SLEEP DISORDERS AND MEDICATIONS

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GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.
SPEAKER DISCLOSURES

✓ NO CONFLICTS OF INTEREST
OBJECTIVES

1. Sleep disorders: definitions
2. Hypnotics and pharmacologic management
3. Cannabis and sleep
SLEEP DISORDERS:

• Primary
• Comorbid – due to a general medical condition, related to a psychiatric disorder, secondary to substance abuse
SLEEP-WAKE DISORDERS:

- Primary insomnia
- Breathing-related disorders (e.g., obstructive sleep apnea)
- Narcolepsy
- Parasomnias
- Circadian rhythm sleep-wake disorders
# EPWORTH SLEEPINESS SCALE

## Chart 1. Epworth Sleepiness Scale.

<table>
<thead>
<tr>
<th>Likelihood to fall asleep in the following situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sitting and reading ........................................</td>
</tr>
<tr>
<td>2. Watching TV ..................................................</td>
</tr>
<tr>
<td>3. Sitting, inactive in a public place (e.g., waiting room, a theater or a meeting)</td>
</tr>
<tr>
<td>4. As a passenger in a car for an hour without a break</td>
</tr>
<tr>
<td>5. Lying down to rest in the afternoon when circumstances permit</td>
</tr>
<tr>
<td>6. Sitting and talking to someone ..............................</td>
</tr>
<tr>
<td>7. Sitting quietly after lunch without alcohol .............</td>
</tr>
<tr>
<td>8. In a car, while stopped for a few minutes in traffic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>would never doze off</td>
</tr>
<tr>
<td>1</td>
<td>slight chance of dozing off</td>
</tr>
<tr>
<td>2</td>
<td>moderate chance of dozing off</td>
</tr>
<tr>
<td>3</td>
<td>high chance of dozing off</td>
</tr>
</tbody>
</table>
PRIMARY INSOMNIA DISORDER:

- Dissatisfaction with sleep quantity or quality, associated with one or more of the following:
  - 1) Difficulty initiating sleep
  - 2) Difficulty maintaining sleep
  - 3) Early morning awakening
- Significant distress or impairment
INSOMNIA DISORDER:

- Occurring at least 3 nights/week, for at least 3 months
- Occurs despite adequate opportunity for sleep
- Exclusions
  - 1) Does not occur during the course of another sleep-wake disorder
  - 2) Not due to a substance
  - 2) Coexisting psychiatric disorders and medical conditions do not explain the insomnia
MISCONCEPTIONS: DURATION OF SLEEP

• Lowest mortality hazard was experienced by participants reporting usual sleep of 7 hours (6.5-7.4)

• Participants sleeping 8 hours or more, or 6 hours or less, experienced significantly increased mortality hazard

MISCONCEPTIONS: DURATION OF SLEEP

CURRENT GUIDELINES PER AMERICAN ACADEMY OF SLEEP MEDICINE: TREATMENT OF PRIMARY INSOMNIA:

• Start CBT (for both primary and secondary insomnia)
• If that is not effective, can consider trial of a short or intermediate acting hypnotic or ramelteon.
• Consider symptom pattern, past response, cost, patient preference, individual factors.
• Use lowest effective dose.
• Brief, intermittent use (initial treatment period of 2-4 weeks, then re-evaluate)
• If trial fails, try alternative drug from same class
• If still not response, consider sedating antidepressant (e.g. trazodone, doxepin) in low dose
SPECIAL POPULATIONS:

- Comorbid depression and insomnia ➔ consider sedating antidepressant at an earlier stage
- Bipolar disorder with insomnia ➔ consider quetiapine or olanzapine
- PTSD with sleep disturbance ➔ Prazosin for nightmares/or nighttime hyperarousal; trazodone for sleep initiation
- Patients with hx of substance abuse disorders ➔ avoid benzodiazepines
- Chronic pain and insomnia ➔ gabapentin or pregabalin may be appropriate
HYPNOTIC MEDICATIONS: INDICATIONS

• FDA indications:
  • 1) Sleep initiation only
  • 2) Sleep initiation and sleep maintenance

• For increased sleep latency
  • 1) Medications with fast onset and short duration of action (to avoid excessive daytime sedation)

• For increased nocturnal awakenings and early morning awakenings
  • 1) Medications with longer duration of action
  • 2) Medications with sleep initiation/maintenance indication
### HYPNOTIC MEDICATIONS:

Benzodiazepines

<table>
<thead>
<tr>
<th>Hypnotic agent</th>
<th>Recommended Dose Range (mg)</th>
<th>Half-life (hours)</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>quazepam</td>
<td>7.5 - 15</td>
<td>39 - 200</td>
<td>fast</td>
</tr>
<tr>
<td>flurazepam</td>
<td>15- 30</td>
<td>4 days + (metabolites)</td>
<td>fast</td>
</tr>
<tr>
<td>estazolam</td>
<td>0.5 - 2</td>
<td>10 - 24</td>
<td>fast-moderate</td>
</tr>
<tr>
<td>temazepam</td>
<td>7.5 - 30</td>
<td>8 - 20 hr</td>
<td>fast-moderate</td>
</tr>
<tr>
<td>triazolam</td>
<td>0.125 – 0.5</td>
<td>1.5 - 5.5</td>
<td>fast</td>
</tr>
</tbody>
</table>
HYPNOTIC MEDICATIONS:

Non-benzodiazepines

<table>
<thead>
<tr>
<th>Hypnotic agent</th>
<th>Recommended Dose Range (mg)</th>
<th>Half-life (hours)</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone</td>
<td>1 - 3</td>
<td>6 – 9</td>
<td>fast</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5 - 10</td>
<td>2 - 5</td>
<td>fast</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>5 - 20</td>
<td>1</td>
<td>fast</td>
</tr>
</tbody>
</table>
BENZODIAZEPINE VS. NON-BENZODIAZEPINE HYPNOTICS:

• Abuse potential for non-benzo hypnotics purportedly less than benzodiazepines, however they are still not free from the risk of dependence and other side effects

• Insufficient evidence that non-benzo hypnotics are more effective or safer than benzos
BENZODIAZEPINE HYPNOTICS:

- Commonly prescribed for treatment of anxiety and insomnia, despite many potential risks.
- An estimated 1.8-8.2% of hip fractures in five Western European countries and the US may be attributable to benzo use (Khong, de Vries et al. 2012).
- Short-acting benzos appeared associated more with hip fractures than long-acting benzos.
- Memory and cognitive impairment.
- Increased risk of traffic accidents.
- Risk of tolerance, dependence, abuse potential.
- Avoid in: elderly, patients with TBI, OSA, dementia, substance use disorders, if receiving other CNS depressants.
NON-BENZO HYPNOTICS:

• Adverse effects:
  • Automatic sleep behaviors: may occur with zolpidem at high doses
  • Rebound insomnia
  • Impaired motor function
  • Falls
  • Impaired cognitive function, including amnesia
  • Daytime impairment
FDA SAFETY ANNOUNCEMENTS:

• 2013:
  
  • Women: recommended dose of zolpidem lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR)
  
  • Men: consider prescribing the lower doses—5 mg for immediate-release products and 6.25 mg for extended-release products
FDA SAFETY ANNOUNCEMENTS:

• 2014:
  • Eszopiclone 3 mg dose causes impairment to driving skills, memory, and coordination lasting more than 11 hours after evening dose
  • Recommended starting dose of 1 mg for both men and women
HYPNOTIC MEDICATIONS:

• NIH-sponsored meta-analysis raised a question of whether hypnotics (“Z” drugs) produce any significant increase in objective (EEG) total sleep time for chronic insomnia.

• Found that the drug groups had a “significantly higher risk of harm” than placebo. Participants taking “Z” drugs experienced more adverse symptoms.

IS USAGE OF HYPNOTICS ASSOCIATED WITH MORTALITY?

• Mallon et al. found that patients taking hypnotics died sooner than hypnotic-free patients, controlled for many variables.

• Men with regular hypnotic use had 4.54 times the all-cause mortality; was a risk factor for coronary artery disease death, cancer death, suicide and death from "all remaining causes."

HYPNOTICS:

...een studied with intermittent dosing at this time...
MELATONIN:

• Secreted by pineal gland; decreases with age
• Darkness stimulates release, light suppresses it
• Melatonin as sleep aid:
  • Significantly decreases sleep onset latency in delayed sleep phase syndrome
  • Marginally decreases sleep onset latency in primary insomnia (better effectiveness in children) and not at all in secondary insomnia
• Need more controlled studies of long-term usage
• Lack of systematic data on side effects
RAMELTEON:

- Melatonin agonist – binds to M1 and M2 receptors
- Half-life of 1.5 to 5 hours
- Metabolized by the liver; used with caution in hepatic insufficiency
- Weak evidence for reduction of sleep latency at recommended prescribed dosage (8 mg)
- No consistent evidence of improvement in other objective or subjective parameters
- Benign side effect profile
TRAZODONE FOR INSOMNIA:

• Start at 25-50 mg qhs; increase in 25-50 mg qhs increments, as tolerated; typical dose of 50-200 mg qhs.

• Onset of action: 20-60 minutes

• Effect on sleep stages:
  • Increases stage 4
  • Slight decrease in REM
TRAZODONE FOR INSOMNIA:

• Advantages
  • Rapid onset of action
  • Usually minimal or no tolerance

• Disadvantages
  • Hypotension, dizziness
  • GI disturbance
  • Daytime sedation
  • Priapism in men
  • Cardiac rhythm effects
  • Efficacy not well-established
  • Not many studies of hypnotic efficacy beyond 2 weeks
MIRTAZAPINE:

• H1 antagonism
• Lower doses (7.5-15 mg qhs) may be more sedating
• Low risk of medication interactions
• Less sexual side effects than SSRIs
• Side effects: drowsiness, orthostasis, increased appetite, weight gain
DOXEPIN:

- FDA approved at low doses (3 or 6 mg) for treatment of insomnia; licensed as Silenor
- Acts primarily as an H1 antagonist and has a side effect profile comparable to placebo at low doses
- May be useful for sleep maintenance, e.g., for early awakening.
- Risk of toxicity in overdose
QUETIAPINE:

- Antihistaminic effects
- Minimal evidence to support use in insomnia
- Increase in subjective total sleep time and decrease in subjective sleep latency were found, but differences were not statistically significant
- Metabolic side effects; even at low doses may still be associated with weight gain
- Should not be used for sleep unless there is an approved indication for use of an antipsychotic (eg. acute bipolar depression)
ANTIHISTAMINES:

• Hydroxyzine may have more acute effects on sleep compared to OTC antihistamines
• Limited evidence
• May cause insomnia or worsen existing insomnia
• Negative effects on next-day functioning
• Onset 45 min - 1 hour; variable duration—frequently longer than 8 hours
ANTIHISTAMINES – SIDE EFFECTS:

• Confusion - especially in elderly
• Anticholinergic - e.g., urinary retention
• Morning sedation
• Habituation
• REM rebound on withdrawal
  – Causes and/or worsens insomnia
  – Can result in chronic use when acute treatment was planned
SUVOREXANT (BELSOMRA):

- Selective, dual orexin (hypocretin) receptor antagonist made by Merck & Co.
- Promotes sleep by reducing arousal and wakefulness
- Narcolepsy like side effects - cataplexy, impaired driving, nighttime behaviors, suicidal ideation
- 12 hour half-life
- Schedule IV
- Insufficient evidence to support use at this time
VALERIAN ROOT

- Binds to GABA-A receptors
- Produces subjective improvement in sleep quality
- No improvement in quantitative measures of sleep
- Effective dosage unclear, possible side effects, drug interactions
CANNABIS AND SLEEP

• Low doses of THC (4 to 20 mg) - mild suppressive effects on REM; total sleep time or stage 3-4 sleep was increased but then decreased to baseline levels after a week of repeated nightly use.

• High doses of THC (50 to 210 mg) – also suppress REM; no effects on total sleep time; stage 3-4 sleep reduced in one report.
CANNABIS AND SLEEP (CONTINUED)

• Upon discontinuation: REM rebound, as well as reduction in total sleep time, and an increase in sleep latency

KEY POINTS:

• Cognitive-behavioral therapy is the best treatment for chronic insomnia, with long-term efficacy and least side effects

• The risks of hypnotics may outweigh their benefits in some patients. Consider alternative strategies to reduce risk. Long-term use is not recommended.

• Association between cannabis and impaired sleep quality
REFERENCES:


• Cappuccio et al., Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. Sleep 2010; 33:585-592


• Morin CM. Contributions of cognitive-behavioral approaches to the clinical management of insomnia. Primary Care Companion J Clin Psychiatry 2002;4(suppl 1):21-6


• Walsh JK, Krystal AD, Amato DA et al. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. Sleep 2007;30(8):959-68
