythms, melatonin suppression, exposure

- Night shift work associated with increased cancer risks:
  - Breast
  - Ovarian (Bhatti 2013)
  - Prostate (Kubo 2006)
  - Colorectal (Schernhammer 2003)
  - Endometrial (Viswanathan 2007)
  - Lung (Schernhammer 2013; Logan 2012)

Breast Cancer

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>ES (95% CI)</th>
<th>Weight</th>
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<tr>
<td>Davis et al</td>
<td>2001</td>
<td>1.60 (1.00, 2.50)</td>
<td>9.59</td>
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<tr>
<td>Hansen et al</td>
<td>2001</td>
<td>1.50 (1.30, 1.70)</td>
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<tr>
<td>Reynolds et al</td>
<td>2002</td>
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<td>Linnerström et al</td>
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<td>1.79 (0.31, 10.45)</td>
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<td>O’Leary et al</td>
<td>2006</td>
<td>1.04 (0.79, 1.38)</td>
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<td>Schwartzbaum et al</td>
<td>2007</td>
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<tr>
<td>Pesch et al</td>
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<td>Pronk et al</td>
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<td>Overall (I² = 75.8%, p = 0.000)</td>
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<td>1.21 (1.00, 1.47)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Kamdar et al, Epidemiology, 2013
How does shift work cause cancer

Cancer

- Melatonin
- Inflammatory cytokines
- Hormone dysregulation
- Light
- Diet
- Lifestyle
- Unknown exposures

Diabetes Mellitus

- Nurses’ Health Study I and II
- HR for DM2 increased in dose-dependent manner with years of shift work

PloS Med 2011
Shift Work

Obesity

Lifestyle

Desynchronized sympathetic output

Disturbed circadian rhythm of feeding

Desynchronized hormonal pathways

Altered glucose and lipid metabolism

Altered patterns of transcriptional genes

Stress

Odds ratio of being obese in 2007

Odds ratio of excessive weight gain

Duration of rotating shift work till 2007

Never 1-2 years 3-9 years 10-19 years ≥20 years

PLoS Med 2011
Melatonin

- Subjects without diabetes at baseline, 370 women identified who developed DM2 from 2000-2012 matched with 370 controls
- Lower melatonin secretion associated with greater risk for DM2
- Women with lowest melatonin had greater than 2 fold increase in OR for developing DM2

McMullan et al, JAMA, 2013

Variable Risks: Melatonin

- Asian night shift workers have less melatonin suppression compared to Caucasian
- Asians night shift workers are at reduced risk of cancer compared to Caucasian night shift workers
- Moring lark night shift workers maintain melatonin levels more consistent with day shift workers, than do night owl night shift workers

Bhatti et al, Am J Epidemiol, 2013
Bhatti et al, Occup Environ Med, 2014
Variation Risks: Hypertension

- Nurses’ Health Study II
- 1510 African-Americans and 94,142 Caucasian females
- 16 year follow up (1991-2007)
- HR incident HTN 1.81 in AA females who worked rotating night shifts > 1 year in previous 2 years
- HR incident HTN 1.46 AA females ever worked rotating night shift versus never worked night shift
- No increased risk in Caucasian females

J of Hypertension, 2012

"Could you reset my biological clock? They put me on the nightshift."

Treating Shift Work Sleep Disorder
Sleep Tips:

• If you work rotating shifts, ask your manager to schedule a clockwise rotation. This means that your new shift will have a start time that is later than your last shift.
• If possible, take a 20 to 30 minute nap during a break in your shift or before reporting for a night shift.
• Arrange for someone to pick you up after a night shift, or take a bus or cab home.
• Try to keep the same schedule on work days and days off.

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Sleep Tips:

• Use moderate amounts of caffeine to help you stay alert on the job, but avoid it in the later portions of your shift
• Avoid exposure to sunlight if you need to sleep during the day. Wear sunglasses if you must go outside.
• Make sure others in your home are aware of your work schedule. They should keep the home quiet when they know that you need to sleep

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Sleep Tips:

• Begin to alter your sleep time a few days in advance.

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Sleep Time</th>
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<tr>
<td>Evening Shift (5 pm - 1 am)</td>
<td>3 a.m. — 11 a.m.</td>
</tr>
<tr>
<td>Night 1 of Transition</td>
<td>5 a.m. — 1 p.m.</td>
</tr>
<tr>
<td>Night 2 of Transition</td>
<td>7 a.m. — 3 p.m.</td>
</tr>
<tr>
<td>Night 3 of Transition</td>
<td>8 a.m. — 4 p.m.</td>
</tr>
<tr>
<td>Night Shift (11 pm - 7 am)</td>
<td>9 a.m. — 5 p.m.</td>
</tr>
</tbody>
</table>

Employer

• Schedule design that permits frequent opportunities to obtain nighttime sleep
• Train workers to maximize use of daytime sleep opportunities through education and sleep hygiene
• Environmental and task engineering to maximize alertness on the job
Work Environment

- Work environment can be designed to promote alertness
- Light, temperature, humidity, noise, ergonomic design
- Schedule critical tasks at maximal alertness times
- Bright light increases alertness (but negative health outcomes)
- Strategic breaks and naps

Light Therapy: Phase shift

- Circadian adaptation
- Improved alertness
- Improved cognitive performance

Shifts in Physiologic and Behavioral Measures during the First and Sixth Nights of Work in the Subjects in the Control and Treatment Studies.

Light Therapy: Phase Shift

Hilaire, 2012
Light Therapy: Adverse Effects

- Cancer
- Heart disease
- Insulin resistance
- Obesity
- Hypertension

Hansen 2006; Hublin 2010; Biggi 2008; Kroenke 2007; Kim 2013; Barbadoro 2013; Fonken 2010

Light Therapy: Alertness

![Graph showing alertness levels at different light intensities over time]

JOEM 2012
Nighttime Lighting Strategies

- Light filtering glasses cutoff light <480 nm
- Improved alertness, sleep and mood
- No resetting of circadian system

Melatonin: Phase Shift
Exogenous Melatonin: Sleep Efficiency

- Exogenous melatonin improved sleep efficiency only during circadian day
- No effect during circadian night
- Did not change sleep onset latency

Pharmacological Therapy

**Wake-Promoting**
- High dose targeted caffeine
- Modafinil, armodafinil

**Sleep Aids**
- Exogenous melatonin
- Short acting hypnotics
Modafinil

Patient-Estimated Sleepiness (KSS, by Treatment Month)

Improvements in Objective Measures of Wakefulness by Nap Session

PVT: Lapses of Attention by Treatment Month

Estimated Sleepiness and % Reporting Near Misses or Accidents
## Modafinil in Chronic SWSD

- Improved wakefulness
- Reduced subjected sleepiness during night shift and commute home
- Reduced reported near misses and accidents on commute home
- No adverse effect on patient's ability to sleep when desired
- Despite improvements, high levels of sleepiness and impaired performance during night shift
- Well tolerated

## Do permanent night shift workers eventually re-align their circadian rhythm?

Very rarely
<table>
<thead>
<tr>
<th>Study Day</th>
<th>Time of Day</th>
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<tr>
<td>1-14</td>
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<td>Assessment</td>
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<td>Night Shifts</td>
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<td>35</td>
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</table>

Smith et al, J of Biological Rhythms, 2009
Thank you!

Questions....
Clinical Case: “My wife has HAD it.”

25 year old graduate student presents with exhaustion to sleep clinic. He is struggling to finish his dissertation and his wife “has had it.” He generally cannot go to sleep before 2AM due to a combination of work and insomnia (though some weeks he can). He has difficulty getting up in the morning to help with the kids.

He notes that prior to marriage and kids, he had an erratic sleep schedule in which he would go to bed later and later until he was totally “reversed.” Upon realizing that he was reversed, he would easily reset his schedule within a day to “normal” and then slowly reverse again. Family history reveals that his dad, who is now retired, has totally reversed his sleep schedule and is happy as a clam.
Circadian Disorders are Diseases of Incorrect Sleep Timing

• Human sleep timing is regulated by a MASTER CLOCK located within the suprachiasmatic nucleus of the hypothalamus.
• Each person has a circadian cycle that is approximately but not exactly 24 hours.
• Synchronization between the 24 hour earth day and each person’s circadian cycle (ENTRAINMENT) is accomplished via external circadian cues (ZEITGEBERS).
• Based on ZEITGEBERS, the MASTER CLOCK signals and synchronizes timed AROUSAL across organ systems such that sleep occurs during the night and wake occurs during the day.

• Circadian disorders occur when the circadian system fails to promote sleep and wake at the correct times.

To Understand Circadian Disorders
We Must First Understand Normal Circadian Functioning

• Basics of circadian rhythm structure in humans
• Factors that influence circadian rhythms (zeitgebers)
• Circadian Disorders
Two Complementary Processes Control Sleep – Wake Patterns

Sleep Drive
(Process S)

- S: Adenosine accumulation during wakefulness causes a steady increase in SLEEP DRIVE which is reset after sleep.

Wake Drive
(Process C)

- C: Oscillating promotion of AROUSAL by the CIRCADIAN MASTER CLOCK combats the sleep drive to promote wake during non-sleep periods.

The 2 Process Model Explains Daily Sleep Timing

http://www.howsleepworks.com/how_twoprocess.html
The Two Process Model Usually Results in Coordination Between Biologic Sleep Time and Desired Sleep Time

**Sleep Drive (Process S)**
- S: Adenosine accumulation during wakefulness causes a steady increase in SLEEP DRIVE which is reset after sleep.

**Wake Drive (Process C)**
- C: Oscillating promotion of Arousal by the CIRCADIAN MASTER CLOCK combats the sleep drive to promote wake during non-sleep periods.

Light Signals the Master Clock which Coordinates Sleep-Wake Physiology

- Nonphotic Zeitgebers
  - Sleep-wake cycle
  - Physical activity
  - Social time
  - Meals

- Light signals the master clock which coordinates sleep-wake physiology.
The Main Output of the Master Clock is Melatonin

The Molecular Basis of Circadian Rhythm is Cyclic Transcription of Proteins which in turn Provide Negative Feedback
Circadian Processes Result in Functional Variation During the 24 Hour Day

Circadian Terminology

Imposed Cycle $T$
Actual Cycle $\tau$
Phase Shift $\Delta \phi = T - \tau$
Phase Angle $\psi = \text{Event} - \phi$

• Basics of circadian rhythm structure in humans
• Factors that influence circadian rhythms (zeitgebers)
• Circadian Disorders

Morning and Evening Circadian Types are Not Disorders

• There are 2 broad classifications of personality associated with circadian type which are differentiated between the “morning larks” and the “night owls”
• Morning types (M-types) aka larks: more alert in the morning hours, early bed and wake times
• Evening types (E-types) aka owls: more alert later at night, late bed and wake times
• This is not pathologic.
Intrinsic Circadian Disorders

- Delayed Sleep-Wake Phase Disorder
- Advanced Sleep-Wake Phase Disorder
- Non-24 Sleep-Wake Disorder
- Irregular Sleep-Wake Disorder

Delayed Sleep-Wake Phase Disorder is Defined by a Significant Delay in Sleep Onset versus Desired Sleep Time

Criteria A-E must be met:
A. Significant delay in the phase of the major sleep episode in relation to the desired or required sleep and wake-up time. Clinically evidenced by inability to fall asleep and difficulty awakening.
B. Symptoms persist for at least 3 months.
C. Ad libitum schedule allows patient to improve sleep quality and maintain a delayed phase of the 24-hour sleep-wake pattern.
D. Sleep log / actigraphy of 7 to 14 days demonstrates delay in timing of habitual sleep.
E. Not better explained by another diagnosis.
Advanced Sleep-Wake Phase Disorder is Defined by a Significant Advance in Sleep Onset versus Desired Sleep Time

Criteria A-E must be met:
A. Significant advance in the phase of the major sleep episode in relation to the desired or required sleep and wake-up time. Clinically evidenced by maintenance “insomnia.”
B. Symptoms persist for at least 3 months.
C. Ad libitum schedule allows patient to improve sleep quality and maintain an advanced phase of the 24-hour sleep-wake pattern.
D. Sleep log / actigraphy of 7 to 14 days demonstrate advance in timing of habitual sleep.
E. Not better explained by another diagnosis.

Treatment of Delayed and Advanced Phase Sleep-Wake Disorders Reflects Light Phase Response Curve

Phase Advance
EAST
Clock Earlier

Phase Delay
West
Clock Later
Non-24-Hour Sleep Wake Rhythm Disorder is Defined by Regular Sleep Bouts that Cycle in/out of Phase with Light-Dark

Criteria A-D must be met:

A. Insomnia and excessive daytime sleepiness which alternate with asymptomatic episodes due to NONENTRAINMENT.

B. Symptoms persist for at least 3 months.

C. Sleep log/actigraphy of 7 to 14 days demonstrate a pattern of sleep and wake times that typically delay each day with a circadian period that is usually LONGER than 24 hours.

D. Not better explained by another diagnosis.

Rx: Low dose melatonin prior to desired sleep time.

Irregular Sleep-Wake Rhythm Disorder is Defined by Irregular Sleep and Wake Episodes

Criteria A-D must be met:

A. Recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period characterized by insomnia and excessive daytime sleepiness.

B. Symptoms persist for at least 3 months.

C. Sleep log/actigraphy of 7 to 14 days demonstrate a lack of major sleep period.

D. Not better explained by another diagnosis.

Rx: enhancing zeitgebers including bright light during day, avoidance of light at night, regular and circadian appropriate timing of meals and social activities.
Summary of Intrinsic Circadian Disorders

Jet Lag Disorder is an Extrinsic Circadian Disorder

Phase **Advance**
EAST
Clock Earlier

Phase **Delay**
West
Clock Later
The Circadian Light Phase Response Curve Predicts Phase Changes in Response to Light Exposure: i.e. NYC to Germany

- **Phase Advance**
  - EAST Clock Earlier

- **Phase Delay**
  - West Clock Later

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New Time

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Germany

FLIGHT ➔

DAYTIME
The Circadian Light Phase Response Curve Predicts Phase Changes in Response to Light Exposure: i.e. NYC to Germany

- Phase Advance: EAST Clock Earlier
- Phase Delay: West Clock Later

New SLEEP | SLEEP

Start Time: 14 17 20 23 02 05 08 11 14 17
New Time: 21 00 03 06 09 12 15 18 21 00
NYC

FLIGHT ➔ PM DAYTIME

The Circadian Light Phase Response Curve Predicts Phase Changes in Response to Light Exposure: i.e. NYC to Hawaii

- Phase Advance: EAST Clock Earlier
- Phase Delay: West Clock Later

New SLEEP | SLEEP

Start Time: 14 17 20 23 02 05 08 11 14 17
New Time: 08 11 14 17 20 23 02 05 08 11
Hawaii

= PHASE ADVANCE

FLIGHT ➔ PM DAYTIME

= PHASE DELAY
25 year old graduate student presents with exhaustion to sleep clinic. He is struggling to finish his dissertation and his wife “has had it.” He generally cannot go to sleep before 2AM due to a combination of work and insomnia (though some weeks he can). He has difficulty getting up in the morning to help with the kids.

He notes that prior to marriage and kids, he had an erratic sleep schedule in which he would go to bed later and later until he was totally “reversed.” Upon realizing that he was reversed, he would easily reset his schedule within a day to “normal” and then slowly reverse again. Family history reveals that his dad, who is now retired, has totally reversed his sleep schedule and is happy as a clam.

Actigraphy reveals a stepwise delay in bedtime over 1 month. Diagnosis is Non-24 hour sleep-wake disorder. He is prescribed QHS melatonin (2 mg).

Thank you.

Melissa Knauert is supported by the following:
- Yale Claude D. Pepper Older Americans Independence Center (P30AG021342)
- Yale Center for Clinical Investigation (CTSA Grant Number UL1 TR000142)
- Past support: Yale P20 Center for Sleep Disturbance in Acute and Chronic Conditions (1P20NR014126)
Sleepiness due to Medical Disorders

Meir Kryger MD FRCPC
Professor, Yale University

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What you will learn later this morning

❖ Systems controlling sleep and wakefulness are complex
❖ A large number of chemicals and pathways are involved
❖ It’s a wonder how well they work
If this isn’t complicated enough there there are other sleep factors that include …

- **Adenosine**
  - Increases with wakefulness
  - Adenosine receptor antagonists (e.g. caffeine) cause arousal

- **Proinflammatory cytokines**

- **Prostaglandin D2**

- **Growth hormone releasing hormone**
What you will take away from this lecture

- The complexity of the sleep-wake system makes it vulnerable and medical disorders can lead to:
  - Excessive sleepiness
  - Excessive wakefulness
  - Both sleepiness and wakefulness
- Sleepiness has many causes
  - Diseases in almost all organ systems

Cardinal Symptoms of Sleep Disorders

- Hypersomnia
- Snoring
- Insomnia
- Difficulty staying still
- The weird stuff
What do patients complain about?

- Falling asleep at the wrong time and place
  - Examples: at school, at work, at movies, driving, flying, accidents...
- Poor memory, concentration, performance
- Onset
  - Slow, rapid
- Denial of symptoms
- Differentiate from “fatigue” and “tired”

What causes sleepiness?

- Insufficient Quantity of sleep
- Insufficient Quality of sleep
  - Fragmented sleep
  - Abnormal architecture
- Out of phase circadian rhythm
- Sleep pathologies
  - Insomnia, apnea, narcolepsy, RLS
What can fragment sleep? Anything that can cause an arousal.

- Sleep disorders
- Medical conditions
- Drugs (e.g. Antidepressants, alcohol, caffeine)
- The “hyperarousable” brain

Snoring

- Partial blockage of airway causing abnormal breathing and sleep disruptions
- 90 million; 37 million experience on a regular basis
- Males, those who are overweight and with large neck size most at risk
- Loud snoring can be a symptom of sleep apnea and can be associated with high blood pressure.
- Causes arousals in bedpartner
- Upper airway resistance syndrome may cause arousals and sleepiness.
Sleep Apnea
- Pauses in breathing due to obstruction in airway that causes gasps and arousals during sleep
- 18 million; mostly males, those who are overweight and/or have high blood pressure and persons with upper airway physical abnormality
- Lowers blood-oxygen levels, puts a strain on the heart and is associated with cardiovascular problems and daytime sleepiness

Narcolepsy
- Chronic disabling neurological disorder
- Excessive daytime sleepiness; may include sudden loss of muscle tone in response to strong emotion, hallucinations and sleep paralysis
- In 1/2000 persons; often diagnosed in 2nd decade of life
- Seems to be caused by a defect in orexin system
**Restless Legs Syndrome**

- Unpleasant, tingling, creeping feelings or nervousness in legs during inactivity and sleep with an irresistible urge to move; 80% may have involuntary jerking of limbs
- 12 million persons; can be genetic
- A neurological movement disorder leading to **arousals** from sleep, daytime sleepiness; can be associated with other medical conditions.

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**Medical conditions causing sleepiness**

- Apnea
- Brain
- Lungs
- Diabetes
- Prostate
- Muscle
- Heart
- GI Tract
- Kidney
- Joints
### ICD – 10 Categories of diseases

<table>
<thead>
<tr>
<th>Category</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Infectious</td>
<td>11 Digestive</td>
</tr>
<tr>
<td>2 Neoplasms</td>
<td>12 Dermatologic</td>
</tr>
<tr>
<td>3 Hematologic and Immune</td>
<td>13 Muscle &amp; Connective Tissue</td>
</tr>
<tr>
<td>4 Endocrine, Nutritional, Metabolic</td>
<td>14 Genitourinary System</td>
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<td>5 Mental and Behavioral</td>
<td>15 Pregnancy, Childbirth, Puerperium</td>
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<td>16 Perinatal</td>
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<td>7 Eye and Adnexa</td>
<td>17 Congenital &amp; Genetic</td>
</tr>
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<td>8 Ear &amp; Mastoid</td>
<td>18 Symptoms, Signs</td>
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<tr>
<td>9 Circulatory System</td>
<td>19 Injury, Poisoning, eternal causes</td>
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<td>10 Respiratory System</td>
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### Diseases that can cause sleepiness

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</tr>
</tbody>
</table>
1. Infectious disease examples

- Influenza
- Sepsis
- HIV
- Malaria


2. Neoplastic disease examples

- Cancer involving the CNS
- Cancer not involving the CNS
- “Cancer-related fatigue”
- Cancer survivors


3. Hematologic and immune disease examples

- Systemic lupus erythematosus
- Granulomatosis and Polyangiitis


4. Endocrine, nutritional, metabolic examples

- Diabetes mellitus
- Hypothyroidism
- Acromegaly

Acromegaly develops slowly

Hypothyroidism develops slowly
5. Mental and behavioral examples

- Depression
- Medications used to treat psychiatric disorders

6. Nervous system examples

- Narcolepsy
- Idiopathic hypersomnia
- Parkinson’s disease
- Multiple sclerosis
- Epilepsy
9. Circulatory system examples

- Congestive heart failure
- Stroke


10. Respiratory system examples

- Sleep apnea
- COPD
- Asthma


11. Digestive system examples

- GERD
- Peptic ulcer disease
- Pancreatic islet cell tumor
- Nocturnal diarrhea in diabetic neuropathy


13. Muscle & Connective Tissue disease examples

- Rheumatoid arthritis
- Osteoarthritis
- Fibromyalgia
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

http://iom.nationalacademies.org/Activities/Disease/DiagnosisMyalgicEncephalomyelitisChronicFatigueSyndrome.aspx. 2015


14 Genitourinary System examples

- End stage renal disease
  - Associated with RLS, PLMS
  - Fatigue is common

- Nocturia

15 Pregnancy, Childbirth, Puerperium examples

- Normal pregnancy
  - Sleepiness is common throughout
  - Mechanisms vary
Pregnancy and Postpartum Sleep Changes

<table>
<thead>
<tr>
<th>Hormone levels</th>
<th>Postpartum</th>
<th>2nd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>No</td>
<td>Fluctuating prolactin levels with breastfeeding</td>
</tr>
<tr>
<td>Estrogen</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

| Sleep disruption       | Infant care; feeding | First-time mothers have greatest sleep disruption |
| Accompanying symptoms | Breast-feeding mothers awake longer at night | Difficulty with sleeping positions |

| Accompanying symptoms | Increased daytime sleepiness; Napping may occur | Difficulty with sleeping positions |

<table>
<thead>
<tr>
<th>Sleep characteristics</th>
<th>Tendency to sleep later into the morning</th>
<th>Issues of co-sleeping and bed sharing</th>
</tr>
</thead>
</table>

17 Congenital & Genetic examples

- Down Syndrome
- Prader-Willi Syndrome

19 Injury, Poisoning, eternal causes - examples

- Traumatic brain Injury
- Anti-epilepsy medications
- Psychiatric medications


Why worry about sleepiness in medical conditions?

- Safety concerns
- Performance concerns
Safety is compromised with sleepiness

- 100,000 sleep-related crashes per year; 1,500 fatalities and 71,000 injuries
- 51% of adults report driving drowsy; 17% dozed off at the wheel
- 27% report being sleepy at work at least 2 days/week
- 19% of adults report making errors at work; 2% injured

Principles of managing sleepiness in medical disorders

- Determine the cause of the sleepiness
- Treat the specific cause
- If that doesn’t work . . .
There are few options to treat sleepiness

There are some FDA approved medications that are wake promoting

- The medications are expensive
- They have not been evaluated in RCTs in most of the clinical conditions causing sleepiness
- One must rely on published less than perfect medical literature
- Approved indications ....
How to code for sleepiness – using ICD-10

- **G47.1** Disorders of excessive somnolence [hypersomnias]  
- **G47.2** Disorders of the sleep-wake schedule  
  - Incl.: Delayed sleep phase syndrome Irregular sleep-wake pattern
- **G47.3** Sleep apnoea  
  - Incl.: Sleep apnoea: central  
  - obstructive
  - Excl.: pickwickian syndrome (E66.2) sleep apnoea of newborn (P28.3)
- **G47.4** Narcolepsy and cataplexy
- **G47.8** Other sleep disorders  
  - Incl.: Kleine-Levin syndrome
- **G47.9** Sleep disorder, unspecified

---

How to code for sleepiness – using 2012 ICD-9 CM

- **327.1** Organic disorder of excessive somnolence
- **327.10** Organic hypersomnia, unspecified
- **327.11** Idiopathic hypersomnia with long sleep time
- **327.12** Idiopathic hypersomnia without long sleep time
- **327.13** Recurrent hypersomnia
- **327.14** Hypersomnia due to medical condition classified elsewhere
- **327.15** Hypersomnia due to mental disorder
- **327.19** Other organic hypersomnia
- **347** Narcolepsy with cataplexy
- **347.0** Narcolepsy without cataplexy
How to code for sleepiness – using 2012 ICD-9 CM

How about using “Symptoms, signs, and ill-defined conditions (780–799) Codes?

780.53 Hypersomnia with sleep apnea

780.54 Hypersomnia, unspecified

Problems facing doctors wanting to treat hypersomnia

CMS and Insurance carriers want an Indication

☆ There are few medical causes of sleepiness that have an acceptable code that would link to an authorization

☆ Some insurance carriers will deny treatment because a product has not been approved by FDA for that indication

☆ They usually will not accept published studies
Problems facing doctors wanting to treat hypersomnia 2

- Many diseases are not in ICD-9 and treatment is automatically rejected.
- Even when indication is met, there is a huge problem in patients under age 18.

Sleepiness can be the result of ...

- Insufficient sleep
- Fragmented sleep
- Sleep, psychiatric and medical disorders
- Circadian factors
- Many, many chemicals
- In the words of George Bush: There’s still lots that is underestimated and unknown
Thank you for your attention
Narcolepsy
Master of disguise

Management of Patients with Narcolepsy

Vahid Mohsenin, M.D., FCCP, FAASM
Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine

Disclosures

Teva Pharma (Speaker Bureau)
Jazz Pharmaceutical (Speaker Bureau)
Definitions and Severity Criteria

Prevalence of narcolepsy in US

Prevalence: 40 cases/100,000 people, higher than cystic fibrosis: 8.7 cases/100,000
Incidence: 1 in 3000 persons

Age of onset of symptom of narcolepsy
(bimodal pattern of age distribution)

Won...Mohsenin. J Clin Sleep Med. 2014
**Narcolepsy Symptom Overlap**

Narcolepsy should be considered as a potential diagnosis when a patient complains of excessive daytime sleepiness or falling asleep at inappropriate times or places.

![Diagram showing symptom overlap]

EDS: Excessive Daytime Sleepiness; DNS: Disrupted Nocturnal Sleep

**Diagnosis**

Narcolepsy can be difficult to recognize, and challenging to diagnose because:

- Patients often present with subtle, non-specific symptoms, or they may have difficulty describing their symptoms.
- Symptoms may overlap with those of other conditions, such as obstructive sleep apnea, depression, and medication effects.
- Diagnosis of narcolepsy can be confounded by the presence of comorbid sleep disorders, such as obstructive sleep apnea.
- Cataplexy
- Hypnagogic hallucinations
- Excessive daytime sleepiness
- Sleep paralysis
- Sleep disruption

**Forms of Cataplexy:**
- Head dropping
- Drooping of the face or jaw
- Leg weakness
- Neck weakness
- Slurred speech
- Arm weakness
- Eyelid drooping
- Buckling of the knees
- Complete collapse to the ground
Sleep architecture in Narcolepsy

- Sleep fragmentation
- Sleep attacks
- REM sleep intrusion into wakefulness (sleep paralysis, hypnogogic hallucinations and cataplexy)

Multiple Sleep latency Test

The MSLT may identify a profile that is characteristic of narcolepsy:
- Mean sleep latency ≤8 minutes
- ≥2 SOREMPs (sleep-onset REM Periods)

Approximately 15% of patients with narcolepsy with cataplexy may have a normal or borderline MSLT result.
- Borderline results are either a mean sleep latency of ≥8 minutes or only 1 SOREM.

The presence of multiple SOREMPs during the MSLT is a more precise determining factor in diagnosing narcolepsy than is a mean sleep latency of ≤8 minutes.
Management of Narcolepsy

- A careful sleep history
  - Determine onset and duration of symptoms
  - Sleep diary
  - Ascertainment of cataplexy and other REM-related symptoms
- Epworth Sleepiness Scale (initially and during follow-up)
- Polysomnography followed by multiple sleep latency test (MSLT)
- Treatment
  - Sleep hygiene, avoidance of confounding factors (alcohol, sedating meds)
  - Assess potential for medication abuse or diversion
  - Choose an alerting medication for excessive daytime sleepiness
  - Address the importance of cataplexy in patient’s life
    - Social interactions, academic/sport/work performance

Overall Goal of Management of Narcolepsy

Daytime Sleepiness

- All patients with narcolepsy have some degree of daytime sleepiness. Although a few manage this successfully with only an afternoon nap, most patients require a medication that improve wakefulness/alertness and functioning.
- Setting realistic goals and expectations with the patient is essential before initiating treatment. Alerting medications improve performance (measured by reaction time and simulated driving tasks), but performance rarely exceeds 70 to 80 percent of normal.
- People with narcolepsy have a three- to four-fold increased risk of having a car accident, and over one-third have had an accident due to sleepiness. It can be helpful to impose some limits, e.g., long monotonous highway drive.
- Treatments for underlying sleep-wake disorders: obstructive sleep apnea and shift work disorder
- Regular and timely follow-up is crucial to assess effectiveness of and compliance with treatment.
Behavioral Measures to Improve Sleep

- Improving duration of sleep and ensuring proper sleep hygiene (sleep-related behaviors) are essential first steps in helping to alleviate symptoms of excessive sleepiness in all patients.
- Patients should be encouraged to allow enough time in their schedules for an adequate amount of sleep to feel refreshed or well rested.
- Maintaining a regular sleep-wake schedule (7 days a week).
- Avoidance of caffeine, nicotine, alcohol, heavy meals, and strenuous exercise at least 3 hours before bedtime.
- Scheduled short nap around the time of peak sleepiness.

<table>
<thead>
<tr>
<th>Symptoms and Medication</th>
<th>Initial Dose mg/day</th>
<th>Maximum Dose mg/day</th>
<th>Common or Serious Side Effects</th>
<th>FDA-Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excessive Sleepiness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modafinil</td>
<td>200 qd</td>
<td>600</td>
<td>Headache, nervousness, cardiovascular (rare)</td>
<td>Yes</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>150-250 qd</td>
<td>250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>10 bid</td>
<td>60 ER</td>
<td>Nervousness, palpitation, anhydria</td>
<td>Yes</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>10 qd</td>
<td>60 ER</td>
<td>Palpitation, restlessness, cardiovascular</td>
<td>Yes</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>2.25 g (1st dose at bedtime and 2nd dose 4 hr later) Total dose, 4.5 g</td>
<td>4.5 g (1st dose at bedtime and 2nd dose 4 hr later) Total dose, 9 g</td>
<td>Nausea, headache, respiratory depression</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cataplexy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs/NRIs</td>
<td></td>
<td></td>
<td>Sexual dysfunction, headache, nausea, insomnia, withdrawal symptoms</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (SSRI/NRI)</td>
<td>37.5 bid</td>
<td>150</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Fluoxetine (SSRI)</td>
<td>20 qd</td>
<td>80</td>
<td></td>
<td>No</td>
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<tr>
<td>Atomoxetine (NRI)</td>
<td>40 qd</td>
<td>100</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>TCA's</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Imipramine</td>
<td>20 qd</td>
<td>200</td>
<td>Drowsiness, anticholinergic, cardiovascular</td>
<td>No</td>
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<td>Nausea, dizziness, headache, respiratory depression (rare at recommended dose)</td>
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Modafinil and Armodafinil

- Modafinil is a non-amphetamine wakefulness-promoting medication
- Armodafinil is the (R)-enantiomer of modafinil with a longer half-life.

Armodafinil improved alertness (maintenance of wakefulness test, MWT) throughout the day compared to placebo.


Armodafinil improved alertness (maintenance of wakefulness test, MWT) throughout the 12-week follow-up period or final visit without evidence of tolerance to the drug.

Percentage of patients with improved overall clinical condition as assessed by Clinical Global Impression of Change (CGI-C) by treatment visit.

- Lower abuse potential and lower risk for adverse cardiovascular events than sympathomimetic agents.
- Does not adversely affect nighttime sleep when used as directed.


Amphetamines and Methylphenidate

- Patients treated with amphetamines may require increasingly greater doses ('Adderall Creep') to sustain improvements in alertness; and tolerance and tachyphylaxis may occur over time.
- On the basis of their higher potential for abuse, these DEA schedule II medications require careful patient monitoring and should be used with caution.
- Commonly reported side effects of these stimulants include anxiety, agitation, anorexia, tachycardia, and elevated blood pressure. At high doses, hallucinations and psychosis may occur.
- After sudden discontinuation, rebound hypersomnolence, often referred to as a “crash” can occur.
Cataplexy

- About 30 percent of people with narcolepsy have cataplexy that is substantial enough to warrant treatment. Although hypnagogic hallucinations and sleep paralysis usually do not require pharmacological treatment, these symptoms are often improved by medications that suppress cataplexy.
- Brainstem circuits that generate REM sleep are strongly inhibited by norepinephrine and serotonin. Thus, drugs that increase noradrenergic and serotonergic signaling suppress REM sleep and reduce cataplexy.

<table>
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<th>Medication</th>
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<td>37.5 bid 150</td>
<td>Sexual dysfunction, headache, nausea, insomnia, withdrawal symptoms</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (SSRI)</td>
<td>20 qd 80</td>
<td>Headache, dizziness, insomnia</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (NRI)</td>
<td>40 qd 100</td>
<td>Headache, dizziness, insomnia</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>20 qd 200</td>
<td>Drowsiness, anticholinergic, cardiovascular</td>
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Sodium oxybate

- Sodium oxybate (a sodium salt of γ-hydroxybutyrate [GHB]) is a CNS depressant approved by the FDA for the treatment of:
  - Excessive daytime sleepiness in narcolepsy
  - Cataplexy in narcolepsy.
- Sodium oxybate improves sleepiness and frequency of cataplexy in narcolepsy.
- CNS depressant; abuse potential (mitigated by central pharmacy and close monitoring)

The U.S. Xyrem® Multicenter Study Group. Sleep, 2002
Narcolepsy
Master of disguise

A life-long neurologic disorder without a cure (not yet)

• It is estimated that 50% or more of individuals with narcolepsy remain undiagnosed. In other words: You are not recognizing the symptoms and not diagnosing it.

• Few patients with narcolepsy ever feel fully alert despite optimal therapy. The goal of therapy is to improve alertness to the point where performance and safety are not adversely affected.

• Management is challenging, but the outcome is satisfying with improvement in quality of life in most individuals afflicted with narcolepsy.
Things That Go Bump in the Night: Parasomnias and Sleep-Related Movement Disorders

Brian B. Koo, MD
Yale Sleep Symposium
September 18, 2015

No Disclosures
Sleep

- What is sleep?
  - State characterized by
    - Decreased responsiveness to external stimuli
    - Decreased awareness of self or environment
    - Relative suspended sensory activity
    - Relative suspended motor activity
    - Rapid reversibility

Movement During Sleep

- Excessive Movement is abnormal

- Clinician
  - Your job is to figure out what it is.
What is it?

- **Behavioral**
  - Kids
- **Seizure**
  - Often occur in sleep
  - Can be stereotyped, but often more complex and perhaps less recurrent (meaning second to second)
- **Parasomnia**
  - More complex behavior like walking, punching
- **Sleep-Related Movement Disorder**
  - Often simple stereotyped, often recurrent movement

Is it Dangerous?

- Behavior or movement causing physical harm?
  - Seizures, parasomnia, rhythmic movement d/o
  - Padded walls/rails, remove night stands
- Anatomical/physiologic harm
  - Seizures causing brain damage
  - Ongoing poor sleep, delaying development
Is it Disruptive?
- Is it associated with poor sleep for the patient?
- Poor sleep for the partner?

Is it Treatable?
- Depends on what it is.

Briefly About Nocturnal Seizures
Nocturnal Seizures

- Sleep especially NREM sleep is very pro-epileptic
- Seizures types/syndromes occurring mainly in sleep
  - Benign epilepsy of childhood with centrotemporal spikes
  - Childhood occipital epilepsy
  - Juvenile myoclonic epilepsy
  - Certain temporal lobe epilepsy
  - Landau Kleffner syndrome ESES
  - Nocturnal frontal lob epilepsy

Nocturnal Frontal Lobe Epilepsy

- Semiology depends on localization
- Primary motor cortex: partial motor; dystonic posturing
- Supplementary Motor: bilateral tonic posturing; complex behavior like kicking or pelvic thrusting
- Orbitofrontal: pelvic thrusting, bicycling, thrashing, rocking
Nocturnal Paroxysmal Dystonia

- Choreaathetoid, dystonic and ballic movements occurred in 12 patients, repeatedly each night and over a period of years.
- The nocturnal attacks were short-lasting, responded well to carbamazepine and were sometimes associated with clearly or possibly epileptic seizures during night- or daytime.

What is it?

Parasomnias
- Complex Behavior
- Usually lasting minutes
- Usually not recurrent second to second
- May or may not be recollection
- About equally prevalent in kids and adults

Slp-Related Movement Disorder
- More simple behavior
- Usually lasting seconds
- Often recurrent second to second or minute to minute
- No recollection
- More prevalent in adults
Parasomnia

**NREM**
- Somnoambulism
- Night Terrors
- Sleep eating/sexsomnia

**REM**
- Nightmares
- REM Behavior Disorder

**Timing**
- First half of night
- Latter night

**Remember**
- Amnesia for event
- Remember event

**Interaction**
- Interact with env’t
- Purposeful but no interaction with env’t

**Violence**
- Less violent
- Can be very violent

**Eyes**
- Usually open
- Usually closed
Parasomnia

- About the actual Behavior
  - Describe behavior
  - Quantify times per week
  - Timing at night
  - Dangerous

- Screen for other sleep disorders
  - Disrupted sleep often precipitates parasomnic behavior
  - OSA, insomnia, insufficient sleep

NREM Parasomnias

- Somnambulism
- Sleep related Eating Disorder
- Night Terrors
- Confusional arousals

- Destabilization of slow wave sleep
- Dissociative thalamic output; ↑ thalamocingulate; ↓ thalamocortical
- Usually not diagnostic dilemma
- Patient does not recollect event; often history comes from observer
- Treatment: treat other sleep disorders
  - Clonazepam
Sleepwalking

Night Terror
REM Sleep Behavior Disorder

- Acting out dreams
- Often violent: punching, kicking, running
- Loss of atonia or paralysis of REM sleep

HISTORY TAKING
- Memory for event
- Falling out of bed
- Yelling, talking
- More common in older persons
- More common in men
- Often violent behavior but can be nonviolent
Loss of REM atonia: RBD

REM Sleep Behavior Disorder
REM Sleep

- Lateral dorsal/pedunculopontine tegmentum
- Very active
- Acetylcholine

- NE, 5-HT, Hist
- No activity
- LDT/PPT
- Inhibits \( \alpha \)-motor neurons through glycineergic neuron
- Which results in REM atonia/paralysis

LDT: lateral dorsal tegmentum
PPT: pedunculopontine tegmentum
REM Behavior Disorder

REM Sleep Behavior Disorder

- Acting out dreams
- Often violent: punching, choking, run into walls
- Loss of atonia or paralysis of REM sleep
- Associated w/ and may predate Parkinson’s disease
- Very predictive of cognitive impairment
- Occurs with synucleinopathies >> tauopathies
  - Parkinson’s disease, Lewy body disease, multiple system atrophy
  - Alzheimer’s disease, progressive supranuclear palsy, corticobasal degeneration
REM Behavior Disorder: Differential

- Dream enactment can be seen
  - OSA: pseudoRBD
  - Narcolepsy
  - Antidepressant medication
  - PTSD: usually in PTSD there is no memory of thrashing

REM Behavior Disorder: Treatment

- TREATMENT
- Treat co-morbid sleep disorders
- First line
  - Melatonin: start with 3mg going up to 6 and 9mg
- Second line
  - Clonazepam: start with 0.25 mg go to 0.5 then 0.75 mg
  - Be careful in elderly
Sleep Related Movement Disorders

Types of Movements

- **Myoclonus**: rapid jerky large amplitude movement of large muscle group(s), often singular but can be recurrent
  - Hypnic jerks
  - Propriospinal myoclonus
  - PLMS
  - Segmental myoclonus
- **Twitch**: rapid small amplitude movement often of small number of muscle units
  - Twitches in REM sleep
  - Twitches related to radiculoneuropathy
- **Movements like chorea, athetosis, tremor, tics go away during sleep**
Vignette

- 39-year old man with stereotyped episodes during sleep since childhood
  - Rhythmic, side-to-side head and body rolling movements lasting 1-10 minutes
  - Occur most days of the week
  - Distressing for bed partner
- No daytime sleepiness
- Unremarkable neurological & physical examination.
- No history of cognitive problems or autism

EEG during event
A. Patient exhibits rhythmic body movements in drowsy or sleep.
B. At least one of the following types of disorder is present:
   • Head forcibly moved in anter-posterior direction (headbanging)
   • Head moved laterally while in supine position (headrolling type)
   • Whole body is rocked while on hands and knees (bodyrocking)
   • Whole body is moved laterally while supine (bodyrolling type)
C. Onset typically occurs within the first two years of life.
D. Polysomnographic monitoring during an episode shows both 1. Rhythmic movements during any stage of sleep or in wakefulness 2. No other seizure activity occurs in association with the disorder
E. No other medical or mental disorder (e.g., epilepsy) causes
F. Symptoms do not meet diagnostic criteria for other sleep disorders (e.g., sleep bruxism).
**Diagnostic Criteria: Sleep Starts**

- A. Patient has complaint of either difficulty initiating sleep or an intense body movement at sleep onset.
- B. Patient complains of sudden brief jerks at sleep onset, affecting the legs or arms.
- C. The jerks are associated with at least one of the following:
  - 1. A subjective feeling of falling
  - 2. A sensory flash
  - 3. A hypnagogic dream
- D. Polysomnographic monitoring during an episode demonstrates one or more of:
  - 1. Brief, high-amplitude muscle potentials during transition from wakefulness to sleep
  - 2. Arousals from light sleep
  - 3. Tachycardia following an intense episode

---

**Sleep Bruxism**

- A. Patient has complaint of tooth-grinding or -clenching in sleep.
- B. One or more of the following occurs:
  - 1. Abnormal wear of the teeth
  - 2. Sounds associated with the bruxism
  - 3. Jaw muscle discomfort
- C. Polysomnographic monitoring demonstrates both:
  - 1. Jaw muscle activity during the sleep period
  - 2. Absence of associated epileptic activity

**Severity Criteria:**

- **Mild:** Episodes occur less than nightly, without evidence of dental injury or impairment of psychosocial functioning.
- **Moderate:** Episodes occur nightly, with evidence of mild impairment of psychosocial functioning.
- **Severe:** Episodes occur nightly, with evidence of dental injury, TMJ disorders, other physical injury, or moderate or severe impairment of psychosocial functioning.
Alternating Leg Movement Activity

- (1) The minimum number of discrete and alternating bursts of leg muscle activity needed to score ALMA is 4 bursts,
- (2) the minimum frequency of the alternating EMG bursts in ALMA is 0.5 Hz,
- (3) the maximum frequency of the alternating bursts in ALMA is 3.0 Hz.
- The scoring manual notes that the usual range for duration of ALMA EMG bursts is 100–500 msec. The ALMA burst frequency range of 0.5 to 3 Hz corresponds to a range of 0.33 to 2 sec between the onsets of consecutive EMG bursts.
Hypnagogic foot tremor

- Coarse tremor of one or both feet occurring with sleep onset.

- (1) the minimum number of bursts needed to make a train of bursts in hypnagogic foot tremor is 4 bursts,
- (2) The minimum frequency of the EMG bursts is 0.3 Hz,
- (3) The maximum frequency of the EMG bursts is 4.0 Hz.
- Duration of HFT bursts is 250–1000 msec
Restless Legs Syndrome

- Restless Legs Syndrome:
- Name has changed to WED

Willis-Ekbom Disease
ICSD-3 Criteria WED/RLS

- Urge to move the legs, usually accompanied by uncomfortable sensations in the legs. These symptoms must:
  - Begin or worsen during periods of rest such as lying down or sitting
  - Be partially or totally relieved by movement, such as walking or stretching
  - Occur predominantly in the evening or night rather than the day.
- Above features are not solely accounted for by another medical or behavioral condition (e.g., leg cramps, positional discomfort, myalgia, venous stasis, edema, arthritis, habitual foot tapping).
- Symptoms cause concern, distress, sleep disturbance, impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.\(^5\)

RLS: History

- Ask them to describe it.
- Urge to move the legs often associated with a sensory discomfort
- Worse at night
- Worse with inactivity
- Temporary relief with movement

- Mimics: neuropathy, leg cramps, spinal cord
- Red flags: pain, unilateral

- Sleep disturbance
RLS: History

- Frequency
- Onset of symptoms: What time
- How much does it bother them

- Family history
- Sleep disturbance

- Description: not painful, bilateral often difficult to explain, but urge to move is prominent
- Ask what do to get rid of it: typical to get up and walk

RLS Evaluation

- Exam:
  - Make sure there is not a neuropathy
  - Make sure no myelopathy
  - Check pulses
  - Serum ferritin if Dx RLS
RLS Epidemiology

- **REST study**: RLS Epidemiology, Symptoms, Treatment
  - Multicenter trial Europe and U.S.
  - Face to face or phone interview asking all four criteria
  - N = 15,391

<table>
<thead>
<tr>
<th>Country</th>
<th>Questionnaires Distributed, No.</th>
<th>Fully Completed Questionnaires, No. (%)</th>
<th>Any Frequency</th>
<th>≥ 3 times/week</th>
<th>≥ 7 times/week</th>
<th>Moderate or Extensive Discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>2040</td>
<td>1894 (91.7)</td>
<td>363/1894 (19.8)</td>
<td>12/1894 (0.6)</td>
<td>1/1894 (0.05)</td>
<td>7/1894 (0.4)</td>
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<tr>
<td>Germany</td>
<td>2004</td>
<td>1903 (94.6)</td>
<td>57/1903 (2.9)</td>
<td>7/1903 (0.37)</td>
<td>4/1903 (0.21)</td>
<td>15/1903 (0.78)</td>
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<tr>
<td>Italy</td>
<td>2090</td>
<td>1710 (82.9)</td>
<td>110/1710 (6.4)</td>
<td>5/1710 (0.29)</td>
<td>2/1710 (0.12)</td>
<td>30/1710 (1.75)</td>
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<tr>
<td>Spain</td>
<td>2003</td>
<td>1902 (90.0)</td>
<td>66/1902 (3.5)</td>
<td>6/1902 (0.32)</td>
<td>2/1902 (0.10)</td>
<td>27/1902 (1.41)</td>
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<tr>
<td>United Kingdom</td>
<td>2002</td>
<td>1851 (95.7)</td>
<td>67/1851 (3.6)</td>
<td>6/1851 (0.32)</td>
<td>4/1851 (0.21)</td>
<td>15/1851 (0.80)</td>
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<tr>
<td>United States</td>
<td>6214</td>
<td>5944 (96.4)</td>
<td>464/5944 (7.8)</td>
<td>346/5944 (5.8)</td>
<td>219/5944 (3.7)</td>
<td>638/5944 (10.7)</td>
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<td>Total</td>
<td>15282</td>
<td>15381</td>
<td>1114/15381 (7.2)</td>
<td>72/15381 (0.47)</td>
<td>63/15381 (0.41)</td>
<td>416/15381 (2.7)</td>
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</tbody>
</table>

Table 2. Prevalence of RLS Symptoms by Country and Degree of Severity

---

RLS/Cardiovascular disease in SHHS

**RLS**
- Possible relation to hypertension
- Coronary artery
- Cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Frequencies</th>
</tr>
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<tbody>
<tr>
<td>RLS (n=179)</td>
<td>No RLS (n=3254)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>63.7%</td>
</tr>
<tr>
<td>Coronary Artery</td>
<td>24.6%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>29.6%</td>
</tr>
</tbody>
</table>

**Adjusted Model**: Age, Sex, BMI max, DM, BP, smoking, cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Odds ratios</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.60</td>
<td>(0.92-1.82)</td>
</tr>
<tr>
<td>Coronary Artery</td>
<td>2.05</td>
<td>(1.38-3.04)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.07</td>
<td>(1.43-3.00)</td>
</tr>
</tbody>
</table>

Winkelmann 2008
RLS Treatment

- Can be once at night but can be evening plus bedtime if symptoms are bothersome in early evening

- Ropinirole / pramipexole
  - 0.25/0.125 mg x 3 nts → 0.5/0.25 mg x 3 nts → 1.0/0.5 mg
  - Side effects: compulsive behavior, insomnia

- Gabapentin
  - Start 100-300mg QHS going up by 100-300 every 3-5 nights until 900-1200mg
  - Side effects: swelling, depression, sleepiness

Periodic Limb Movements During Sleep

PLMS
Periodic Limb Movements During Sleep

- Periodic Limb movements during sleep (PLMS)
  - Occurs in up to 80%-90% of patients with RLS
  - Occur in up to 40% of elderly or w/ sleep apnea, stroke, neuropathy
  - Contraction of the anterior tibialis muscle, less often hamstring, iliopsoas and arms
  - Movements in sleep most often legs: every 30-40 sec over 4-6 hours

PLMS Video
PLMS & Sympathetic Activity

• **PLMS**
  - Sympathetic activation
  - Immediate increase SBP
  - Increase DBP
  - Increase in HR

Pennestri, Neurol 2007

Individual Leg Movements

• Individual limb movements
  - Dorsiflexion of foot (anterior tibialis)
  - Dorsiflexion great toe and extension of toes
  - Flexion at knee
  - Flexion at hip
  - Duration between 0.5 and 5 seconds
  - On EMG amplitude at least 8μv
Periodic Limb Movements

- Periodic limb movements during sleep (PLMS)
  - Series of at least four individual leg movements in succession
  - No less than 5 sec and no more than 90 sec apart
  - Seen on polysomnography

Quantification of PLMS

- Periodic limb movement index (PLMI): total number of periodic limb movements per hour of sleep
  - PLMI: anywhere between 0 and 150
    - More typically PLMI between 30 and 60
  - PLM arousal index (PLMAI): total number of PLMS followed by EEG arousal per hour of sleep; PLMAI > 5
Hypnogram

- Total sleep time
  - PLMI of 60.2
  - PLMAI of 12.2
- During first half of night
  - PLMI of 134.4
  - PLMAI of 24.3

Kaplan Meier Curve for incident cCVD by PLMAI
Should We Treat PLMS?

- PLMI and PLMAI are associated with incident cardiovascular disease.
- PLMS could be marker for CV disease or something else that is associated with CV disease
- No evidence that treatment of PLMS affects CV outcomes

Treatment of PLMS is Indicated When

- Periodic Limb Movement Disorder: PLMS and daytime dysfunction or complaint of unrefreshing sleep
- When it is disturbing to bed partner
- Similar to RLS Rx: Dopamine agonists, gabapentin, clonazepam

Summary

- Nighttime movement is common
- In most cases, behavior is benign
- But can be dangerous when behavior is bed-partner/self-injurious or when activity could be seizure
- Can cause substantial sleep disruption and affect quality of life even daytime life quality
- In all cases a complete sleep history is essential
It’s Not All Terrible

Questions?
A Multidisciplinary Treatment Approach for Obstructive Sleep Apnea

Lauren A. Tobias MD
Instructor of Medicine
Yale University School of Medicine

Disclosures

• I have nothing to disclose
Outline

- OSA pathophysiology
- Benefits of CPAP
- Challenges to PAP adherence
- Behavioral modification
- Oral appliances
- Surgical approaches

OSA Pathophysiology
Reduced upper airway size in OSA

Overnight Polysomnography (PSG)
Whom Should We Treat?

American Academy of Sleep Medicine (AASM) recommends offering positive airway pressure therapy to all patients who have been diagnosed with OSA

- AHI \( \geq 15 \), *regardless of symptoms*

- AHI 5-14 *with symptoms*
  - Sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
  - Waking up with breath holding, gasping, or choking
  - Habitual snoring and/or breathing interruptions
  - Hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes

Benefits of CPAP (lots!)

- Successfully eliminates OSA in >95% of pts
- Decreases sleepiness
- Improves quality of life
- Improves cognitive function
- Decreases hospitalizations
- Decreases car accidents
- Improves gas exchange
- Improves HTN (esp. nocturnal)

- Decreases pulmonary artery pressures
- Improves glucose control
- Reduces GERD
- Reduces cardiac arrhythmias during sleep
- Improves cardiac function in heart failure patients
- ? Reduces MI, CHF, stroke, mortality
Cardiovascular outcomes in Obstructive Sleep Apnea With and Without Treatment

Marin; Lancet 2005

CPAP Interfaces

- Nasal pillows
- Nasal mask
- Full face mask
CPAP adherence

• Many patients cannot tolerate CPAP
• Adherence rates 60-70%
• Must measure adherence objectively
• Adherence problems not unique to CPAP
  – Among pts w/acute MI discharged with prescriptions for aspirin, statin, and β-blockers, 34% stopped at least 1 med within 1 month of hospital discharge

Predictors of CPAP Adherence

• CPAP titration via attended polysomnography
• Adherence with CPAP during the first week of therapy
• Increased self-reported daytime sleepiness
• More severe oxygen desaturation during sleep
• Large nasal passages and low nasal resistance
Predictors of CPAP Adherence (cont’d)

• Psychological traits
  – lack of claustrophobic tendencies
  – presence of problem solving skills
  – optimism regarding the benefit of CPAP therapy
  – self-efficacy (defined as a positive subjective assessment of one's motivation, volition, and confidence to engage in a healthy behavior)

• Patient (vs. partner) sought medical attention
• Severity of OSA (weak relationship)

Managing poor adherence

• Refer back to sleep physician/tech for formal assessment of the problem
• Education, participation in mask selection, early counseling, psychosocial support may help
• Common issues:
  – Poorly fitting interface
  – Dry mouth (increase humidification, change to full face mask, add chin strap)
If at first CPAP doesn’t succeed...


How much CPAP use is enough?

More CPAP = More Benefit!
Never give up!

Alternatives to CPAP

- Weight Loss
- Positional therapy
- Oral appliances
- Surgical approaches
- Hypoglossal nerve stimulation
- Tracheostomy
Behavior Modification

- Weight loss
- Avoid alcohol or sedatives at bedtime
- Avoid sleeping in a supine position (back)


Weight Loss

- 1% change in weight $\rightarrow$ 3% change in AHI
- Weight loss usually not curative for OSA
- Continue CPAP until repeat objective testing after surgery

JAMA. 2012;308(11):1142-1149
Surgical vs Conventional Therapy for Weight Loss Treatment of Obstructive Sleep Apnea
A Randomized Controlled Trial

- Surgical group achieved greater weight loss at 2 years than conventional therapy (27.8 kg vs. 5.1 kg, p<0.001)
- BMI reduction from 46.3 → 36.6 w/surgery and 43.8 → 42.3 with conventional therapy
- AHI decreased by 25 events/hour in surgery group and 14 events/hour) w/conventional weight loss group
- Conclusion: differences in weight loss, not AHI

JAMA. 2012;308(11):1142-1149

Positional Therapy

- Positional OSA prevalence is >50%
- Techniques include:
  - Tennis Ball Therapy (TBT)
  - alarm training
  - position vests
- Compliance not well reported -- one study of TBT found only 38% still using after 6 months
- Efficacy suboptimal in most studies (AHI reduction <50%)
Oral Appliances (OA)  
(mandibular advancement devices, mandibular repositioning devices)

- Anchored to dental arches
- Induce mandibular protrusion $\rightarrow$ enlarged upper airway cross-sectional area $\rightarrow$ improved airway patency
- Titratable
- Need regular dental follow-up

Examples of oral appliances
Effect of oral appliance on airway diameter

Velopharyngeal

Without OA

With OA

Oropharyngeal

Oral appliances: Patient Selection

**Appropriate:**
- Mild to moderate OSA
- Preference for an oral appliance over PAP
- Supine-predominant OSA
- Non-adherence to, or refusal of, PAP

**Contraindicated:**
- When treatment is urgent
- Severe oxygen desaturation
- Certain dental conditions
- Insufficient manual dexterity

*Difficult to predict who will respond successfully*
Oral appliances: Side effects

- temporomandibular joint (TMJ) pain
- myofascial pain
- tooth pain
- Salivation
- TM joint sounds
- dry mouth
- gum irritation
- morning-after occlusal changes

Oral appliances: Evidence

- Superior to placebo device in reducing AHI
- Studies: heterogeneous methodology/population/outcome definition
- Paucity of trials comparing particular devices
- Not easy to measure adherence objectively
- Consider follow-up sleep testing

Oral appliances vs. CPAP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>No. of patients</th>
<th>No. of studies</th>
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<tbody>
<tr>
<td>$AHI_{\text{base}}$</td>
<td>31</td>
<td>2,816</td>
<td>74</td>
</tr>
<tr>
<td>$AHI_{\text{app}}$</td>
<td>14</td>
<td>2,724</td>
<td>73</td>
</tr>
<tr>
<td>Response rate</td>
<td>21%</td>
<td>1,577</td>
<td>51</td>
</tr>
<tr>
<td>Success rate</td>
<td>54%</td>
<td>2,087</td>
<td>59</td>
</tr>
</tbody>
</table>

- “Response” – 50% reduction in AHI (still >10)
- “Success” – AHI < 10
- Overall, with baseline AHI ~30/hr, CPAP achieves AHI <5/hr & OA achieves AHI 10-15/hr

Oral appliances: Evidence (cont’d)

- Less effective than PAP overall but adherence probably superior
- No reliable way to predict treatment response in individual patients or select appropriate candidates
- Cutoff pressure requirement of 13 cmH2O?
- Combination therapy (PAP + OA) an option
Upper Airway Surgery

• Aimed at addressing obstruction in the nasal, retropalatal, and retroglossal/hypopharyngeal regions
• Many patients have multiple levels of obstruction
• Primary role is patients with severe, obstructing lesions of the upper airway who have failed PAP therapy and an oral device
• Small case series of selected pts

Surgical Options for OSA

• Uvulopalatopharyngoplasty (UPPP)
• Laser-Assisted Uvulopalatoplasty
• Inferior turbinate reduction
• Soft Palatal Implants
• Genioglossus advancement
• Hyoid advancement
• Maxillomandibular advancement
• Upper airway radiofrequency treatment and robotic tongue base reduction
Uvulopalatopharyngoplasty (UPPP)

- Excision of tonsils & posterior soft palate/uvula
- Potential complications:
  - velopharyngeal insufficiency
  - voice change
  - nasopharyngeal stenosis
- 40-50% response rate
- AHI reduced to <10 events/hr in ~30%

Maxillomandibular Advancement (MMA)

- Most complex upper airway surgery
- 80-90% achieve AHI<20 and 50% reduction
- Mean post-op AHI 7.7
- Small uncontrolled studies

Before & After MMA

Tracheostomy

- Bypasses all obstructions
- Almost always curative
- Life-threatening OSA (often w/OHS) intolerant of /nonadherent with CPAP
- Quality of life impacted

Summary

- CPAP remains first-line therapy for OSA in most patients
- Early & aggressive & management of adherence problems is key
- Oral appliance therapy an option for mild-moderate OSA
- Surgical options are primarily reserved for severe OSA
Thank you!

Lauren.Tobias@yale.edu
A Novel Therapy for Obstructive Sleep Apnea: Upper Airway Neurostimulation

Klar Yaggi, MD, MPH
Director, Yale Centers for Sleep Medicine
Associate Professor of Medicine
Yale University School of Medicine

DISCLOSURES

• NO relevant financial disclosures
OUTLINE

• The Clinical Problem of Severe Sleep Apnea
• Design of Upper Airway Neurostimulation Device
• Evidence of effectiveness
Sleep Apnea Ranks Among the Most Prevalent Disorders in US Adults

OSA affects approximately 18 million US adults with roughly 2 million being diagnosed annually.

Sleep Apnea Prevalence in Cardiovascular Comorbidities

Logan et al. Hypertens 2001
Yaggi and Mohsenin, Lancet Neurology 2006
Garrigue et al. CIRC 2007
Gami et al. CIRC 2004
Giles et al. Endocr Pract 2007
Sparrow et al. Thorax 2003
Schaffer et al. Cardiology 1999
Resistant Hypertension & OSA

3x more likely to have moderate / severe OSA

Patients with resistant hypertension and OSA have a higher likelihood of severe OSA compared to those without.

- **Severe OSA**: 58%
- **Moderate OSA**: 28%
- **No / Mild OSA**: 14%

Patients treating their OSA have improvements in both:
- Blood pressure
- Cardiovascular risk

(Treatment defined by > 5.8 hours/night of CPAP)

Dose-Response (Trend) Analysis

<table>
<thead>
<tr>
<th>Severity of Syndrome</th>
<th>Stroke or Death</th>
<th>Follow-up yrs</th>
<th>Hazard Ratio (95% C.I.)</th>
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<tbody>
<tr>
<td>AHI ≤ 3 (ref)</td>
<td>13/271</td>
<td>3.08</td>
<td>[1.00]</td>
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<tr>
<td>AHI 4-12</td>
<td>21/258</td>
<td>3.06</td>
<td>1.75 (0.88-3.49)</td>
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<tr>
<td>AHI 13-36</td>
<td>20/243</td>
<td>3.09</td>
<td>1.74 (0.87-3.51)</td>
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<tr>
<td>AHI &gt;36</td>
<td>34/250</td>
<td>2.78</td>
<td>3.30 (1.74-6.26)</td>
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</tbody>
</table>

P=0.005 (Chi-square test for linear trend)

Yaggi; NEJM 2005
Heart Failure & OSA

Recent studies have demonstrated that patients with a compromised EF have a prevalence of 25-44% OSA NYHA II-IV or EF ≤ 40%

Ischemic HF patients treating their OSA have improvements in both:
- Ejection fraction
- Blood pressure

Greater improvements in patients with EF < 30 and AHI > 15

Survival (%)

Months of Follow Up

OSA with AHI < 15

OSA with AHI ≥ 15

P = 0.029

Bradley, CIRC 2003
Bradley, JACC 2011
Somers, JACC 2008
Wang, JACC 2007

Atrial Fibrillation & OSA

49% of AF patients also have moderate to severe OSA

Proportion of patients with OSA

OSA’s impact on treatments

Post cardioversion, the risk of recurrence is almost 2x higher

Controlled for Rx

25% increase in recurrence for moderate-severe OSA patients, post ablation

Somers, JACC 2009
Nebel, JAMA 2013
Fein, JACC 2014
Gami, CIRC 2004
Untreated OSA affects mortality

OSA Prevalence & Impact If Untreated

**OSA prevalence in US adults (%)**

- **AHI: <5 and/or snoring**
  - 67%
- **Mild OSA**
  - AHI: 5-15
  - 14%
- **Moderate OSA**
  - AHI: 15-30
  - 5%
- **Severe OSA**
  - AHI ≥ 30
  - 4%

~7 million US adults have moderate-severe OSA

Years of Follow Up

Survival (%)

0 5 10 15 20

AHI < 5
AHI 5-15
AHI 15-30
AHI ≥ 30

Peppard, Am J Epidemiology 2013
Young, SLEEP 2008

Continuous Positive Airway Pressure (CPAP)
Cardiovascular Outcomes in Obstructive Sleep Apnea

![Graph showing cumulative incidence of non-fatal CVS events (%) over months for different groups: Controls, Snorers, Mild OSAH, Severe OSAH, OSAH with CPAP.]

Marin; Lancet 2005

Stroke Mortality in Sleep Apnea With and Without Treatment

![Graph showing survival analysis with different AHI levels and treatment groups: AHI<10 (n=31), AHI 10-19 (n=39), AHI>20 with CPAP (n=28), AHI>30 without CPAP (n=42).]

Martinez-Garcia; AJRCCM 2009
CPAP Results in Improvement in Stroke Severity at 30-days in Patients with Sleep apnea and Acute Stroke

<table>
<thead>
<tr>
<th>Outcome:</th>
<th>Overall ITT</th>
<th>Sleep Apnea by CPAP Use†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (N=31)</td>
<td>Control (N=24)</td>
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<tr>
<td>Stroke severity (NIHSS) median change from baseline to 30-days</td>
<td>-3.0</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

Yaggi, Sleep 2012

Cost of OSA

The estimated annual medical costs resulting from untreated OSA is $3.4 Billion

PAP adherence

- Adherence patterns determined early
- Patients tend to overestimate adherence
- Predictors of adherence
  - Daytime sleepiness/symptomatic benefit
  - Getting it right up front

Strategies for Improving PAP Adherence

- Center PAP adherence programs
- Education
- Acclimation/early troubleshooting
- Eszopiclone
- Heated humidification
- Expiratory relief/ramps
- Behavioral/motivational interventions
- Wireless Monitoring/objective monitoring

Aloia, Sleep Med Rev, 2011
Weaver, Proc Am Thor Soc, 2008
Alternative Treatments for Sleep Apnea

Mild-Moderate OSA
- Position therapy
- Weight reduction
- Mandibular advancement devices (MADs)
- Soft tissue surgical interventions (e.g., UPPP, RFA)
- Nasal EPAP
- Negative pressure devices

Severe Sleep
- Maxillo-mandibular Advancement
- Tracheostomy

OUTLINE

- The Clinical Problem of Severe Sleep Apnea
- Design of Upper Airway Neurostimulation Device
Pathogenesis of Obstructive Sleep Apnea

- Negative pressure on inspiration
- Extraluminal positive pressure
- Fat deposition
- Small mandible
- Pharyngeal dilator muscle contraction (genioglossus)
- Lung volume (longitudinal traction)

Inspire System

- Three implanted components
- Sleep remote

Stimulation lead
Small generator
Sensing lead
Mechanism of action - stimulation affects multi-level collapse (VIDEOS)

Therapy Can Be Titrated

- Therapeutic effect is evident at both the palate and tongue-base
- More prominent response with increasing stimulation energy – within therapeutic range
Upper Airway Stimulation Effect: PSG

Inspire therapy turned on

Airflow

SpO2

Severe OSA
Events Resolved

Inspire therapy effect during polysomnography

OUTLINE

• The Clinical Problem of Severe Sleep Apnea
• Novel Design of Upper Airway Neurostimulation
• Evidence of Effectiveness
## Inspire Clinical Evidence Development

<table>
<thead>
<tr>
<th>Inspire 1</th>
<th>Inspire 2</th>
<th>Inspire 2 &amp; 3</th>
<th>Inspire STAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proof of Principle</strong></td>
<td><strong>Feasibility Study</strong></td>
<td><strong>Feasibility Studies</strong></td>
<td><strong>Pivotal Trial (Phase 3)</strong></td>
</tr>
<tr>
<td>8 patients @ 4 centers</td>
<td>22 patients @ 4 centers</td>
<td>12 patients @ 7 centers</td>
<td>126 patients @ 22 centers</td>
</tr>
<tr>
<td>2001</td>
<td>2009/10</td>
<td>2010/11</td>
<td>2012/13</td>
</tr>
<tr>
<td>First in man</td>
<td>Patient selection Implant technique</td>
<td>Safety / Efficacy</td>
<td>Safety / Efficacy</td>
</tr>
<tr>
<td>1 publication</td>
<td>1 peer reviewed publication</td>
<td>2 peer reviewed publications</td>
<td>FDA approval</td>
</tr>
</tbody>
</table>

*FDA full approval in May 2014*

---

## Upper-Airway Stimulation for Obstructive Sleep Apnea

Strollo P et al. for the Star Group Investigators  
*N Engl J Med* 2014;370:139-49
Methods: Design

- Two phases:
  - Multicenter, prospective cohort, followed by
  - A randomized controlled therapy-withdrawal study of a subgroup of consecutive patients who responded to treatment
- Participants served as own control
- No Concurrent control group

Methods: Patients

- Inclusion:
  - Adults Mod-Severe OSA (AHI 20-50)
  - Difficulty accepting/adhering CPAP
- Exclusion:
  - BMI >32*
  - Concentric collapse on DISE*
  - Neuromuscular disease
  - Severe pulmonary disease
  - NYHC III or IV
  - Recent MI/severe arrhythmia (<6 mos)
  - Persistent uncontrolled hypertension
  - Active psychiatric disease
  - Co-existing sleep disorder
Drug Induced Sleep Endoscopy

A-P Collapse
Device candidate

Concentric Collapse
Not an device candidate

Methods: Outcomes

• Primary Outcomes: (Baseline to 12 months)
  – “Response”
    • A reduction of AHI ≥ 50% and
    • AHI < 20
    • Reduction of ODI of at least 25%
  – Change in AHI/ODI

• Secondary Outcomes: (Baseline to 12 months)
  – Epworth Sleepiness Scale (ESS)
  – Functional Outcomes of Sleep Questionnaire (FOSQ)
  – Percentage of sleep with O₂sat < 90% (T₉₀)
Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>54.5±10.2</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>105 (83)</td>
</tr>
<tr>
<td>White race — no. (%)‡</td>
<td>122 (97)</td>
</tr>
<tr>
<td>Body-mass index;</td>
<td>28.4±2.6</td>
</tr>
<tr>
<td>Neck size — cm</td>
<td>41.2±3.2</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.7±16.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81.5±9.7</td>
</tr>
<tr>
<td>Hypertension — no. (%)</td>
<td>48 (38)</td>
</tr>
<tr>
<td>Diabetes — no. (%)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Asthma — no. (%)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Congestive heart failure — no. (%)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Uvulopalatopharyngoplasty — no. (%)</td>
<td>22 (17)</td>
</tr>
</tbody>
</table>

Results: Response Rates

- 68% had an AHI reduction of at least 50% and an AHI <20
- 75% had a 25% reduction in ODI
Results: Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline</th>
<th>12 Months</th>
<th>Change</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AH1 score†</td>
<td>33.9±11.8</td>
<td>15.3±16.1</td>
<td>-18.6±16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>29.3</td>
<td>9.0</td>
<td>-20.3</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>23.7 to 38.6</td>
<td>4.2 to 22.5</td>
<td>-19.4 to -9.3</td>
<td></td>
</tr>
<tr>
<td>ODI score‡</td>
<td>28.9±12.0</td>
<td>13.8±15.7</td>
<td>-15.1±15.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>25.4</td>
<td>7.4</td>
<td>-18.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>19.3 to 36.6</td>
<td>3.5 to 20.5</td>
<td>-15.7 to -8.6</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOSQ score§</td>
<td>14.3±3.2</td>
<td>17.3±2.9</td>
<td>2.9±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>14.6</td>
<td>18.2</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>12.1 to 17.1</td>
<td>16.2 to 19.5</td>
<td>4.1 to 4.7</td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score†</td>
<td>11.6±5.0</td>
<td>7.6±4.2</td>
<td>-4.0±5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>11.0</td>
<td>6.0</td>
<td>-5.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>8.0 to 15.0</td>
<td>4.0 to 10.0</td>
<td>-4.0 to -1.0</td>
<td></td>
</tr>
<tr>
<td>Percentage of sleep time with oxygen desaturation &lt;90%</td>
<td>8.7±10.2</td>
<td>3.8±12.4</td>
<td>-5.9±11.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Median</td>
<td>5.4</td>
<td>0.9</td>
<td>-4.5</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2.3 to 10.0</td>
<td>0.2 to 5.3</td>
<td>-6.8 to -0.3</td>
<td></td>
</tr>
</tbody>
</table>

Results: Therapy Withdrawal

**Apnea-Hypopnea Index**

- Baseline: 31.3 (±6.3)
- Month 12: 25.4 (±7.6)

**Oxygen Desaturation Index**

- Baseline: 30.7 (±6.9)
- Month 12: 26.7 (±7.8)
- Randomized, therapy withdrawal trial: 27.8 (±6.2)
Objective and Patient Reported Outcome at 18 Months

Self and Partner-Report Snoring

- "Partner leaves room" reduced from 30% to 5%
- "No or Soft Snoring" increased from 17% to 85%

Courtesy of Strollo et al (APSS 2015)
Self-report Nightly Use

![Bar chart showing nightly use percentages.]

- 12 Month N=123: 86%
- 18 Month N=123: 84%

Courtesy of Strollo et al (APSS 2015)

Multi-disciplinary Care Teams

Screen:
- Consultation
- Sleep study
- DISE

Office Visit & In-lab PSG:
- Activation
- Home use and acclimatization
- In-lab sleep titration

Office Visit:
- Battery
- Adherence
Summary: “The Problem”

- Severe sleep apnea associated with significant cardiovascular morbidity and mortality
- High population-attributable risk
- CPAP adherence is ~60-70%
- There is a need for an effective non-PAP treatment for severe sleep apnea

Summary: “Design”

- Upper airway stimulation novel therapeutic modality
- Less invasive than other Non-PAP alternatives for severe sleep apnea (i.e., maxillo-mandibular advancement and tracheostomy)
- Stimulates multiple regions of collapse (velopharynx and base of tongue)
- Titratable
- Multi-disciplinary approach
Summary: “Evidence”

• **Strengths:** safe and effective non-PAP treatment for severe OSA, titratable, well-tolerated, less invasive than alternative txs
• **Limitations:** not blinded study, BMI cut-point, non-responders
• **Conclusion:** Additional tool for the treatment of moderate-severe sleep apnea among patients who are not able to accept/adhere to CPAP who meet eligibility criteria

THANK YOU, FOR YOUR ATTENTION
Patient Centered Care for Patients with Sleep Disorders

Janet Hilbert MD
Yale Pulmonary, Critical Care, and Sleep Medicine
Yale Centers for Sleep Medicine
September 18, 2015

Disclosures

None
Case SJ: Initial Presentation

- **Presentation**
  - 66 yo woman with chronic tiredness, observed “noisy breathing”, stress
  - BT 9-11 PM, rise time 6-7 AM, variable SL and awakenings
  - BP 112/60, BMI nl, exam unremarkable
- **HST:** REI 6, mean SaO2 91, nadir SaO2 83%
- **FU:** Discussed results and therapeutic options in context of symptoms; Elected PAP
### Case SJ: F/U PAP management visit:

- **Subjective:**
  - Feeling much more rested
  - Only c/o puffiness under eyes
- **Download:** Usage 7+ hrs, AHI 2.7
- **Mask refit at visit**
- **Followup planned**

### Case SJ: Patient email/EMR patient portal:

**Dear Dr. Hilbert,**

WOW!!! Yesterday for the first time in YEARS I was able to drive to Hartford from Branford and then back WITHOUT having to eat popcorn or sunflower seeds to stay awake!!!! It was GREAT!!! I have been retired from my job in Hartford for about three years now and for the last several years my husband would make me fresh popcorn every morning so that I could safely commute to and from work. What a joy to no longer need any props!! Thank you sooooooo much!

I am continuing to try adjustments to the new mask ....If I exhaust creative ways to try to wear the xs mask I will follow up with Laurie, as she suggested.

**Best regards,**
Institute of Medicine 2001 Report:
Crossing the Quality Chasm: a New Health System
for the 21st Century

6 Aims for Improvement
- Safe
- Effective
- Patient-centered
- Timely
- Efficient
- Equitable

10 Rules for Redesign
- Continuous relationships
- Customized for needs/values
- Patient is source of control
- Knowledge is shared
- Evidence based decision making
- Safety is a system property
- Transparency
- Needs anticipated
- Waste is decreased
- Clinician/institutional cooperation
What Patient Centered Care is NOT:

Patient Centered Care

Institute of Medicine Definition:

Providing care that is respectful and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions
Personalized Care

- Different from patient centered care
- Not just “Will this treatment work?”, but “Will this treatment work for me?”
- National Human Genome Research Institute: Using an individual’s genetic profile to guide decisions made in regard to prevention, diagnosis, and treatment of disease
- Preferred term by US National Research Council: precision medicine rather than personalized medicine

Patient Centered and Personalized Care in Patients with OSA

- How can we determine patient-specific needs?
- How can we better educate patients and encourage shared decision-making?
- How can we engage patients in their care?
- How can we determine patient centered outcomes?
Moving Toward Personalized Care in Obstructive Sleep Apnea

- Early evidence of genetic association: familial and twin studies
- Assessment of heritable risk factors:
  - Body weight/fat distribution
  - Craniofacial morphology
  - Ventilatory control
  - Upper airway control
- Assessment of individual susceptibility to sleep apnea:
  - Sleepiness/neurocognitive disorders
  - Cardiovascular disorders
- Genomics, proteomics, epigenetics, biomarkers
- Phenotypic variability

Physiologic Phenotypes of OSA

- Rationale: characterize pathophysiologic causes including:
  - anatomically compromised or collapsible upper airway (high passive critical closing pressure of the upper airway [Pcrit])
  - waking up prematurely to airway narrowing (a low respiratory arousal threshold)
  - oversensitive ventilatory control system (high loop gain)
  - inadequate responsiveness of the upper-airway dilator muscles during sleep (minimal increase in EMG activity to negative pharyngeal pressure)
- Physiologic parameters + PSG in 75 subjects w/ and w/o OSA
- Results: Pcrit clearly important, but 58% patients also had nonanatomic contribution to OSA
- Suggested possible therapeutic implications

Clinical Phenotypes by Cluster Analysis

- Icelandic Sleep Cohort
- N=822, AHI 44.9 ± 20.7, age 54.5 ± 10.6, 81% men
- Questionnaires re: symptoms and comorbidities
- 3 Distinct Clusters
  - Cluster 1: Disturbed sleep group
  - Cluster 2: Minimally symptomatic group
  - Cluster 3: EDS group
- Prevalence of HTN and CVD highest in Cluster 2


Clinical Phenotypes by Cluster Analysis

Conclusions:
- OSA is clinically heterogeneous
- Identifying profiles allows for development of personalized therapies

Patient Centered and Personalized Care in Patients with OSA

- How can we determine patient-specific needs?
- How can we better educate patients and encourage shared decision-making?
- How can we engage patients in their care?
- How can we determine patient-centered outcomes?

Shared Decision Making Literature Review

- In general, patients want to be informed of treatment alternatives
- In general, patients want to be involved in treatment decisions when more than one treatment alternative exists
- Extent to which patients want to be involved in treatment decisions is variable
- Some studies suggest benefits including improved patient satisfaction and better compliance (methodologic limitations)

Patient Expectations and Factors Impacting Treatment Choices in OSA

- Qualitative analysis of four focus group sessions with current CPAP and OA users, n=22
- Expectations of treatment (most to least frequently mentioned):
  - improved health, apnea elimination, improved sleep, reduced fatigue, reduced snoring, bed-partner benefits
- Factors impacting treatment choice (most to least mentioned):
  - device effectiveness, transportability, embarrassment, cost

Almeida FR et al. Sleep Breath 2013;17(3):659

---

Educational, Supportive, and Behavioral Interventions Improve PAP Adherence

<table>
<thead>
<tr>
<th></th>
<th>↑Device usage (hours) (CI)</th>
<th>Change in % used &gt; 4 hs/night %before ➔ %after (OR)</th>
<th>N (# studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational</td>
<td>0.60 (0.27-0.93)</td>
<td>59% ➔ 70% (1.80)</td>
<td>683 (8)</td>
</tr>
<tr>
<td>Supportive</td>
<td>0.82 (0.36-1.27)</td>
<td>59% ➔ 75% (2.06)</td>
<td>803 (13)</td>
</tr>
<tr>
<td>Behavioral</td>
<td>1.44 (0.43-2.45)</td>
<td>28% ➔ 47% (2.23)</td>
<td>584 (6)</td>
</tr>
</tbody>
</table>

Wozniak DR, Lasserson TJ, Smith I. Cochrane Database Syst Rev 2014 Jan 8;1
Patient Centered and Personalized Care in Patients with OSA

- How can we determine patient-specific needs?
- How can we better educate patients and encourage shared decision making?
- How can we engage patients in their care?
- How can we determine patient centered outcomes?

Evaluation of PAP Data

<table>
<thead>
<tr>
<th>Compliance Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Range: 11/20/2012 - 12/4/2012</td>
</tr>
<tr>
<td>Days with Device Usage: 0 days</td>
</tr>
<tr>
<td>Days without Device Usage: 0 days</td>
</tr>
<tr>
<td>Percent Days with Device Usage: 100.0%</td>
</tr>
<tr>
<td>Cumulative Usage: 1 day 12 hrs, 9 mins, 52 secs.</td>
</tr>
<tr>
<td>Maximum Usage (1 Day): 8 hrs, 17 mins, 18 secs.</td>
</tr>
<tr>
<td>Average Usage (60 Days): 6 hrs, 1 mins, 39 secs.</td>
</tr>
<tr>
<td>Average Usage (Days Used): 6 hrs, 1 mins, 30 secs.</td>
</tr>
<tr>
<td>Minimum Usage (1 Day): 45 mins, 8 secs.</td>
</tr>
<tr>
<td>Percent of Days with Usage &lt;= 4 Hours: 63.9%</td>
</tr>
<tr>
<td>Percent of Days with Usage = 4 Hours: 16.7%</td>
</tr>
<tr>
<td>Total Blow Time: 1 day 12 hrs, 10 mins, 17 secs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep Therapy Statistics (Phillips Respironics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Time in CPAP Per Day: 10 secs.</td>
</tr>
<tr>
<td>Average Breathe: 30, 31, 32, 33, 34, 35, 36, 37, 38, 39</td>
</tr>
<tr>
<td>CPAP Pressure: 10.0 cmH2O</td>
</tr>
</tbody>
</table>
**Patient Access to PAP Data**

**Web-Based Access to PAP Data Improves PAP Adherence**

<table>
<thead>
<tr>
<th></th>
<th>Usual care Mean (SD)</th>
<th>Web Mean (SD)</th>
<th>Web+FI Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st wk</td>
<td>Avg daily hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.7 (3.3)</td>
<td>6.3 (2.5)*</td>
<td>5.9 (2.5)*</td>
</tr>
<tr>
<td>3 mo</td>
<td>Avg daily hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.8 (3.3)</td>
<td>5.0 (3.2)*</td>
<td>4.8 (3.0)*</td>
</tr>
</tbody>
</table>

Randomized trial (3 mo) of usual care, web based access, or web-based access + financial incentive

* P<0.0001

Kuna ST et al. Sleep 2015;38(8):1229
Use of Peer Buddies Improves PAP Adherence

- Pilot study (3 mo) of peer buddy system + usual care vs usual care
- 91% patients rated PBS as very satisfactory or satisfactory
- CPAP adherence at 1 wk
  - PBS 5.3 ± 2.0 hr/day
  - Control 4.0 ± 2.4 hr/day
- CPAP 4 hrs/night
  - PBS 63.6%
  - Control 40%


Patient Centered and Personalized Care in Patients with OSA

- How can we determine patient-specific needs?
- How can we better educate patients and encourage shared decision making?
- How can we engage patients in their care?
- How can we determine patient centered outcomes?
Patient-Centered Outcomes Research Institute (PCORI)

- Independent nonprofit, nongovernmental organization located in Washington, DC, authorized by Congress in 2010
- Mandate: to improve the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy makers make informed health decisions
- Support comparative clinical effectiveness research (CER)

Retrieved from http://pcori.org

Sleep Apnea Patient Centered Outcomes Network (SAPCON)

- Principal Investigator: Susan Redline, MD, MPH
- Collaborators:
  - American Sleep Apnea Association (ASAA)
  - Brigham and Women’s Hospital
  - Informatics for Integrating Biology & the Bedside (i2b2)/Shared Health Research Informatics Network (SHRINE)
  - Centers for Translational Science Award (CTSA) Sleep Research Network (SRN)
Sleep Apnea Patient Centered Outcomes Network (SAPCON)

- **Mission:**
  - to improve the diagnosis and treatment of sleep apnea through the active engagement of patients, families, researchers, and healthcare providers in a community that facilitates patient-centered research

- **Goals**
  - Recruit at least 50,000 members
  - Foster a patient-centered approach to focus research on questions and results that are most important to people with sleep apnea or at risk of sleep apnea
  - Build an online community that is representative of all appropriate racial/ethnic and socioeconomic backgrounds

MyApnea.Org

- Public face of SAPCON
- Patient-Powered Research Network (PPRN) within PCORnet
- Organized and governed by patients
- Members:
  - Have access to tools to help manage their condition
  - Connect with and learn from others through forums
  - Enter and share data about themselves
  - Suggest and vote on research ideas
Patient Centered and Personalized Care
Back to SJ:

Where we are:
- Personalizing care based on clinical presentation, current evidence, and patient preferences
- Multidisciplinary education and support
- Patient engagement through personal contact and new technologic advances
- Patient centered research

The future:
- Genetic studies or biomarkers to identify individual susceptibility
- More specific targeted therapies
- New models of care, e.g. telemedicine, coordinated care management
- Patient centered research
Conclusions

- A patient centered approach including multidisciplinary education/support programs and information technology advances for communication/monitoring can improve patient adherence to therapy and patient engagement.

- Personalized treatment for patients with sleep disorders is still on the horizon, but new research exploring individual susceptibility shows promise.

- Innovative patient-powered research networks focusing on issues that are most important to patients may improve the ability to make informed health decisions.

Patient Centered and Personalized Care

It Takes a Village…

- Nurse
- Resp Therapist
- Peer Buddy
- Sleep Specialist
- Sleep Researcher
- Pulmonologist
- Neurologist
- Family
- PCP
- PAP Educator
- Dentist/OMFS
- DME Support Team
- ENT
- Social Worker
- Nutritionist
- Psychologist
# Acknowledgements

<table>
<thead>
<tr>
<th>Technical, Scoring, and Respiratory staff</th>
<th>Vickie Asard, Dawn Bickley, Laurie Crowther, Laura Hall, John Kowalczyk, Katie Lucey, Keith Sabo, Jason Scherff, Laurie Skinger, Tom Whelan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative and Liaison staff</td>
<td>Adam Bennett, Geoff Blum, Donna Canepari, Gary Lavalette</td>
</tr>
<tr>
<td>Office staff</td>
<td>Lee Barraco, Jen Conte, Kathy Kishel, CJ Polaske, Danielle Tully, Shanoune Wooten</td>
</tr>
<tr>
<td>Nursing staff</td>
<td>Ruby Harper, Stevie Lockett, Lilly Tyson</td>
</tr>
<tr>
<td>Medical staff</td>
<td>Vickie Gerdon, Janet Hilbert, Melissa Knauert, Brian Koo, Meir Kryger, Vahid Mohsenin, Lynelle Schneeberg, Lauren Tobias, Christine Won, Klar Yaggi</td>
</tr>
<tr>
<td>Sleep fellows</td>
<td>Mo’d Al-Halawani, Suman Baddam, Pnina Weiss</td>
</tr>
</tbody>
</table>