LEARNING OBJECTIVES

- List key differences between insomnia and obstructive sleep apnea
- Identify at least two appropriate pharmacologic treatment options for insomnia
- Assess how current FDA warnings have affected options for the treatment of insomnia

INTRODUCTION – OBSTRUCTIVE SLEEP APNEA

- Obstructive Sleep Apnea (OSA)
  - Affects up to 4% of middle-aged adults
  - Common complaints
    - Loud snoring
    - Disrupted sleep
    - Daytime sleepiness
  - Up to 80% of patients with OSA are undiagnosed
    - 50% of patients who present with a stroke have sleep apnea
    - 35% of patients with high blood pressure have sleep apnea

SLEEP APNEA

- “Apnea” is Greek for “without breath”
- Breathing ‘pauses’ during sleep
  - At least ten-second intervals of absence of breathing
  - Multiple seconds to minutes (up to 30 times/hr)
  - Snorting/choking/gasping sound may occur when breathe again
- Usually not associated with breathing problems during the day
  - Difficult to diagnose
  - Symptoms usually recognized by spouse (loud snoring)
- Polysomnogram (sleep study) for diagnosis
OBSTRUCTIVE SLEEP APNEA

Normal airway

Abnormal airway during sleep

Obstruction

Sleep Apnea Questionnaire

If you snore excessively and have any of the additional problems listed below, you may have sleep apnea. Please consider discussing a sleep evaluation with your doctor.

1. Do you snore loudly?
2. Does your bedroom partner complain about your snoring?
3. Does your snoring wake you up at night?
4. Do you or your bedroom partner notice that you make grunting and choking noises during sleep?
5. Do you have a dry mouth or sore throat or headache in the morning?
6. Do you often feel asleep during the daytime or after you want to sleep?
7. Are you often tired during the day?
8. Do you have high blood pressure?

Sleep Apnea Risk Factors

- Age
  - 40-60 years highest risk
- Ethnicity
  - African American, Pacific Islander, and Hispanic groups at higher risk
- Family history
- Obesity
- Physical characteristics
  - Large neck (>17" in men; >16" in women)
  - Facial/Scull characteristics (narrow upper jaw, receding chin, overbite, large tongue, soft palate changes)
- Smoking and alcohol use
- Other medical conditions
  - Diabetes, GERD

Consequences of Sleep Apnea

- Increased risk of the following:
  - Heart conditions
    - Chest pain
    - Cardiac arrhythmias (irregular heartbeat)
    - Heart attack
  - Stroke
  - Motor vehicle accidents
  - Work-related accidents
  - Depression
TREATING SLEEP APNEA

- First line → Behavioral measures
  - Lose weight
  - Decrease alcohol intake
  - Decrease/stop taking medications that make you drowsy
- Second line → CPAP
  - CPAP (continuous positive airway pressure) machine
- Other options
  - Dental appliances/devices
  - Surgery
- There are currently NO medication therapies available to treat obstructive sleep apnea

CPAP THERAPY

- Mask over nose/mouth
  - Connects to machine kept at the bedside
  - Mild air pressure used to keep airway open
- Decreases sleep disruptions from decreased oxygen intake
  - Decreases snoring
  - Leads to decreased daytime sleepiness

DENTAL APPLIANCES/DEVICES

- Used for OSA in patients unable to tolerate or have not have improvement with CPAP therapy
- Mandibular advancement device (MAD)
  - Most widely used
  - Forces lower jaw forward and down
- Tongue retaining device (TRD)
  - Splint that holds the tongue in place
- Disadvantages
  - Not as effective as CPAP
  - Pain, dry lips, tooth discomfort
  - May cause long term changes in dental structure

CPAP THERAPY

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  - Connects to machine kept at the bedside
  - Mild air pressure used to keep airway open
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  - Decreases snoring
  - Leads to decreased daytime sleepiness
INTRODUCTION - INSOMNIA

- One of the most common medical complaints
  - 35% of the population reports insomnia within the last year
- Increasing prevalence with increasing age
- More common in:
  - Females
  - Unemployed
  - Divorced, widowed, separated
  - Lower socioeconomic status
- Only 30% of patients with insomnia report the problem to their physician

CLASSIFICATION OF SLEEP DISORDERS

<table>
<thead>
<tr>
<th>Primary Sleep Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyssomnias – abnormality in amount, quality, or timing of sleep</td>
</tr>
<tr>
<td>Primary insomnia</td>
</tr>
<tr>
<td>Primary hypersomnia</td>
</tr>
<tr>
<td>Narcolepsy</td>
</tr>
<tr>
<td>Breathing-related sleep disorder</td>
</tr>
<tr>
<td>Circadian rhythm sleep disorder</td>
</tr>
<tr>
<td>Jet lag</td>
</tr>
<tr>
<td>Shift work</td>
</tr>
<tr>
<td>Parasomnias – abnormal behavioral or psychological events associated with sleep</td>
</tr>
<tr>
<td>Nightmares/Sleep terror disorder</td>
</tr>
<tr>
<td>Sleepwalking</td>
</tr>
<tr>
<td>Sleep disorders related to another mental disorder</td>
</tr>
</tbody>
</table>

DURATION

- Transient (2-3 days) or short term (up to 3 weeks)
  - Jet lag
  - Shift work changes
  - Acute illness
  - Major life events
- Chronic insomnia (greater than 1 month)
  - Medical disorder
  - Psychiatric disorder
  - Medication-related cause

INSOMNIA DIAGNOSIS

- One or more of the following:
  - Difficulty initiating sleep
  - Difficulty maintaining sleep
  - Waking up too early or nonrestorative/poor sleep quality
- Problems with sleep despite adequate opportunity for sleep
  - Different from sleep deprivation
- Must also have daytime impairment from sleep difficulty
DAYTIME IMPAIRMENT

- One of the following to qualify for daytime impairment
  - Fatigue or lethargy
  - Problems with attention, concentration, or memory
  - Poor school/work performance
  - Irritability
  - Low motivation or energy
  - Increased errors/accidents at work or while driving
  - Headaches
  - GI symptoms
  - Concerns or worries about sleep loss

HOW MUCH SLEEP IS ENOUGH?

![Graph showing average amount of required sleep](Image)

INSOMNIA OR NOT?

- Some people require only a few hours of sleep with no residual daytime sleepiness
  - As people age, they require less sleep
  - NOT considered insomnia due to absence of daytime symptoms
  - Does not appear to be associated with adverse health outcomes
  - Called “short sleep requirement” or “short sleepers”
- Spending less time sleeping due to busy lifestyle
  - NOT considered insomnia if sleep comes easily when given the opportunity
  - Known as “sleep deprivation”

HOW IS OSA DIFFERENT THAN INSOMNIA?

- Obstructive sleep apnea is caused by a physical obstruction of the airway
  - Awakening due to decreased oxygen intake
  - Given the opportunity to sleep (without the obstruction), individuals are able to sleep
  - Similar to “sleep deprivation” problem
  - Would sleep if had adequate opportunity
  - CANNOT be treated with medication
    - Many medications used to treat insomnia need to be avoided in patients with obstructive sleep apnea
    - Avoid central nervous system depressants (i.e. benzodiazepines)
CONSEQUENCES OF INADEQUATE SLEEP

- Decreased quality of life
  - Tired, sleepiness, confusion, anxiety, depression
  - Less likely to receive job promotions, more sick time
- Comorbidities
  - May have increased risk of high blood pressure, heart attacks, and other heart conditions
  - Strongly associated with development of psychiatric disorders
    - Depression, anxiety, drug abuse

MEDICATION-RELATED CAUSES

- Beta blockers
  - Metoprolol
- Asthma medications
  - Albuterol, theophylline
- Antidepressants
  - Fluoxetine, nortriptyline
- Decongestants
  - Pseudoephedrine
- Stimulants
  - ADHD medications
- Steroids
  - Prednisone, methylprednisolone

MEDICATION-RELATED CAUSES *List not inclusive of all medication-related causes

INSOMNIA AND OTHER MEDICAL CONDITIONS

Prevalence of Chronic Insomnia in other Medical Conditions

MENOPAUSE AND INSOMNIA

- More sleep complaints during perimenopausal period
  - Insomnia common complaint in women with early menopause
  - May be secondary to vasomotor symptoms (hot flashes, night sweats) during menopause
- Sleep quality has shown to be better after menopause
  - More deep sleep and longer sleep times
  - More self-reported dissatisfaction with sleep (even though getting ‘better’ sleep)
MANAGEMENT

- Identifying cause of insomnia (if identifiable)
  - Treat comorbid conditions

- Education
  - Sleep hygiene
  - Stress management
  - Monitoring of mood symptoms
  - Eliminating unnecessary pharmacotherapy

- Pharmacologic therapies

BEHAVIORAL THERAPY

- Sleep hygiene
- Stimulus control
- Relaxation
- Sleep restriction
- Cognitive therapy
- Cognitive behavioral therapy

SLEEP HYGIENE

- Sleep only as long as you need to feel rested
  - Get out of bed
  - Maintain a regular sleep schedule
  - Do NOT force sleep
  - Avoid caffeine after lunch
  - Avoid alcohol near bedtime
  - Avoid smoking/nicotine intake
  - Decrease stimuli in bedroom
  - Take care of worries before bed
  - Exercise 20 mins. during the day
  - 4 – 5 hours prior to bedtime
  - Avoid daytime naps

STIMULUS CONTROL

- People who suffer from insomnia associated the bed/bedroom with fear of not sleeping
- Do not go to bed unless sleepy
  - Only used the bed for sleep or sex
- Do not spend ≥ 20 mins in bed without falling asleep
  - Get up and do something relaxing
  - Alarm set to wake a same time everyday
  - No naps allowed
**RELAXATION THERAPY**
- Used each evening prior to sleep
- Progressive muscle relaxation
  - Head-to-toe progression of contraction followed by relaxation
- Relaxation response
  - Lie or sit comfortably
  - Close eyes and focus on deep breathing
  - Focus on one neutral image
    - Peaceful word or place

**SLEEP RESTRICTION THERAPY**
- Stay in bed longer to make up for lost sleep
- Shift in circadian rhythm
- Decrease time spent in bed to time actually sleeping (not < 5 hours)
  - No naps during the day
- Sleep efficiency calculated
  - Time sleeping/time in bed (%)
  - ↑ time by 15-30 mins when ≥ 85%

**COGNITIVE THERAPY**
- Patients awake at night
  - Concern of poor functioning next day
  - Worry exacerbates difficulty sleeping
- Work with therapist
  - Deal with anxiety
  - Establish realistic expectations

**COGNITIVE BEHAVIORAL THERAPY**
- Combines many strategies over several weeks

- Education
- Stimulus Control
- Sleep Hygiene
- Sleep Restriction
- Cognitive Therapy
**Pharmacological Therapy**

- Benzodiazepines
- Non-benzodiazepine sedatives
- Melatonin agonist
- Antihistamines

**Pharmacological Treatment**

- Caution in the following patient groups
  - Pregnancy
  - Fetal malformations in first trimester
  - Alcohol consumption
  - Excessive sedation
  - Renal/hepatic disease
  - Accumulation of drug
  - Pulmonary disease/Sleep apnea
  - Worsen disease/hypoventilation
  - Nighttime decision-makers
  - On-call, taking care of children
  - Older adults
  - Increased risk of side effects

**Benzodiazepines**

- Benzodiazepines have sedative, anxiolytic, muscle relaxant, and anticonvulsant properties
  - Reduce time to onset of sleep
  - Increase total sleep time
  - All schedule IV controlled substances

- Medications commonly used
  - Triazolam (Halcion®)
  - Quick-acting, but also short-acting
  - Lorazepam (Ativan®)
  - Short-intermediate acting
  - Estazolam (Prosom®) and temazepam (Restoril™)
  - Intermediate-acting
  - Flurazepam (Dalmane®) and quazepam (Doral®)
  - Long-acting due to active metabolites

- Adverse Effects
  - Drowsiness, incoordination, decreased concentration, and cognitive deficits
  - Daytime tolerance to these effects may occur
  - Anterograde amnesia
  - Abuse risk
  - Tolerance
    - May develop after 2 – 12 weeks of continuous use
  - Rebound insomnia
    - Decrease risk by taking lowest dose and tapering medication
  - Increased falls and hip fractures
    - Longer-acting flurazepam and quazepam increase falls/fractures especially in the elderly
NON-BENZODIAZEPINES

- Zolpidem (Ambien™)
  - Minimal anxiolytic activity
  - No muscle relaxant properties
  - Not an anticonvulsant
  - Comparable efficacy to benzodiazepines

- Zaleplon (Sonata®)
  - Rapid onset, half-life of 1 hour
  - Does NOT reduce nighttime awakenings or help increase total sleep time

- Eszopiclone (Lunesta™)
  - Rapid onset
  - Approved to help with sleep onset and maintenance


NON-BENZODIAZEPINES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem</td>
<td>Sleep onset insomnia</td>
<td>~2.5 hrs</td>
<td>New warnings released in January 2013</td>
</tr>
<tr>
<td>Zolpidem CR</td>
<td>Sleep onset or maintenance insomnia</td>
<td>1.4 – 4.5 hrs</td>
<td>Controlled-release formula</td>
</tr>
<tr>
<td>Zolpidem sublingual (Intermezzo)</td>
<td>Sleep maintenance insomnia</td>
<td>1.4 – 6.7 hrs</td>
<td>To be given in the middle of the night</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>Sleep onset insomnia</td>
<td>1 hour</td>
<td>Not indicated for long-term use</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>Sleep onset or maintenance insomnia</td>
<td>6 – 9 hrs</td>
<td>For sleep onset and maintenance</td>
</tr>
</tbody>
</table>

UpToDate, Treatment of Insomnia, 2013, www.uptodate.com

NON-BENZODIAZEPINES

- Adverse effects
  - Similar to benzodiazepines
    - Less severe
    - Dizziness
    - Headache
    - Somnolence
    - Daytime sedation
  - Complex-sleep related behaviors
  - Unpleasant taste (Eszopiclone)
  - Hallucinations (Zolpidem)
  - Less risk of abuse versus benzodiazepines


COMPLEX SLEEP-RELATED BEHAVIORS

- Non-benzodiazepines
  - Sleep eating
  - Sleep driving
  - Phone calls while sleeping
  - Engaging in sexual behaviors while not fully awake

- Higher doses of medications have been attributed to these complex sleep behaviors

U.S. Food and Drug Administration, Consumer Updates, 2013.
**Melatonin Agonist**
- Ramelteon (Rozerem™)
  - Involved with circadian rhythm
  - Fewer and less severe side effects than benzodiazepines and non-benzodiazepines
  - Less daytime residual effects
  - No withdrawal or rebound insomnia
  - Not known to be habit-forming
  - Only sedative-hypnotic that is not a controlled substance
  - Common side effects
    - Somnolence
    - Nausea
    - Fatigue
    - Headache

**Antihistamines**
- First-generation (sedating) antihistamines
  - Most common
    - Diphenhydramine (Benadryl®)
    - Doxylamine (Unisom®)
  - Less effective than other options
  - Anticholinergic side effects
    - Dry mouth
    - Blurred vision
    - Urinary retention
    - Constipation
  - Side effects usually more severe in elderly patients

**Insomnia Treatment**
- General recommendations
  - Do not take medications for insomnia unless you have a full 7-8 hours to dedicate to sleep
  - Lowest doses needed
    - Decrease daytime sleepiness/side effects
    - Easier to taper off medication
  - Use for the shortest time necessary
    - Decrease risk of tolerance
    - Try other non-medication therapies
  - Caution during next day when starting new insomnia medications
    - Recognize how the medication will affect you

**Zolpidem Warning**
- January 2013 FDA Safety Communication
  - Blood levels of zolpidem in certain patients may be high enough in the morning to impair activities requiring alertness (i.e. driving)
  - Highest risk in extended-release product (Ambien CR®)
  - New recommendations to consider lower doses in all patients
    - Decrease dose especially in women due to slower elimination of the drug from the body
    - Slower elimination has not been demonstrated in men, but lower doses should be recommended in general
INSOMNIA IN THE ELDERLY
- Up to 60% of adults > 65 years of age suffer from insomnia
  - Age-related changes in sleep patterns
  - Underlying illness
  - Medication side effects
  - Less sleep necessary
- Risk of using traditional sleep aids is higher in elderly patients
  - 5-33% of elderly patients receive a benzodiazepine or other non-benzodiazepine sleep aids

NON-PHARMACOLOGIC OPTIONS IN THE ELDERLY
- Identify and manage exacerbating factors
  - Pain
  - Shortness of breath (heart failure)
  - Chest pain
  - COPD
  - GI disease (acid reflux, ulcer)
  - Neurologic or mood disorders
    - Parkinson’s, dementia, anxiety, depression

NON-PHARMACOLOGIC OPTIONS IN THE ELDERLY
- Target sleep hygiene
  - Avoid nicotine, alcohol, and caffeine
  - Increase exercise and light exposure in the day
  - Limit napping
  - Reduce light and noise in the sleep environment
    - Keep temperature comfortable
  - Avoid meals and liquids close to bedtime

PHARMACOLOGIC OPTIONS
- Some evidence that newer non-benzodiazepine hypnotics are safer for the elderly
  - ↓ sleep cycle changes, rebound insomnia, tolerance, and hangover
- Start with lower doses in older patients
- May try ramelteon (Rozerem)
  - No dependence/abuse risk
  - Helps in sleep initiation, but not maintenance
**PHARMACOLOGIC OPTIONS**

- Other options
  - Trazodone, an antidepressant, may increase deep sleep
  - Not well studied, early on appears to be beneficial
  - Non-habit forming
  - AE: Dry mouth, nausea, arrhythmias, orthostatic hypotension

**SELF-TREATMENT IN THE ELDERLY**

- Alcohol
  - Causes early awakening
- Antihistamines (i.e. diphenhydramine)
  - Anticholinergic effects, cognitive impairment, urinary retention
- Residual daytime sleepiness
- Melatonin
  - Helps with difficulty falling asleep
- Valerian
  - May takes several night/weeks to see benefit
- Kava
  - AVOID, may cause hepatotoxicity

**META-ANALYSIS - ELDERLY INSOMNIA**

- 24 Randomized Controlled Trials
  - 2,417 subjects with insomnia > 60 years of age
  - No other psychiatric/psychological disorders
  - Treated with benzodiazepines, zopiclone, zolpidem, zolpidem, diphenhydramine, and placebo

**META-ANALYSIS – TREATMENT BENEFIT**

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Means (SD)</th>
<th>95% CI for Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Sleep</td>
<td>15 min</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Sleep</td>
<td>12 min</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Sleep</td>
<td>10 min</td>
</tr>
<tr>
<td>Valerian</td>
<td>Sleep</td>
<td>8 min</td>
</tr>
</tbody>
</table>

Results

- Benzodiazepines increased sleep by ~15 min/night
- Adverse effects: Cognitive events ~5 times as common
- Daytime fatigue ~4 times more common
- Adverse events similar between benzodiazepine and non-benzodiazepines

References:

**SUMMARY**

- **Insomnia diagnosis**
  - Difficulty initiating, maintaining, or poor quality/nonrestorative sleep
  - Daytime impairment
  - Difficulty despite adequate time for sleep

- **Obstructive sleep apnea treatments**
  - Lifestyle changes
  - CPAP therapy
  - No medication therapies available

- **Insomnia treatments**
  - Behavioral therapies are first line

- **New zolpidem recommendations**
  - Lower doses in women due to slower elimination

- **Risks of pharmacologic treatment in the elderly may outweigh the benefit**

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**REFERENCES**

REFERENCES (CONT.)

- University of Maryland Medical Center [Internet]. Obstructive sleep apnea - Dental Devices. c2011 University of Maryland Medical Center (updated 23 Jun 2009, cited 13 Mar 2013). Available from: http://www.umm.edu/patiented/articles/what_dental_devices_used_treat_sleep_apnea_00065_d.html