Insomnia
Physiology, Diagnosis and Treatment

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Objectives

1. To discuss the definition and epidemiology of insomnia

2. To provide a general overview of the psychiatric, medical and primary sleep disorders to consider in insomnia

3. To review the pharmacologic and non-pharmacologic treatment of insomnia
one or more

i.) Difficulty falling asleep  
    (Sleep Onset)

ii.) Waking up frequently during the night with difficulty returning to sleep  
    (Sleep Maintenance)

iii.) Waking up too early in the morning

iv.) Non restorative sleep

** Sleep disturbance occurs despite adequate opportunity for sleep
AASM Insomnia Diagnostic Criteria

At least one of the following:

- Fatigue/Malaise
- Mood disturbance/Irritability
- Decreased memory and concentration
- Absenteeism
- Decreased QOL
- Proneness for errors/accidents
- Concerns or worries about sleep
- Social/Vocational dysfunction or poor school performance
- Motivation/energy/initiative reduction
- Greater health care utilization
- Daytime sleepiness
- Tension headaches/GI symptoms
Prevalence of Insomnia by Age Group

Mellinger GD, Arch Gen Pysch 1985
Insomnia Risk Factors

– Age (Elderly: 50%)
– Gender (Female: Male, 2:1, especially post and perimenopausal)
– Psychiatric disorders
– Substance Abuse
– Recurrent health problems
– Shift work
– Family history of insomnia
– Medications
– Cigarette smoking
– Psychosocial stressors (divorce/separation)
Distribution of Insomnia Etiology

- Psychiatric: 50%
- Medical Illness/Medication: 25%
- Other Sleep Disorder: 10%
- Primary Insomnia: 15%

Ford DE, JAMA, 1989
Insomnia Etiology: Hyperarousal

- ↑ basal metabolic rate
- ↑ levels of circulating catecholamines (HR, BP, NE secretion)
- ↑ hypothalamic-pituitary-adrenal axis activity: ↑ CRH/ACTH/Cortisol
- ↑ brain glucose metabolism in sleep
- ↓ parasympathetic tone
- ↑ in beta/gamma and decreased in delta EEG activity
Models for Insomnia Etiology: Spielman Model (3-P)

- **Predisposing Factors (traits)**
  - Age
  - Female Gender

- **Precipitating Factors (acute events)**
  - Medical Illness
  - Life stress

- **Perpetuating Factors (maladaptive coping)**
  - Napping
  - Excessive time in bed
Prevalence of Insomnia in Chronic Medical Conditions

- Hip Impairment
- MI
- Obstructive Airway Disease
- Angina
- Prostate Problems
- CHF
- Diabetes

MI = myocardial infarction; CHF = congestive heart failure
Insomnia (10-15% of general population)

Psychiatric Diagnosis
80-90% of individuals with Major Depressive Disorder report insomnia

40-50% of individuals with insomnia report a psychiatric diagnosis

Ford DE, JAMA, 1989
Ohayon MM, Sleep Med Rev, 2002
## Objective Sleep Abnormalities in Psychiatric Patients

<table>
<thead>
<tr>
<th></th>
<th>TST</th>
<th>SE</th>
<th>SL</th>
<th>SWS</th>
<th>REM L</th>
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<tbody>
<tr>
<td>Mood</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anxiety disorders</td>
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<td>↓</td>
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<td>↓</td>
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<tr>
<td>Insomnia</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison of sleep EEG in groups of patients with psychiatric disorders or insomnia to age-matched normal controls.

TST = Total sleep time; SE = sleep efficiency; SL = sleep latency; SWS = slow-wave sleep; REM L = rapid eye movement latency; EEG = electroencephalogram.

Primary Sleep Disorders Causing Insomnia

- Psychophysiologic Insomnia
- Sleep State Misperception
- Idiopathic Insomnia
- Obstructive Sleep Apnea Syndrome
- Central Sleep Apnea Syndrome
- Restless Legs Syndrome
- Periodic Limb Movement Disorder
- Inadequate Sleep Hygiene
- Adjustment Sleep Disorder

- Environmental Sleep Disorder
- Sleep-Onset Association Disorder
- Circadian Rhythm Disorder
- Parasomnias, Nightmares
- Fatal Familial Insomnia
- Pregnancy/Menstrual Associated Sleep Disorders
- Sleep-Related Movement Disorders (REM-Sleep Behavior Disorder, Nocturnal Paroxysmal Dystonia)
Psychophysiologic Insomnia

- Symptoms present for at least 1 month
- Excessive focus on and heightened anxiety about sleep
- Somatized tension is characteristic
- Learned sleep-preventing associations
- Trying too hard to fall asleep
- More common in females
- PSG – ↑ sleep latency, ↓ sleep efficiency, and reverse first night effect
Idiopathic Insomnia

- Inability to obtain adequate sleep, decreased feeling of well-being and normal psychological functioning
- Neurochemical imbalance
- Usually lifelong
- Patients often self-medicate with hypnotics and alcohol

Paradoxical Insomnia

- Incongruence between subjective symptoms of insomnia and objective evidence of sleep disturbance
- Extreme, improbable sleep complaints
- More common in females and middle to late adulthood
Adjustment Insomnia

- Symptoms present for <3 months
- Temporally related to acute stress, conflict or environmental change that causes emotional arousal
- Clear change from the patient’s norm and usually remits within 3 months
- Symptoms include lethargy, excessive time in bed, anxiety, somatic symptoms, and sad/depressed emotional reactions
Circadian Rhythm Disorder

- Delayed Sleep Phase Syndrome
  (Night Owl)
- Advanced Sleep Phase Syndrome
  (Morning Lark)
- Irregular Sleep Wake Pattern
- Non-24 Hour Sleep-Wake Disorder
- Jet-Lag (Time Zone Change) Syndrome
- Shift Work Sleep Disorder
Approach to Insomnia

Health care practitioners should screen for
Approach to Insomnia

- PSG is not routinely indicated*
- Self-administered questionnaires (PSQI, Insomnia Severity Index), at-home sleep logs, symptom checklists, psychological screening and bed-partner interviews are helpful**
- MSLT is not routinely indicated**

*Standard* and guideline** recommendations per the American Academy of Sleep Medicine Practice Parameters
Psychological/Behavioral Treatments

(Treatment Targets)

**BEHAVIORAL**
- Sleep Restriction
- Stimulus Control
- Progressive Muscle Relaxation

**COGNITIVE**
- Beliefs/Attitudes
  - Unrealistic Sleep Expectations
  - Sleep misconception
  - Sleep anticipatory anxiety
  - Poor coping skills

**EDUCATION**
- Sleep Hygiene Education

**Excessive time in bed**
- Irregular Sleep Schedules
- Sleep incompatible activities
- Hyperarousal

**Inadequate sleep hygiene**
Treat underlying issues:

**Medical Disorders:**
- Bronchodilators for COPD, asthma
- Increase HOB, PPI for GERD

**Psychiatric Disorders:**
- Bupropiron for anxiety disorder

**Sleep Disorders**
Treatment

Sleep Disorders

OSA/CSA:
Pharmacologic Treatment

Basic Principles:

- Use in combination with behavioral measures
- Goal is relief of daytime sequelae of insomnia, not simply increased sleep time
- Target to specific medical/psychiatric conditions if applicable
- Favor hypnotic medications with lesser risk of daytime residual effects
Hypnotics

Relative contraindications to hypnotics:
# FDA-approved hypnotics

## Benzodiazepine Receptor Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>$t_{1/2}$ (h)</th>
<th>Active metabolite</th>
<th>Metabolism</th>
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<tbody>
<tr>
<td>Triazolam</td>
<td>0.25</td>
<td>2–4</td>
<td>N</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15–30</td>
<td>8–20</td>
<td>N</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Estazolam</td>
<td>1–2</td>
<td>10–24</td>
<td>N</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Quazepam</td>
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<td>25–41</td>
<td>Y</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15-30</td>
<td>24-100</td>
<td>Y</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>10</td>
<td>1</td>
<td>N</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5–10</td>
<td>1.5–2.5</td>
<td>N</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1-3</td>
<td>5-7</td>
<td>N</td>
<td>Oxidation</td>
</tr>
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</table>
### Newer Generation BZRA

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Onset of Action (Min)</th>
<th>½ life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem</td>
<td>Ambien</td>
<td>15 – 30</td>
<td>Short (1.5-2.5h)</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Sonata</td>
<td>15 – 30</td>
<td>Ultra-short (1h)</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Imovane</td>
<td>15 – 30</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Lunesta</td>
<td>15 – 30</td>
<td>Intermediate (5-7h)</td>
</tr>
</tbody>
</table>

**Indication for newer agents (eszopiclone, zolpidem CR) does not limit length of use**
Benzodiazepines

**Adverse effects:**
- Daytime sedation
- Rebound insomnia/anxiety after discontinuation
- Anterograde memory impairment
- Disinhibition
- Tolerance/dependence
- Distortion of normal sleep-decreased sleep latency, increase stage 2, decrease stage 3
- Cognitive/psychomotor impairment
Newer Generation BZRA

Safety and efficacy make first-line medication choice

- Generally not associated with tolerance, dependence difficulties, and withdrawal
- Rebound insomnia (may have transient worsening of insomnia 3-5 days after discontinuance)
- Minimal abuse potential
- Generally well tolerated
- No absolute contraindications (though not recommended in pregnancy)
- Headache, dizziness, nausea, drowsiness
- Dose escalation is rare
- Discontinuation effects are minimal (prevent with gradual dose decrease)
- Receptor selectivity and shorter half-life may lead to: preservation of sleep architecture
- Rapid onset of action
Hypnotics

- Treatment should not exceed 4 weeks without re-evaluation
- Minimal dosing for brief periods
- Long-term off label prescribing of hypnotics is common and may be justified based on limited data from open-label long term studies

May be defended if:
- No response to non-pharmacologic strategies
- Persistent insomnia
- No reversible cause
- Continuous reevaluation occurs
- Patient is apprised of off-label use of hypnotics
- Alternative approaches discussed
- Documentation
Sedating Antidepressants

- TCA associated with orthostatic hypotension, cardiac conduction delay, weight gain, sexual dysfunction, and anticholinergic effects
- Not FDA approved for use in insomnia (except for low dose doxepin 3-6 mg)
- Amitriptyline, Trazodone, Doxepin, Mirtazapine
- Can be considered in depression and anxiety, psychoactive substance use
Ramelteon

Melatonin agonist with high selectivity for the MT1 and MT2 receptor
- 3-16 fold higher than melatonin itself

Not a controlled substance

Dose: 8mg-reduces sleep latency

Half-life: 1.2 hours

Benign side effect profile:
- No effects on sleep apnea in mild-moderate apneics
- No worsening of pulmonary function in COPD patients
- Side effects-dizziness, nausea, fatigue, headache, increased serum prolactin and decreased serum testosterone
OTC Agents: Antihistamines

- H-1 antihistamines are the most common active ingredients in OTC sleep aids (e.g. diphenhydramine)
- Habitual users may develop tolerance
- Can induce daytime hangover effects in 10-25% of users (particularly the elderly)
- Adverse effects include anticholinergic effects, cognitive impairment and daytime sedation
Comparative Meta-Analysis of Pharmacotherapy and Cognitive Behavioral Therapy in Persistent Insomnia

Comparative Effects on Sleep

% Change

-70 -60 -50 -40 -30 -20 -10 0 10 20 30 40

Sleep Latency NOA WASO TST SQR

Pharmacologic treatment
Cognitive treatment

Analyzed 21 treatment outcome studies of primary insomnia of >1 month’s duration

NOA = number of awakenings; SQR = sleep quality rating.
Conclusions

- Prevalence of clinical chronic insomnia is 10-15%.
- Consider psychiatric and medical disorders as etiology of insomnia.
- Off-label use of medications for insomnia is widespread, with limited data supporting efficacy.
- NBRA may be safer than traditional benzodiazepines.
- Stimulus control, relaxation strategies and CBT are effective and the latter appears to have long-lasting benefits.