THE WRONG SIDE OF THE BED: CHRONIC INSOMNIA

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OVERVIEW
• Prevalence and impact
• Definitions
• Sleep architecture
• Causes and diagnosis
• Non-pharmacological treatment
• Pharmacological treatment: natural, OTC, and RX

PHARMACIST OBJECTIVES
I. Explain impact of chronic insomnia on daily life
II. Apply two principles of sleep hygiene and non-pharmacological methods to patients
III. Predict the most likely side effects or consequences of agents used in insomnia
IV. Compare the efficacy of pharmacologic options for insomnia
V. Devise a plan to manage insomnia based upon clinical presentation and history

TECHNICIAN OBJECTIVES
I. Describe the prevalence of insomnia in the US
II. Recognize two medications and two disease states that can cause or contribute to insomnia
III. Identify one pharmacologic and one non-pharmacologic option for insomnia
IV. Contrast the efficacy and safety of OTC options for the management of chronic insomnia
V. Recognize safety concerns with using natural products

PREVALENCE OF INSOMNIA
• During the past 12 months, have you regularly had insomnia or trouble sleeping?
• An estimated 64% of US population experiences sleep problems at least a few nights a week
  • 7% of adults report the use of alcohol
  • 7% a nonprescription sleep aid
  • 8% a prescription hypnotic

DISCLOSURE STATEMENT
• I do not have any actual or potential conflict of interest in relation to this presentation
• Off-label use of medications for insomnia will be presented

Trends in validated tools. Macey 2014
Handbook of Nonprescription Drugs 18th Edition.
IMPACT OF INSOMNIA

- Drowsy driving
- A CDC report of 150,000 adults across 19 states stated 4.2% reported falling asleep at the wheel in previous 30 days
- Slowed reaction time, impaired decision-making, less attentive
- Loss of productivity
- Cognitive impairment
- Chronic diseases
- Sleep duration ≤ 6 hrs significantly associated with CHD, stroke, and diabetes among adults over 45 years
- Depression and anxiety increased
- Obesity


SLEEP ARCHITECTURE

Types of Sleep

<table>
<thead>
<tr>
<th>Non-REM Sleep</th>
<th>REM Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1:</strong> Drowsiness, easily awakened, slow eye movements (5% of total sleep)</td>
<td>Occurs ~ 90 minutes after falling asleep with longer, deeper periods during second half of the night</td>
</tr>
<tr>
<td><strong>Stage 2:</strong> Light sleep. eye movements stop, slower brain waves with occasional bursts of rapid (45-55% of total sleep)</td>
<td>Eyes move rapidly behind closed eyes</td>
</tr>
<tr>
<td><strong>Stages 3 &amp; 4 (Slow Wave Sleep):</strong> occur after falling asleep and in the first half of right. Deep sleep, difficult to awaken, slow brain waves, heart and respiratory rate slowed</td>
<td>Breathing, HR, BP irregular</td>
</tr>
<tr>
<td></td>
<td>Dreaming occurs</td>
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<tr>
<td></td>
<td>Arms and legs are temporarily paralyzed</td>
</tr>
</tbody>
</table>

Adapted from NIH Guide to Healthy Sleep, Aug 2011.

COMMON CAUSES

- Medications and Substances
  - Antidepressants
  - Stimulants
  - Corticosteroids
  - Decongestants
  - Antihypertensives
  - Antidepressants
  - Asthma medications
  - Alcohol
  - Caffeine
  - Nicotine

- Comorbidities
  - Pain conditions
  - Respiratory disease
  - Neurological disorders
  - Psychiatric illnesses
  - Cardiovascular disease

- Situational
  - Work or financial stress
  - Jet lag or shift work


TYPES OF INSOMNIA

- Early morning awakening
- Difficulty falling asleep
- Difficulty maintaining sleep

TYPES OF INSOMNIA

- **Short-term/transient**: symptoms present for < 3 months, but accompanied by significant concern
- **Intermittent**: on and off over a course > 1 month; can develop into chronic
- **Chronic**: symptoms occur at least 3 times/week for ≥ 1 month and are not related to an inadequate opportunity to sleep
- **Other**: symptoms of difficulty initiating or maintaining sleep but do not meet either above criteria

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**PATIENT CASE**

- ZZ is a 72 y/o male with a history of asthma, HTN, depression, and BPH
- He presents to his primary care provider stating he has had trouble falling asleep over the past 2 months
- He feels distracted at work and drinks 2-3 cups of coffee throughout the day to stay awake
- He reports being so tired by the time he arrives home he takes a nap before dinner
- His wife recently passed away and he has been adjusting to his new lifestyle

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**DIAGNOSIS OF INSOMNIA: AMERICAN ACADEMY OF SLEEP MEDICINE**

- A complaint of:
  - Difficulty initiating sleep
  - Difficulty maintaining sleep
  - Waking too early
  - Sleep that is chronically nonrestorative or poor in quality
- Requires associated **daytime dysfunction** in addition to insomnia symptomology
- Occurs despite adequate opportunity and circumstances for sleep
- **Diagnosis**: clinical evaluation
- **Differentials** include medical, psychiatric, and environmental factors

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**DIAGNOSIS OF INSOMNIA DISORDER: DSM V CRITERIA**

- Predominant complaint of dissatisfaction with sleep quality or quantity, of ≥ 1 of the following:
  - Difficulty initiating sleep
  - Difficulty maintaining sleep
  - Early morning awakenings
- Significant impairment in social, occupational, or other areas of functioning
- Sleep disturbance ≥ 3 nights/week
- Sleep difficulty is present for ≥ 3 months
- Occurs despite adequate opportunity for sleep
TREATMENT GOALS

- Improve sleep quality and quantity
- Improve insomnia-related daytime impairments
- Avoid adverse effects from selected therapy

TREATMENT SELECTION CONSIDERATIONS

- Age
- Comorbidities
  - Psychiatric conditions
  - History of substance abuse
- Type of insomnia
- Duration of symptoms
- Side effect profile of chosen therapy

NON-PHARMA TREATMENT

- Cognitive behavioral therapy (CBT)
- Sleep restriction
- Light therapy
- Stimulus control
- Relaxation therapy
- Physical activity
- Sleep hygiene education

SLEEP HYGIENE TECHNIQUES

1. Stick to a sleep schedule, even on weekends.
2. Avoid alcoholic drinks before bed.
3. Avoid exercise 2-3 hours before bedtime.
4. Avoid caffeine or nicotine in the late afternoon.
5. Designate the bed for sleep and intimacy.
6. Create a sleeping environment (noise, temp., light).
7. Avoid large meals before bedtime.
8. Avoid naps after 3 pm.

Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-Analysis

Methods
- 21 randomized, controlled trials including 1,162 participants
- CBT-I incorporated at least 3 of the following: cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation
- 64% female; mean age 56 years

Purpose
To determine the efficacy of CBT-I, compared to control, on diary measures of overnight sleep in adults with chronic insomnia

Results
- Sleep onset latency (SOL)
  - Improved by 19.03 min
- Wake after sleep onset (WASO)
  - Improved by 26.00 min
- Total sleep time (TST)
  - Improved by 7.61 min
- Sleep efficiency (%)
  - Improved by 9.91%
- Changes sustained at later time points (1 - 12 months)
  - Some studies found improvement in sleepiness, psychomotor vigilance, mood, anxiety, beliefs and attitudes about sleep, health status, and daytime functioning

Conclusions
- Effect sizes reported similar in magnitude to those seen in meta-analyses of hypnotic agents, though these studies are often limited by short duration and absence of long term follow-up
- CBT-I is a highly effective treatment for chronic insomnia with well-maintained responses
PATIENT CASE

• ZZ now presents to the pharmacy asking for something to help him sleep, stating he rarely gets > 3 hours/night
• ZZ tells you he is often awoken because he has to go to the bathroom but also has trouble falling asleep at night. He states he is retired now and often takes nap into the afternoons.

WHAT FACTORS NEED TO BE CONSIDERED WHEN SELECTING INITIAL TREATMENT?

A. Type of insomnia
B. Age
C. Results of polysomnography
D. All of the above
E. A and B only

WHICH OF THE FOLLOWING IS NOT A SLEEP HYGIENE RECOMMENDATION?

A. Avoid alcohol at bedtime
B. Exercise regularly before bedtime
C. Create a bedtime ritual-waking at the same time
D. Sleep in a quiet, cool environment

PHARMACOLOGICAL OPTIONS

Prescription Agents
• Benzodiazepines (BZDs)
• Non-benzodiazepine hypnotics
• Sedative antidepressants
• Melatonin receptor agonist
• Orexin receptor antagonist

Over-the-Counter Agents
• Antihistamines
• Melatonin
• Natural products

MEDICATIONS ON THE RISE

BENZODIAZEPINES

FDA Approved:
- Short Half-Life: Triazolam (Halcion®)
- Intermediate Half-Life: Estazolam (ProSom®), Temazepam (Restoril®)
- Long Half-Life: Quazepam (Doral®), Flurazepam (Dalmane®)

Off-Label:
- Intermediate Half-Life: Alprazolam (Xanax®), Lorazepam (Ativan®), Clonazepam (Klonopin®)
- Long Half-Life: Diazepam (Valium®)

Short-Acting:
- difficulty initiating sleep
Intermediate/Long-Acting:
- difficulty maintaining sleep
Short Term Use: 7-14 days
**BENZODIAZEPINES & SAFETY**

**Benefits:**
- Increased total sleep time, decreased number of nighttime awakenings, decreased sleep latency

**Harms:**
- Sedation with feeling of heaviness, dysphoria, disorientation
- Memory impairment
- Falls and hip fractures
- Increased mortality with long term hypnotic use
- Tolerance, withdrawal, abuse potential
- Impact sleep architecture, decreasing REM sleep

National Institute for Health and Clinical Excellence (NICE) urge great caution with BZD in treatment of insomnia, using only for short term when insomnia is severe, disabling, or subjecting the individual to extreme distress

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**ZOLPIDEM (AMBIEN®)**

**Best Use**
- Time to onset: 30 minutes
- Duration: 6-8 hours
- Half-life: 2.6 hours; CR 2.8 hours
- Decreases sleep latency, preserves time spent in stages 3 and 4, increases total sleep

**Side Effects**
- Abnormal behaviors and thoughts (sleep driving, eating, walking)
- Hallucinations, anterograde amnesia
- Schedule IV controlled substance

**Dose**
- Adults: 10 mg daily immediately before bedtime
- Hepatic: 5 mg; half-life extended up to 10 hours
- Females & elderly: 5 mg
- Cost: generic $4.63/IR tab; $6.11/CR tab

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**ZOLPIDEM IR VS CR**

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**ZOLEPLON (SONATA®)**

**Best Use**
- Time to onset: rapid, within 30 minutes
- Duration: 4-6 hours
- Decreases time to sleep onset only; can be used for middle of night awakenings

**Side Effects**
- Comparable SE as zolpidem in headaches, dizziness, somnolence, CNS depression
- Schedule IV controlled substance

**Dose**
- Adults: 5-20 mg on an empty stomach
- FDA warning May 2014
- Elderly: 5 mg, max 10 mg
- Cost: generic 5 mg $3.64/cap; 10 mg $3.74/cap

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**ESZOPICLONE (LUNESTA®)**

**Best Use**
- Time to onset: rapid, 20 minutes
- Duration: 6-8 hours
- Reduces time to sleep onset, number of awakenings, increase total sleep time, improves sleep quality, sleep maintenance
- Approved for long term use (up to 6 mo)

**Side Effects**
- Unique: unpleasant taste (8-34%)
- Schedule IV controlled substance

**Dose**
- Adults: 1 mg immediately before bed, max 3 mg
- FDA warning May 2014
- Elderly: 1 mg, max 2 mg
- Cost: generic $11.60/tab regardless of strength

Study Design: Multicenter, randomized, crossover study.

Population: 65 participants, 21-64 years old, meeting the DSM-IV criteria for primary insomnia.

Purpose: To evaluate the PSG efficacy and safety of a range of eszopiclone doses relative to placebo in patients with primary insomnia using zolpidem 10 mg as active control.

Results:
- **Latency to Persistent Sleep (LPS)**
  - All active treatments reduced LPS relative to placebo, 13.1 min for 3 mg and zolpidem.
- **Sleep Efficiency (SE)**
  - Eszopiclone 2, 2.5, 3 mg and zolpidem 10 mg demonstrated significantly higher SE compared to 1 mg and placebo.
- **Adverse Effects**
  - Zolpidem had significantly higher rates of all CNS adverse effects (23.4% vs 12.9%, 3 mg) and hallucinations (4.7% vs 0%) for all doses of eszopiclone.
  - Unpleasant taste more common in all doses of eszopiclone vs zolpidem.

Suvorexant (BELSOMRA®)

**Best Use**
- Time to onset: 30 minutes, delayed with food.
- Duration: intermediate, ~12 hours.

**Side Effects**
- Decreases sleep latency, increases total sleep time.
- Unique: REM sleep effects—sleep paralysis, increased serum cholesterol, diarrhea (2%), xerostomia (2%).
- Schedule IV controlled substance.
- A major substrate of CYP3A4 and minor substrate of CYP2C19.

**Dose**
- Adult: 10 mg within 30 minutes of bed, max 20 mg.
- Hepatic: none in mild/mod; not studied in severe.
- Cost: brand only $11.36/tab regardless of strength.

**Differential Effects of Suvorexant and Zolpidem in Sleep Initiation and Consolidation.**

Study Design: Randomized, double-blind, double-dummy, placebo-controlled, four-period crossover study.

Population: 44 healthy males, 18-55 years old, BMI 18.5-29.9 kg/m² with sleep apnea.

Purpose: To investigate a single and a dose of suvorexant 10 or 30 mg, with a placebo control, zolpidem 10 mg.

Results:
- **Total Sleep Time (TST)**
  - Suvorexant 10 mg and 30 mg > TST by 17 and 31 min vs placebo.
  - Zolpidem 10 mg TST by 11 min vs placebo.
- **Wake After Sleep Onset (WASO)**
  - Significantly reduced for 30 mg dose only.
- **Sleep Structure**
  - Suvorexant 10 mg: time in stage 1 and 30 mg: % of time spent in REM sleep.
  - Interval between sleep onset and first occurrence of REM sleep <15 min were observed for 10 and 30 mg suvorexant.
- **Adverse Effects**
  - Frequency similar for all active groups.
  - Suvorexant 30 mg: >2x as many reports of somnolence and disturbance of attention than placebo and zolpidem.

Ramelteon (ROZEREM®)

**Best Use**
- Unique: disturbances of reproductive hormone regulation (decl libid, disruption of menses).
- Alpha-2 Antagonist/H1 antagonist.
- Not a controlled substance.

**Dose**
- Adult: 8 mg within 30 minutes of bedtime.
- Hepatic: not recommended in severe.
- Cost: brand only 8 mg tab $12.23/tab.

Antidepressants & Antipsychotics

- Tricyclic Antidepressants (TCAs)
  - Amitriptyline, nortriptyline, doxepin*
  - Alpha-2 Antagonist/H1 antagonist
  - Metabolized: 7.5-15 mg
  - Serotonin Reuptake Inhibitor/Antagonist
  - Trazodone 25-50 mg

Place in Therapy: Due to significant SE profiles, recommended as 3rd line when used in conjunction with treating comorbid depression/anxiety. Evidence suggests efficacy alone is weak. No one agent preferable. Not recommended by Beers Criteria.

- Atypical Antipsychotics
  - Quetiapine, olanzapine
  - May only be suitable for patients with comorbid insomnia who may benefit from primary action of these drugs as well as from the sedating effect. Evidence for efficacy is insufficient.

Antihistamines

<table>
<thead>
<tr>
<th>Dose</th>
<th>Best Use</th>
<th>Side Effects</th>
<th>Efficacy</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine (Benadryl®)</td>
<td>25-50 mg</td>
<td>Sleep latency, transient</td>
<td>Anticholinergic, sedation, mental confusion</td>
<td>Transient anticholinergic, not as effective as BZDs</td>
</tr>
<tr>
<td>Doxylamine (Unisom®)</td>
<td>25-50 mg</td>
<td>Sleep latency, transient</td>
<td>Anticholinergic, sedation, mental confusion</td>
<td>Transient anticholinergic, not as effective as BZDs</td>
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</table>

Diphenhydramine Schedule IV controlled substance, brand only 25 mg tab $7.34/tab. Doxylamine Schedule IV controlled substance, brand only 25 mg tab $12.34/tab.
MELATONIN

• An endogenous hormone capable of affecting circadian rhythm to drive increased total sleep time, sleep quality, and decrease sleep latency

• Dose: 2 – 10 mg given 30 min to 2 hours before bed

• Advantages:
  - Not a controlled substance, no dependence risk
  - No hangover effect or tolerance
  - Cost and availability
  - Safety in select populations

PATIENT CASE

• ZZ’s son, ZZ Jr appreciates all the support you’ve given his father and has some complaints of his own. He is 47 who reports trouble falling asleep. He has tried sleep restriction and lifestyle modifications to no avail.

PATIENT CASE

• Which agent may be most appropriate for ZZ Jr given the following information:
  - PMH: chronic insomnia, HTN, COPD
  - Med list includes:
    - Albuterol HFA 2 puffs Q4-6 hrs prn SOB
    - Tiotropium inhale 1 capsule daily for COPD
    - Losartan 25 mg daily for HTN

A. Eszopiclone (Lunesta®) 1 mg immediately at bed
B. Suvorexant (Belsomra®) 20 mg 30 minutes prior to bed
C. Ramelteon (Rozerem®) 8 mg 30 minutes before bed
D. Temazepam 15 mg at bedtime

BEST OPTIONS IN...

• Trouble Falling Asleep (sleep onset)
  - Rapid onset with short half-life
  - Zaleplon, ramelteon, trazodone
• Trouble Staying Asleep (sleep maintenance)
  - Delayed onset with long half-life
  - Zolpidem, temazepam, trazodone
• Middle of the night awakenings
  - Rapid onset with short half-life
  - Zaleplon, zolpidem CR
• Mixed trouble falling and staying asleep
  - Rapid onset and longer half-life
  - Zolpidem, eszopiclone, suvorexant

SOUR CHERRY

Conflicting evidence in insomnia, some efficacy in insomnia associated with anxiety disorders:
- Mild psychoactive effects
- Hepatotoxicity in clinical trials with only 1 month of use:
  - Banished from market in Germany, Canada, Switzerland
- Interaction with other CNS depressants, CYP 2C19, 3A4, and 2C9 substrates

KAVA

Possible effects on reducing time to sleep onset, improved sleep quality; however, safety with long-term use is unknown:
- Dose 300-400 mg
- Few side effects: headache, excitability (paradoxical), insomnia, dizziness, hepatotoxicity
- Interaction with other CNS depressants

VALERIAN

Possibly effective in reducing time to sleep onset and improved sleep quality, however, safety with long-term use is unknown:
- Dose 300-600 mg
- Few side effects: headache, excitability (paradoxical), insomnia, tachycardia, hepatotoxicity
- Interaction with other CNS depressants


Kava. Natural Medicines. Last Updated 2/15/15
Sour cherry. Natural Medicines. Last Updated 3/13/15.
Valerian. Natural Medicines. Last Updated 2/16/15


BEST OPTIONS IN...

- Elderly
  - CBT +/- pharmacotherapy
  - Melatonin, ramelteon, sedating antidepressant
- History of Substance Abuse
  - CBT +/- pharmacotherapy
  - Ramelteon, melatonin, sedating antidepressant, antihistamines
  - AVOID: BZDs, BZDRAs
- Hepatic Dysfunction
  - CPT +/- pharmacotherapy
  - AVOID in severe: zaleplon, ramelteon, suvorexant

SUMMARY

- While insomnia is prevalent in the US and has a significant impact on QOL, it is not often managed
- A thorough assessment of causes and characterization of insomnia is essential prior to treatment
- Non-pharmacological therapies to improve sleep habits and quality are first line according to American Academy of Sleep Medicine guidelines
- Patient-specific factors should be used to guide selection of therapy for chronic insomnia

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