Behavioral aspects of medication treatment for insomnia

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- Medications for insomnia: A brief review
- Medications as a form of behavioral intervention
- What the patient brings
- What the provider brings
- Take home points
Recommendation 1

- ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder.
- Grade: strong recommendation, moderate-quality evidence

Recommendation 2

- ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful.
- Grade: weak recommendation, low-quality evidence

Medications commonly used for insomnia: National Health and Nutrition Epidemiological Survey, 1999-2010

- NHANES 1999-2010 (n=32,328), ≥ 20 y.o.
- Review of medication bottles for all Rx meds
- Zolpidem = 87% of Non-Bz BzRA
- 55% of hypnotic users take at least one other sedating medication (opioids, Bz)
- 10% take ≥3 other sedating medications
- When specifically asked, 19.2% said they took at least one medication to sleep

Bertisch, SLEEP 2014; 37:343-349.
### Medications used to treat insomnia

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Examples</th>
<th>Potential Advantages</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine receptor agonists (BzRA)</td>
<td>Zolpidem, zaleplon, eszopiclone, temazepam</td>
<td>• Efficacious&lt;br&gt;• Variety of half-lives</td>
<td>• Cognitive effects&lt;br&gt;• Falls&lt;br&gt;• Dependence</td>
</tr>
<tr>
<td>Sedating antidepressants</td>
<td>Doxepin, amitriptyline, nortriptyline</td>
<td>• No abuse&lt;br&gt;• Effective for WASO</td>
<td>• Anticholinergic at high doses&lt;br&gt;• Cardiac effects&lt;br&gt;• Falls</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Diphenhydramine, doxylamine</td>
<td>• Widely available</td>
<td>• Cognitive effects&lt;br&gt;• Limited efficacy data</td>
</tr>
<tr>
<td>Melatonin, receptor agonist</td>
<td>Melatonin, ramelteon</td>
<td>• “Natural” mechanism&lt;br&gt;• Some efficacy data</td>
<td>• Limited efficacy on WASO</td>
</tr>
<tr>
<td>Orexin antagonist</td>
<td>Suvorexant</td>
<td>• Novel mechanism, blocks wake signal</td>
<td>• Limited efficacy, effectiveness data</td>
</tr>
<tr>
<td>Sedating antipsychotics</td>
<td>Quetiapine, olanzapine</td>
<td>• Not BzRA&lt;br&gt;• Efficacy for psychosis, depression</td>
<td>• Metabolic, neurological, cardiovascular effects</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Gabapentin, pregabalin</td>
<td>• Not BzRA&lt;br&gt;• Efficacy for pain</td>
<td>• Limited sleep efficacy data</td>
</tr>
</tbody>
</table>

WASO = Wakefulness After Sleep Onset. *Italics* = Not FDA-approved for insomnia
Weak evidence FOR

- Suvorexant (Belsomra)²
- Eszopiclone (Lunesta)¹,²
- Zaleplon (Sonata)¹
- Zolpidem (Ambien)¹,²
- Triazolam (Halcion)¹
- Temazepam (Restoril)¹,²
- Ramelteon (Rozerem)¹
- Doxepin (Silenor)²

Weak evidence AGAINST

- Trazodone (Desyrel)
- Tiagabine (Gabitril)
- Diphenhydramine (Benadryl)
- Melatonin
- Tryptophan
- Valerian

Clinical practice guideline for pharmacologic treatment of chronic insomnia in adults

- Based on systematic review using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.
- 2,821 studies reviewed, 129 studies included
- ¹ = For sleep onset insomnia. ² = For sleep maintenance insomnia

Sateia, Buysse, Krystal, Neubauer, Heald, 2017; JCSM 13; 307-349.
Insomnia: What patients say

“I can’t sleep.”

“I feel fatigued all the time.”

“I lie awake all night long.”

“I don’t feel rested in the morning.”

“I take forever to fall asleep, but once I’m asleep I’m fine.”

“I can fall asleep, but I keep waking up?”
Possibly: “A lot of my patients have insomnia, and most of them do OK with the generic form of Ambien. Here’s a prescription for a month’s worth. Take one at bedtime, and I think you’ll notice an improvement.”

Or possibly: [Silence as s/he hands patient a prescription or types one in.]
Medications: What patients say

“This medication doesn’t work.”

“I don’t like the way it makes me feel.”

“I think I need a higher dose.”

“My medication stopped working.”

“Medications have the opposite effect on me.”

“I dropped some in the toilet. Can you call in some more?”

“Thanks, doc. This stuff works great.”

“Thanks, doc. This stuff works great.”
How do we treat insomnia?

Treatment for Insomnia

Pharmacologic
Patterns of medication use in insomnia

- **Chronic BzRA users**¹
  - 83% daily use
  - 22% report lower frequency or dose than prescribed
  - 7.5% report higher dose than prescribed

- **prn and intermittent use studies**²,³
  - 3.7-3.9 doses per week for active drug, placebo²,³
  - 60-80% of nights per week⁴,⁵

Patterns of medication timing in patients prescribed hypnotics in the past year

Timing of Prescription Sleep Medication Dosing (n=1,927)

1,927 subjects who received a hypnotic Rx in the past year and took at least one dose

MOTN = Middle of the Night

Slide courtesy T. Roth & R. Kessler, 2011
Behavior: A function of the patient-provider interaction
Behavioral aspects of pharmacotherapy: What the patient brings

- **Suffering → Frustration**
- **Beliefs and attitudes**
  - Regarding sleep
    - “I want 8 hours of sleep like everybody else.”
    - “I read about sleep deprivation in the newspaper and I don’t want to die.”
  - Regarding medications
    - “I just want something to knock me out.”
    - “I should be able to sleep without medications.”
- **Other medications, illnesses**
- **Life circumstances**

*All of these can affect if and how patients take medications*
Behavioral aspects of pharmacotherapy: What the provider brings

- Evaluation knowledge
- Patient education
- Ability to personalize treatment
- Specific instructions
- Follow-up on treatment
Insomnia assessment: 24-hour history

- Sleep quality, satisfaction
- Temporal aspects of sleep
  - Bed time (vs. sleep time)
  - Out of bed time (vs. wake time)
- “Quantitative” aspects of sleep
  - Sleep latency
  - Awakenings
  - Sleep duration
- Sleep-related behaviors (“sleep hygiene”): Caffeine, alcohol, activities
- Day-to-day variability (weekends, vacations)

- Daytime activities and impairments: Napping, fatigue, cognitive function, mood
- Life situation and circumstances
- Other sleep disorder symptoms
  - Apnea (Snoring, sleepiness)
  - Restless legs (Urge to move)
  - Parasomnias (Unusual behavior)
  - Circadian rhythm disorders (Unusual timing)
- Medical and psychiatric disorders
- Sleep diary, wearable fitness/sleep trackers
Education 1: Sleep

- Nature and regulation of sleep
  - Voluntary/ involuntary
  - Homeostatic and circadian (2-process model)

- Realistic expectations
  - Normal and not normal (e.g., sleep duration)
  - Sleep as a behavioral alternative
What controls sleep? The brain!

Saper, Nature, 2005; 1257-63
What controls sleep? The hourglass, the clock, and the alarm

- How long you’ve been awake
- Time of day
- Level of arousal

Homeostatic sleep drive
Circadian sleep propensity
Psychophysiologica arousal
Education 1: Sleep

- Nature and regulation of sleep
  - Voluntary/ involuntary
  - Homeostatic and circadian (2-process model)

- Realistic expectations
  - Normal and not normal (e.g., sleep duration)
  - Sleep as a behavioral alternative
Education 2: Medications

- Realistic expectations
  - Sleeping pills vs. general anesthesia
  - Modest effects
  - The Olympic Sleep Team

- Characteristics of medications
  - Pharmacokinetics
  - Effects
  - Side effects

![Graphs showing blood level of drug over time for Half-Life, Variability, and Proportionality with therapeutic level highlighted.]

Therapeutic level
Personalizing treatment

- Classes of medication
  - Benzodiazepine receptor agonists: Pros and cons
  - Sedating antidepressants: Pros and cons
  - Others (antihistamines, melatonin, alcohol)
- Frequency of administration
  - Every night
  - Intermittent: Targeted, intermittent
Instructions

- **Who:** The patient
- **What:** Medication
  - Types
  - Dose
- **When, where:** Time and place of administration
  - Too early, too late
  - At home
- **How:** Details
  - Food,
  - Alcohol
  - Other medications
  - How long (duration)
Behavioral aspects of pharmacotherapy: Timing is key

[Graph showing sleep drive and biological clock with corresponding times: 7am, 11pm, 7am]

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Follow-up

- Therapeutic effects
  - Sleep
  - Wake
- Side effects
- Challenges, difficulties, and questions
- Education regarding long-term use
  - Daily
  - Targeted, intermittent
  - Discontinuation
Take home points

- Taking medication is a behavior
- The best pharmacotherapy involves behavioral therapy
- Both the patient and the provider bring something to successful (or unsuccessful) pharmacotherapy
- **Key talking points with patients**
  - Sleep is an involuntary biological process *influenced* by behavior and medication
  - Sleep is not a behavioral alternative to wakefulness
  - Reasonable expectations re: sleep, medications
  - Appropriate timing
Clinical scenario #2

- Based on your symptoms, I think a trial of medication would be appropriate. Since you mainly have trouble falling asleep, the generic form of Ambien would probably be a good choice. However, if you feel drowsy the following morning, or if you still wake up a lot in the second half of the night, we may need to change plans.*

- You should take only one pill—never more.
- Take it when you are actually ready to go to bed—never more than 15 minutes before you get into bed, and not in the middle of the night.
- The pills are absorbed best on an empty stomach.
- You can use the medication every night, but if you prefer, you could also take it just a few times per week.*

*May require elaboration, further discussion.
Clinical scenario #2

- If you take the pill every night, don’t stop it suddenly, because you will likely have some “rebound” effects.*
- What we are looking for is faster onset of sleep, fewer awakenings at night, and better sleep quality overall.
- The most common side effects are morning drowsiness, headaches, nausea, and forgetfulness at night. A few patients also have eating or walking during sleep. Let me know if you have these, or any other effects you think could be related to the medication.
- I want you to check in with me in 2 weeks to let me know how it’s going, or sooner if you have questions.
- I usually aim for a month of treatment initially, and after that, we can talk about a longer-term plan.*

*May require elaboration, further discussion.
Clinicians’ and patients’ choices in evidence-based medicine\textsuperscript{1}

\textsuperscript{1}DaCruz, BMJ 2002;324:674.