Optimizing Insomnia Treatment
A Deeper Dive Into Clinical and Pharmacological Considerations

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Disclosures

- **Speaker Bureau:**
  - Amarin Pharmaceuticals
  - Amgen Pharmaceuticals
  - Axsome Pharmaceuticals
  - Eisai Pharmaceuticals
  - Esperion Pharmaceuticals

- Galt Pharmaceuticals
- Harmony Pharmaceuticals
- Idorsia Pharmaceuticals
- Jazz Pharmaceuticals
Today’s Discussion on Insomnia Includes…

- Epidemiology, morbidity, and mortality
- Clinical definition and differential diagnosis
- Treatment goals
- Assessing patients
- Non-pharmacologic and pharmacologic treatment
Epidemiology of Insomnia

- The most reported sleep-related complaint; as a general complaint it is second only to pain

- 30-50% of adults in the U.S. are affected each year\(^1\)

- At any time, around 1/3 of adults have trouble falling asleep, staying asleep, or suffer from overall poor sleep quality\(^2\)

- Chronic, persistent insomnia affects approximately 10% of the U.S. population and is a cause of significant morbidity\(^3\)

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Morbidity and Mortality of Insomnia

Studies show

- Decreased quality of life
- Higher levels of healthcare utilization
- Studies reveal chronic untreated insomnia increases suicide risk

Qualitative studies reveal:

- Feelings of isolation
- Cognitive, emotional, and physical functioning difficulties
- Reduced work and social performance

A 21-study metanalysis shows a two-fold increased risk of developing depression

There is limited data linking difficulty falling asleep with mortality due to coronary artery disease in men

Difficulty initiating and maintaining sleep is associated with an increased risk of hypertension

Chronic insomnia with short sleep duration is associated with an increased risk of developing diabetes

2. Kyle SD, Espie CA, Morgan K. “... Not just a minor thing, it is something major, which stops you from functioning daily”: quality of life and daytime functioning in insomnia. Behav Sleep Med. 2010;8:123–40.
Definition of Insomnia

- Difficulty initiating or maintaining sleep for a specified period of time with adequate time given for sleep but ultimately resulting in daytime disruption

- Associated with comorbid medical / psychiatric conditions and / or with exposure to drugs or other substances

- Should be treated regardless of whether it is associated with a comorbid condition
RULE OUT UNDERLYING MEDICAL, PSYCHIATRIC, OR OTHER PRIMARY SLEEP DISORDERS

- Major depression disorder (MDD)
- General anxiety disorder (GAD)
- Sleep Apnea
- Movement disorders
- Circadian rhythm disorders
- Medical disorders or medications with strong relationships with insomnia: COPD, GERD, BPH
Chronic Insomnia Clinical Subtypes

- Psychophysiological insomnia
- Idiopathic insomnia
- Paradoxical insomnia
- Inadequate sleep hygiene
- Insomnia due to a concomitant mental disorder
- Insomnia due to a drug or substance
- Insomnia due to a medical disorder
Accepted Thresholds and Treatment Goals

**COMMON THRESHOLDS**

- Sleep onset latency (SOL) > 30 minutes\(^1\)
- Wake after sleep onset (WASO) > 30 minutes\(^1\)
- Early morning awakenings (EMA) – at least 30 minutes before desired wake time
- Accompanying complaints about unrefreshing or non-restorative sleep\(^2\)

**TREATMENT GOALS**

- Improved sleep quality and / or duration, as defined by:
  - SOL
  - WASO
  - Decreased early morning awakenings
  - Increased total sleep time (TST)
- Improved insomnia-related daytime disruptions

Diagnostic Workup of Patients with Insomnia

**TAKING A THOROUGH SLEEP, MEDICAL, AND MEDICATION HISTORY IS KEY**

- Medications, substances, medical disorders, sleep, environment, or scheduling issues
- Contributing intrinsic / extrinsic conditions
- Insomnia secondary to other conditions
- Escalating over-concern regarding sleep

*Understanding behaviors and attitudes and beliefs around sleep issues has been demonstrated to be very important to adequately address insomnia symptoms*¹

Assessment Tools

- Screening Questionnaire
- Epworth Sleepiness Scale (ESS)
- Fatigue Severity Scale (FSS)
- Insomnia Severity Index (ISS)
- Pittsburgh Sleep Quality Index (PSQI)
- Actigraphy; Smart Phone Apps
- Sleep Diary
- Beliefs and Attitudes Questionnaire
The 5-Minute Patient Interview
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>How long have you had problems with your sleep?</td>
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<tr>
<td>Do you snore, or have you been told you snore?</td>
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<tr>
<td>Do you or have you been told you experience gasping, choking, or pause between your snoring?</td>
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<tr>
<td>Do you wake you in middle of night with heart racing or coughing?</td>
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<td>Do you wake up in morning with sore throat and/or dry mouth?</td>
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<tr>
<td>Do you have sleepiness and/or fatigue during the day?</td>
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<td>Has your working ability suffered because of your sleepiness?</td>
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<tr>
<td>Have you fallen asleep or become drowsy while driving?</td>
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<td>When waking up or falling asleep, do you have a sensation of inability to move your body, like you are paralyzed?</td>
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<td>When waking up or falling asleep, do you have vivid dreamlike scenes?</td>
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<td>At times, when you become emotional, particularly laughing, do you experience episodes that part of your body becomes heavy or goes limp?</td>
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<tr>
<td>Do you use stimulants OTC or prescribed to help you stay awake during the day?</td>
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<tr>
<td>List meds</td>
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<tr>
<td>On average how many hours of sleep do you get per night?</td>
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<tr>
<td>Do you have problems getting to sleep and/or staying asleep at night?</td>
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<tr>
<td>a. If Yes, What time do you go to sleep on average?</td>
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<tr>
<td>b. How long does it take you to fall asleep after being in the bed with lights off?</td>
<td>minutes</td>
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<tr>
<td>c. After falling asleep, how many times do you wake up during the night?</td>
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</tbody>
</table>
d. After falling asleep, how many total minutes do you think you are awake in the middle of the night? 

☐ 5  ☐ 10  ☐ 20  ☐ 30  ☐ 60  ☐ 90  ☐ 120  ☐ >120

e. What time do you get up in the morning to start your day? _____

f. ☐ Y ☐ N Do you use medication OTC or prescribed to help you sleep? List meds _____

g. ☐ Y ☐ N Do you have racing thoughts keeping you up at night?

15. ☐ Y ☐ N Do you have nightmares?

16. ☐ Y ☐ N Do you sleep walk or talk?

17. ☐ Y ☐ N Do you or have you ever been told you “act out your dreams at night?”

18. ☐ Y ☐ N Do you wake up in the morning feeling refreshed?

19. ☐ Y ☐ N Do you take naps during the day? How many total minutes do you nap daily? _____

20. ☐ Y ☐ N Are you a shift worker? What type/hours? _____

21. ☐ Y ☐ N In the evening time while sitting, do your legs feel restless, unable to keep still?

22. ☐ Y ☐ N While sleeping, does your bed partner complain of your legs constantly moving/kicking?

23. ☐ Y ☐ N Are your sheets in disarray the next morning?

24. ☐ Y ☐ N Do you take any medication for this problem? List meds _____
## Assessing Medication / Substance Induced Insomnia

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Bupropion</th>
<th>Diuretics</th>
<th>OTC Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>CNS Stimulants</td>
<td>SSRIs / SNRIs</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Decongestants + Antihistamines</td>
<td>Nicotine</td>
<td>Thyroid Hormone</td>
</tr>
</tbody>
</table>
Non-pharmacological Treatment

Cognitive Behavioral Therapy for Insomnia (CBT-I)

- Stimulus Control
- Relaxation Training
- Sleep Restriction
- Sleep Hygiene
Better Defining CBT-I

Combines different approaches to treatment and may include cognitive, behavioral, and educational components

Focuses on connections between how we think, how we do things, and how we sleep

Identifies thoughts, feelings, and behaviors that are contributing to the symptoms of insomnia

Clarifies or reframes misconceptions and in a way that is more conducive to restful sleep
Cognitive Restructuring

Changing inaccurate or dysfunctional thoughts about sleep may lead to behaviors that make sleep more difficult, which then reinforce the dysfunctional thoughts.

Begin to break this cycle through identifying, challenging, and altering the thoughts and beliefs that contribute to insomnia.

Common thoughts and beliefs that may be addressed during treatment include anxiety, unrealistic expectations, and worry about daytime fatigue or other consequences of missed sleep.
Many people with insomnia begin to dread their bedroom, associating it with wakefulness and frustration.

Stimulus control attempts to change these associations, reclaiming the bedroom as a place for restful sleep.

To achieve this, the bed is only used for sleep and sex.

It’s important to get out of bed when it’s difficult to fall asleep or when they lie awake for more than 10 minutes, only going back to bed when they are tired again.

Wake up the same time every morning and avoid daytime naps.
Sleep restriction limits time spent in bed in order to reestablish a consistent sleep schedule.

It is intended to increase the drive to sleep, although it can temporarily increase daytime fatigue.

Time in bed is gradually reduced until it is reasonably close to the time spent actually sleeping.
Relaxation Training

Relaxation techniques can help reduce the racing thoughts and tension that can contribute to lying in bed awake. These techniques can increase a natural relaxation response which is helpful for both the body and mind.

Techniques include:
- Breathing exercises
- Progressive muscle relaxation
- Biofeedback
- Hypnosis
- Meditation
- Music
Proven to be effective in 70% to 80% of patients with primary insomnia experience improvements

Benefits include less time to fall asleep, more time spent asleep, and waking up less during sleep

The American College of Physicians recommends that all adult patients receive CBT-I as a first-line approach

It’s been shown to be more beneficial than medications but, in my practice the combination of the two works the fastest; the more disciplined the patient is with this therapy the faster it works
Ledet’s Rules for a Good Night of Sleep

1. Choose a consistent 8-hour slot of time for sleep

2. Preferably a few hours before bedtime, have processing time to:
   - To make a “to do” list, “worry” list, or “whatever” list
   - To avoid mind racing in bed

3. Have only two pleasant things in bed:
   - Sleep
   - Intimacy

4. If not doing one of these things, opt to sit in a chair instead
   - Leave lights off, use pleasant music (without words), prayer, or meditation
   - Return to bed when sleepy

5. Wake up at the same time each morning

6. No naps, strive for 16 hours of wake time

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1. Ledet, Practical Diabetology, Sept/Oct 2010, p 6-9
Pharmacologic Treatment Considerations

Alongside psychological and behavioral therapy the choice of a specific drug within a class can be directed by 1:

- Symptom pattern
- Treatment goal
- Past treatment responses
- Patient preference
- Cost
- Availability
- Comorbid conditions
- Contraindications
- Concurrent medications
- Potential adverse effects
- Abuse potential

### Ideal Properties of a Sleep Medication

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>It starts to work in a reasonable timeframe (within 3-5 days)</td>
<td></td>
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<tr>
<td>No addictive potential</td>
<td></td>
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<tr>
<td>Does not worsen respiratory depression during sleep</td>
<td></td>
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<tr>
<td>Minimal side effects (e.g., does not worsen mood issues)</td>
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<tr>
<td>No rebound insomnia</td>
<td></td>
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<tr>
<td>No morning grogginess or cognitive dysfunction</td>
<td></td>
</tr>
<tr>
<td>No changes in sleep stages / simulates normal sleep</td>
<td></td>
</tr>
</tbody>
</table>
## Rebound Insomnia

1. Difficulty initiating and maintaining sleep worsened by abrupt discontinuation of hypnotic medications and is often worse that the initial insomnia

2. May be more significant with shorter-acting drugs or when a drug is used for longer periods of time

3. Occurs more often when a higher dose of a drug is used

4. Ameliorated by slowly tapering the dose of a drug

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The GABA\(\alpha\) Receptor

This complex receptor is the primary binding site for both benzodiazepines and z-drugs.

Binding to specific \(\alpha\) subunits confer different clinical effects\(^1\):

- \(\alpha1\): sedative, anticonvulsant (BZ1)
- \(\alpha2\): anxiolytic, myorelaxant (BZ2)
- \(\alpha3\): myorelaxant (BZ2)
- \(\alpha5\): myorelaxant, amnesic (BZ2)
- \(\alpha4\) & \(\alpha6\): no known clinical effects

Orexin Receptor Antagonists

- Newest mechanism of action
- Blocks the neuropeptide that regulates wakefulness
- Does not directly influence sleep
- Schedule IV (C-IV) Controlled Substance

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**Medications With an FDA Indication for Insomnia**

**Benzodiazepines**
- Estazolam (Prosom®)
- Flurazepam (Dalmane®)
- Quazepam (Doral®)
- Temazepam (Restoril®)
- Triazolam (Halcion®)

**Non-benzodiazepines**
- Eszopiclone (Lunesta®)
- Zaleplon (Sonata®)
- Zolpidem (Ambien®)

**Histamine (H1) Antagonists**
- Diphenhydramine (Benadryl®)
- Doxepin (Silenor®)
- Doxylamine (Unisom®)

**Orexin Antagonists**
- Suvorexant (Belsomra®)
- Lemborexant (Dayvigo®)
- Daridorexant (Quviviq)

**Melatonin Receptor Agonists**
- Ramelteon (Rozerem®)
Dangers of OTC Sleep Aids

According to the 2015 Consumer Reports Survey:

- 41% of OTC sleep aid users chronically take them for greater than a year, despite tolerance to the sedative effect generally developing after two weeks
- 60% do not talk to their doctors about their OTC sleep aid use

Long-term Risks:
- Nocturia
- Cognitive decline
- Memory loss
- Dementia

Adverse Effects:
- Dry mouth
- Restless leg syndrome
- Dizziness / confusion
- Constipation
- Next-day drowsiness / hangover effect
- Impaired balanced / coordination
- Falls / accidents

1. https://www.consumerreports.org/drugs/over-the-counter-sleep-aids-can-you-get-hooked/
Black Box Warning for Z-Drug Class

Post-marketing data for zolpidem led the FDA to issue a Black Box Warning for the Z-Drug class

APRIL 2019: NEW BOXED WARNING
→ “...rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths.”

APRIL 2019: NEW CONTRAINDICATION
→ “...avoid use in patients who have previously experienced an episode of complex sleep behavior with eszopiclone, zaleplon, and zolpidem.”

Orexin Receptor Antagonists: Adverse Effects

- Headache
- Somnolence
- Diarrhea
- Fatigue
- Vivid Dreaming
- Complex sleep behaviors
- Worsening depression and suicidal thoughts
- Sleep paralysis
- Hypnagogic / hypnopompic effects
- Cataplexy

Medications *Without* an FDA Indication for Insomnia

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Antidepressants</th>
<th>Antipsychotics</th>
<th>Anticonvulsants</th>
<th>Melatonin Receptor Agonists</th>
<th>Antihypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax®)</td>
<td>Trazodone (Desyrel®)</td>
<td>Olanzapine (Zyprexa®)</td>
<td>Gabapentin (Neurontin®)</td>
<td>OTC Melatonin</td>
<td>Prazosin (Minipress®)</td>
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<tr>
<td>Chlordiazepoxide (Librium®)</td>
<td>Amitriptyline (Elavil®)</td>
<td>Tramadol (Surmontil®)</td>
<td>Pregabalin (Lyrica®)</td>
<td></td>
<td>Clonidine (Catapress)</td>
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<tr>
<td>Clonazepam (Klonopin®)</td>
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<td>Tiagabine (Gabitril®)</td>
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<td>Diazepam (Valium®)</td>
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<tr>
<td>Lorazepam (Ativan®)</td>
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- **Antidepressants**: Trazodone (Desyrel®), Amitriptyline (Elavil®), Trimipramine (Surmontil®), Mirtazapine (Remeron®)
- **Antipsychotics**: Olanzapine (Zyprexa®), Quetiapine (Seroquel®)
- **Anticonvulsants**: Gabapentin (Neurontin®), Pregabalin (Lyrica®), Tiagabine (Gabitril®)
- **Melatonin Receptor Agonists**: OTC Melatonin
- **Antihypertensives**: Prazosin (Minipress®), Clonidine (Catapress)
22% of patients with chronic insomnia report treating it with alcohol consumption

Chronic use can result in:
- Tolerance, dependence, diminished sleep efficiency and quality
- Disinhibiting and depersonalizing effects during waking
- Affects sleep physiology, hormone function, CNS neurochemicals, and daytime alertness
- Tolerance to sedative effect – this can lead to excessive hypnotic use and excess daytime use for insomniacs
- Can be fatal when used in excess with other sedative hypnotic agents

Insomnia evaluation first starts with a full patient assessment relative to their complaints, medications, and sleep hygiene – thus, the use of sleep questionnaires can be helpful.

Cognitive Behavior Therapy for Insomnia (CBT-I) has been found to be effective and beneficial in the treatment of insomnia.

Discussing proper rules for good sleep is critical to the treatment of patients with insomnia.

If pharmacologic treatment is needed, they should be assessed based on the patient’s individual needs and symptoms.
Thank You!
Questions?