Objectives for Learning Outcomes:

1. Describe insomnia definitions and core concepts.
2. How to perform an in-depth clinical evaluation of insomnia.
3. Select most appropriate drug therapy with understanding of mechanism and side effects.
Pharmacological Management of Insomnia
June 3rd, 2020
Ken He, MD, PharmD
Clinical Assistant Professor, UWSoM
Staff, Hospital & Sleep Medicine, VA PSHCS

Ken He, MD, PharmD
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Conflict of Interest Disclosures
The presenter does not have any potential conflicts of interest to disclose.

- The presenter wishes to disclose the following potential conflicts of interest:

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>None (10/28/2019)</td>
</tr>
<tr>
<td>Consultant</td>
<td>Eisai</td>
</tr>
<tr>
<td>Speakers' Bureau</td>
<td>None</td>
</tr>
<tr>
<td>Financial support</td>
<td>None</td>
</tr>
<tr>
<td>Licensing fees</td>
<td>None</td>
</tr>
<tr>
<td>Educational products</td>
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</table>

The material presented in this lecture has no relationship with any of these potential conflicts.

Learning Objectives
Describe insomnia definitions and care concepts.
Perform an in‐depth evaluation of insomnia.
Select the most appropriate drug therapy.

Insomnia concepts

Short-term vs. Chronic Insomnia
ICSD – 3 Diagnostic Criteria

<table>
<thead>
<tr>
<th>Short-term insomnia</th>
<th>Chronic insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 3 months</td>
<td>Greater than 3 months</td>
</tr>
</tbody>
</table>

ICSD no longer differentiates between primary, secondary or insomnia subtypes.
Insomnia Nosology

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary (comorbid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Secondary (comorbid)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Due to drug or substance</td>
</tr>
<tr>
<td>Paradoxical</td>
<td>Due to medical condition</td>
</tr>
<tr>
<td>Psychophysiological</td>
<td>Due to mental disorder</td>
</tr>
<tr>
<td>Inadequate sleep hygiene</td>
<td>Due to other sleep disorder</td>
</tr>
</tbody>
</table>

American Academy of Sleep Medicine [aasm.org/resources/factsheets/insomnia.pdf]

Short-term* Insomnia Disorder

ICSD – 3 Diagnostic Criteria

All criteria must be present

1. Difficulty falling or maintaining sleep, or waking too early
2. Occurs despite adequate sleep opportunity
3. Occurs ≤ 3 months
4. Daytime impairment (fatigue, sleepiness, mood, cognition, performance, preoccupation with sleep)
5. Cannot be better explained by another sleep disorder

*May be referred to as acute or adjustment insomnia

ICSD-3: International Classification of Sleep Disorders, 3rd edition

Chronic Insomnia Disorder

ICSD – 3 Diagnostic Criteria

All criteria must be present

1. Difficulty falling or maintaining sleep, or waking too early
2. Occurs despite adequate sleep opportunity
3. Occurs ≥ 3 times/week for ≥ 3 months
4. Daytime impairment (fatigue, sleepiness, mood, cognition, performance, preoccupation with sleep)
5. Cannot be better explained by another sleep disorder

ICSD-3: International Classification of Sleep Disorders, 3rd edition

Insomnia in General Adult Population

- The most common sleep disorder
- Estimated prevalence:
  - Any insomnia, 20% to 30%
  - Chronic insomnia, 6 to 10%
- Incidence is increasing
- More problematic in military service

Prevalence of symptoms is roughly double prevalence of disorder.

Risk Factors

- Older age
- Female gender
- Pregnancy
- Medical or psychiatric illness
- Medications
- Stressful experiences
- Social obligations

Sleep in the Era of COVID-19

- Increased stressors
- Home confinement
- Acute illness
- Increased insomnia
- Circadian rhythm disorders

Image from www.uniquemindcare.com

Li. JCSM. 2020; in press.
Bryson. JCSM. 2020; in press.
Image from www.tribunenews.com

Image from www.statnews.com
Understanding these concepts helps inform medication selection.

**Homeostatic Sleep Drive**
- Linear function of time awake
- Longer time awake results in greater pressure to sleep

**Circadian Alerting Drive**
- Complex circadian function
- Hypothalamic “internal clock” regulated by light & melatonin

**Alertness at Any Time is a Balance of these Two Processes**
- Homeostatic drive >> Circadian drive
- “Afternoon slump”
Effect of Insomnia

- What reduces homeostatic drive
  - Naps
  - Sleeping in
- What increases or disrupts circadian drive
  - Shift work
  - Circadian rhythm disorder
  - Light exposure
  - Cognitive or somatic hyperarousal

Evaluating insomnia in the clinic

Timing is Key! (the Sleep History)

- Bedtime routine
- Time in bed & out of bed
- Initial sleep onset
- Awakenings (triggers)
- Naps
- Weekday vs. weekend changes
- Work schedule
- Sleep environment
- Sleep quality
- Symptoms of other sleep disorders
- Caffeine use

What is Normal Sleep?

- Sleep timing (variable)
- Similar timing through the week
- Sleep onset latency < 30 minutes
- WASO < 30 minutes
- Awakenings (few, brief, spontaneous)
- Sleep efficiency 85% to 92%

Sleep Diaries: an Essential Tool

Blank sleep diary available on paper or electronic

- Critical in evaluation of insomnia
- More precise recording of timing and pattern of sleep
- Many formats
- Pen/paper diary (www.yoursleep.aasmnet.org/pdf/sleepdiary.pdf)
- E-diary – CBT-I coach (www.mobile.va.gov/app/cbt-i-coach)
- Sleep trackers
- Actigraphy
- Polysomnography

Sleep Diary Sample (insomnia)
**Issue with Insomniacs…**

- Distorted perceptions & beliefs about sleep
- Subjective sleep loss often exceeds objective measurements
  - Overestimate time to fall asleep
  - Underestimate total sleep time
  - Overestimate time awake after sleep onset
  - Overestimate number of awakenings

**Selecting drug therapy**

**Establish Expectations**

**For sleep**
- Insomnia is chronic and requires time and effort to improve
- Goal is often NOT to normalize, but to improve sleep quality and daytime function

**For drug therapy**
- There is NO magic drug fully effective AND safe
- Timing is KEY!
- Improves objective sleep parameters by MINUTES.

**Avoid pursuit of orthosomnia**

**Commonly Used Insomnia Medications**

- NHANES 1999 to 2010 (n = 32,328, ≥ 20 years old).
- N = 906 (3%) used insomnia med in past month.
- Use nearly doubled in 10 year period.
- Zolpidem = 88% of BzRA
- Concurrent use of 2 meds (55%), ≥ 3 meds (10%)

**Pharmacologic Categories**

<table>
<thead>
<tr>
<th>Non-BZ Benzodiazepine receptor agonists</th>
<th>GABA-A agonist via BZ₁ receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines (traditional)</td>
<td>GABA-A agonist via BZ receptor</td>
</tr>
<tr>
<td>Melatonin receptor agonists</td>
<td>MT₁ and MT₂ receptors</td>
</tr>
<tr>
<td>Orexin (hypocretin) antagonists</td>
<td>OX₁R and OX₂R receptors</td>
</tr>
<tr>
<td>Antidepressants (sedating)</td>
<td>Multimodal (5HT, NE, D₂, H₁, Ach, α₁)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>H₁, Ach receptor blockade</td>
</tr>
<tr>
<td>Antipsychotics (second generation)</td>
<td>Multimodal (D₂, Ser, ACh, H₁, α₁)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Modulatory alpha-2-delta-1 subunit</td>
</tr>
<tr>
<td>Antagonists</td>
<td>α₁ receptor antagonist, α₂ receptor agonist</td>
</tr>
<tr>
<td>Herbs and nutriceuticals</td>
<td>Multimodal</td>
</tr>
<tr>
<td>Substances (recreational)</td>
<td>Multimodal</td>
</tr>
</tbody>
</table>

**Important Neurotransmitters**

**Wake promoting**
- Orexin/hypocretin
- Serotonin
- Norepinephrine
- Dopamine
- Histamine
- Acetylcholine
- Alpha-2-delta
- Glutamate

**Sleep promoting**
- GABA
- GABA ᵃ₁ – sedating
- GABA ᵃ₂ – anxiolysis
- GABA ᵃ₅ – amnesia
- Adenosine
- Melatonin
- Galanin

**Take note of medications with agonist v. antagonist effects**
Specific Medications

<table>
<thead>
<tr>
<th>Non-BZ BZRA</th>
<th>Zolpidem, zaleplon, eszopiclone</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZ (traditional)</td>
<td>Temazepam, triazolam</td>
</tr>
<tr>
<td>Melatonin and derivatives</td>
<td>Melatonin, ramelteon, tasimelteon</td>
</tr>
<tr>
<td>Orexin (hypocretin) antagonists</td>
<td>Suvorexant, lemborexant, (daridorexant, seltorexant)</td>
</tr>
<tr>
<td>Antidepressants (sedating)</td>
<td>Trazodone, mirtazapine, amitriptyline, doxepin</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Diphenhydramine, doxylamine, hydroxyzine</td>
</tr>
<tr>
<td>Antipsychotics (second generation)</td>
<td>Olanzapine, risperidone, quetiapine, etc</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Gabapentin, pregabalin, tiagabine, barbiturates</td>
</tr>
<tr>
<td>Sympatholytics</td>
<td>Prazosin, clonidine, tizanidine, guanfacine</td>
</tr>
<tr>
<td>Herbals and nutriceuticals</td>
<td>Kava kava, valerian, chamomile</td>
</tr>
<tr>
<td>Substances (recreational)</td>
<td>Alcohol, opioids, marijuana</td>
</tr>
</tbody>
</table>

BRZA = benzodiazepine-receptor agonist; BZ = benzodiazepines; Italics = FDA approved for insomnia

Advantages | Disadvantages
--- | ---
Non-BZ BZRA & BZ (traditional) effective, various half-lives | cognition, falls, dependence, sleep related behaviors, withdrawal
Melatonin natural, minimal side effect | limited efficacy, not regulated
Orexin new class | limited experience
Antidepressants (sedating) | no abuse, effective for maintenance
doxepin | cardiac, anticholinergic, orthostatic, suicidal thinking, serotonin syndrome
Antihistamines | easily obtained
diphenhydramine, doxylamine, hydroxyzine | cognition, limited efficacy
Antipsychotics | effective for psychosis
trazodone | cardiac, anticholinergic, falls, dystonia
Antiepileptics | effective for nerve pain
temptazolam | edema, cognition, falls, respiratory depression
Sympatholytics | effective for nightmares
tizanidine | hypertension, cardiac
Herbals and nutriceuticals | natural
kava kava, valerian, chamomile | liver toxicity, not regulated
Substances (recreational) | natural
alcohol, opioids, marijuana | dependence, liver toxicity, respiratory depression

Factors When Selecting a Drug

- Timing of symptoms
- Age
- Preference
- Comorbidities
- Substance use history
- Prior sedative use history
- Drug interactions

Timing of Symptoms

Onset & Maintenance

- "Can't fall asleep"
- "Can't stay asleep"
- "Well, now I'm awake..."

- Zolpidem CR
- Eszopiclone
- Temazepam
- Ramelteon
- Melatonin (sustained release)

Timing of Symptoms

- "Can't fall asleep"
- "Can't stay asleep"

What do the Guidelines Say?

**American College of Physicians (2016)**
- All adults receive CBT-I as initial treatment for chronic insomnia (strong)
- Share decision making on deciding to add medications if CBT-I unsuccessful (weak)
- Limit medication use to < 4 to 5 weeks

**European Sleep Research Society (2017)**
- All adults receive CBT-I as initial treatment for chronic insomnia (strong)
- Offer medications if CBT-I effective or not available (weak)
- Limit medication use to ≤ 4 weeks
- Antihistamines, antipsychotics, melatonin, alternative therapies are not recommended (strong to weak)
What do the Guidelines Say?

JAMA Clinical Guidelines (2017)
- Updates:
  - Medications most appropriate for short-term insomnia
  - Use shorter half-life agents, lower dose, intermittent dosing

AASM Guidelines on Drug Therapy (2017)
- All recommendations are WEAK (low quality evidence)
- Sleep onset – zaleplon, triazolam, ramelteon
- Sleep maintenance – suvorexant, doxepin
- Not recommended – zolpidem, temazepam
  - Sedating antidepressants
  - zolpidem
  - zaleplon
  - eszopiclone
  - zopiclone
  - melatonin
  - valerian root
  - tryptophan

On Drug Therapy
- Majority of recommendations are WEAK (low quality evidence)
- Recommend doxepin, BZRA
- Recommend neither for or against ramelteon, suvorexant
- Recommend against kava, chamomile, antipsychotics, benzodiazepines

What explains the Rx Pattern?

Zolpidem
- 12/16/1992: approved for use
- 2006 to 2009: media coverage of bizarre sleep related behaviors
- 2007: FDA warns of complex sleep-related behaviors with use
- 1/10/13: FDA requests to lowers initial dose by half
- 4/30/19: FDA adds boxed warning for complex sleep behaviors

Trazodone
- 1981: approved for use
- Most commonly used insomnia medication
- Being substituted for zolpidem circa 2013

Zolpidem Prescribing Needs Attention

- 3.8 million adults (18 to 85 years old) reported zolpidem use.
- 65% female
- 78% users ≥ 45 years old
- Sustained use is >60 days

Prescribing Trends

- Zolpidem Rx per year
- Trazodone Rx per year

Use pattern from 12/2005 to 11/2014 in the VHA

(From Medical Expenditure Panel Survey (MEPS) 2007-2017. AHRQ, Rockville, MD)

<table>
<thead>
<tr>
<th>Year</th>
<th>Zolpidem Rx per 1000</th>
<th>Trazodone Rx per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>30,000</td>
<td>15,000</td>
</tr>
<tr>
<td>2008</td>
<td>25,000</td>
<td>10,000</td>
</tr>
<tr>
<td>2009</td>
<td>20,000</td>
<td>5,000</td>
</tr>
<tr>
<td>2010</td>
<td>15,000</td>
<td>2,500</td>
</tr>
<tr>
<td>2011</td>
<td>10,000</td>
<td>1,250</td>
</tr>
<tr>
<td>2012</td>
<td>5,000</td>
<td>625</td>
</tr>
<tr>
<td>2013</td>
<td>2,500</td>
<td>312</td>
</tr>
<tr>
<td>2014</td>
<td>1,250</td>
<td>157</td>
</tr>
<tr>
<td>2015</td>
<td>625</td>
<td>75</td>
</tr>
</tbody>
</table>

2015 MEPS in adults

- 3.8 million adults (18 to 85 years old) reported zolpidem use.
- 65% female
- 78% users ≥ 45 years old
- Sustained use is >60 days

Table 2: Increased Risk Among Zolpidem Users

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Zolpidem Users, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained use</td>
<td>65.2 (62.6-67.8)</td>
</tr>
<tr>
<td>Higher dose</td>
<td>66.0 (63.3-68.7)</td>
</tr>
<tr>
<td>Female</td>
<td>66.0 (63.3-68.7)</td>
</tr>
<tr>
<td>Age ≥ 65 y</td>
<td>66.0 (63.3-68.7)</td>
</tr>
<tr>
<td>Other CNS depressant use*</td>
<td>43.4 (34.9-52.9)</td>
</tr>
<tr>
<td>Copied</td>
<td>26.5 (21.8-31.2)</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>20.3 (16.6-24.3)</td>
</tr>
<tr>
<td>≥2 Safety issues</td>
<td>77.4 (70.5-84.3)</td>
</tr>
</tbody>
</table>

Abbreviation: CNS, central nervous system.
*Sustained use, more than 1 medication possible
Non-BZ BZRA vs. Traditional BZ

### Non-BZ BZRA
- FDA indication for insomnia
- "Safer" side effect profile
- Less adverse effect on sleep architecture
- Less rebound insomnia on discontinuation
- Be cognizant of parasomnias

### Traditional BZ
- FDA indication for insomnia
- "Safer" side effect profile
- Less adverse effect on sleep architecture
- Less rebound insomnia on discontinuation
- Be cognizant of parasomnias

**Association with mortality or cancer (stronger at higher doses).**

---

**Drug T Max (hours) Elimination T½ (hours) Usual Dose (mg) Approved for Insomnia Comments**

| Drug            | T max (hours) | Elimination T½ (hours) | Usual Dose (mg) | Approved for Insomnia Definitely Suitable Use Caution Use with Caution
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon</td>
<td>1 – 2</td>
<td>1 (0.8 – 1.3)</td>
<td>5 – 20</td>
<td>Yes</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1.5 (0.5 – 1.5)</td>
<td>5 (4 – 6.5)</td>
<td>5 – 10</td>
<td>Yes</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>1.6 (0.6 – 1.5)</td>
<td>10 (8 – 20)</td>
<td>5 – 10</td>
<td>Yes</td>
</tr>
<tr>
<td>Zolpidem: Extended Release</td>
<td>1.5 (1.5 – 2.0)</td>
<td>2 (1.6 – 4.5)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Zolpidem: Sublingual (Edluar®)</td>
<td>1.4 (0.5 – 3.0)</td>
<td>2 (1.5 – 6.7)</td>
<td>5 – 10</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Non-BZ Benzodiazepine Receptor Agonists**

<table>
<thead>
<tr>
<th>Drug</th>
<th>T max (hours)</th>
<th>Elimination T½ (hours)</th>
<th>Usual Dose (mg)</th>
<th>Approved for Insomnia</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon</td>
<td>1.5 (0.5 – 2)</td>
<td>10 (8 – 20)</td>
<td>5 – 20</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1.5 (0.5 – 2)</td>
<td>6 (5 – 8)</td>
<td>1 – 3</td>
<td>Yes</td>
<td>50% may have unpleasant taste</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>1.6 (0.5 – 1.5)</td>
<td>2.5 (1.6 – 4.5)</td>
<td>5 – 10</td>
<td>Yes</td>
<td>Most widely prescribed</td>
</tr>
<tr>
<td>Zolpidem: Extended Release</td>
<td>1.5 (1.5 – 2.0)</td>
<td>2 (1.6 – 4.5)</td>
<td>6.25 – 12.5</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Zolpidem: Sublingual (Edluar®)</td>
<td>1.4 (0.5 – 3.0)</td>
<td>2 (1.5 – 6.7)</td>
<td>5 – 10</td>
<td>Yes</td>
<td>Mainly absorbed via GI tract</td>
</tr>
</tbody>
</table>

**Side effects**

- **Subjective TST**
- **Objective WASO**

---

**Sedating Antidepressants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>T max (hours)</th>
<th>Receptor effects</th>
<th>T½ (hours)</th>
<th>Usual Dose (mg)</th>
<th>Antidepressant</th>
<th>Hypnotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>1 – 2</td>
<td>Major: H1, α1, Minor: M1</td>
<td>15</td>
<td>6 (3 – 9)</td>
<td>100 – 300</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>2 – 3</td>
<td>Major: α1, M1, Minor: H1, 5HT</td>
<td>30</td>
<td>10 – 100</td>
<td>100 – 300</td>
<td>10 – 100</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>2 – 8</td>
<td>Major: H1, M1</td>
<td>25</td>
<td>25 – 100</td>
<td>100 – 300</td>
<td>25 – 100</td>
</tr>
<tr>
<td>Trazodone</td>
<td>1 – 2</td>
<td>α1, 5HT</td>
<td>6</td>
<td>200 – 600</td>
<td>25 – 300</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>1 – 3</td>
<td>α1, 5HT</td>
<td>3 (0 – 10)</td>
<td>150 – 600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1 – 4</td>
<td>Major: H1, Minor: 5HT</td>
<td>30</td>
<td>15 – 45</td>
<td>7.5 – 15</td>
<td></td>
</tr>
</tbody>
</table>

**Fatigue, headache**

---

**Antidepressants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>T max (hours)</th>
<th>Receptor effects</th>
<th>T½ (hours)</th>
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<th>Hypnotic</th>
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<tr>
<td>Trazodone</td>
<td>1 – 2</td>
<td>Major: H1, 5HT</td>
<td>6</td>
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<td>25 – 300</td>
<td></td>
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<td>100 – 300</td>
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<tr>
<td>Trazodone</td>
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<td>α1, 5HT</td>
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<tr>
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<td></td>
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<td>30</td>
<td>15 – 45</td>
<td>7.5 – 15</td>
<td></td>
</tr>
</tbody>
</table>

**Exacerbates restless legs and sleep apnea (weight gain)**

---

**The Dual Orexin Receptor Antagonists (DORA)**

- **Suvorexant**
  - First in class
  - Well tolerated (side effects are fatigue and headache)
  - Avoid with other CNS depressants
  - Contraindicated in narcolepsy (exceedingly rare side effect)
  - Class IV controlled substance (theoretical low abuse potential)

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**Adapted from Buysse. JAMA. 2013;309(7):706–16 and Tyagi & Buysse, Chapter in PPSM 6th Edition.**
The Dual Orexin Receptor Antagonists (DORA)

**Lemborexant**
- Pivotal SUNRISE 1 phase 3 trial (n = 1,006) over 1 month showed sustained improvement in objective and subjective measures of sleep onset and maintenance without major adverse events (sleepiness, headache, abnormal dreams, sleep paralysis)
- Small study of n = 39 showed no worsening of mild OSA after lemborexant 10 mg vs. placebo
- Take at least 7 hours before planned wake time

**Cheng. J Sleep Res. 2020;e13021.**

Postural Sway from Lemborexant vs. Zolpidem

**Middle of night**

**Morning**

Larger number is greater instability.

What About Melatonin?

**Melatonin**
- Most commonly used OTC agent in USA
- Endogenous hormone secreted at night
- No definitive dose (0.1 to 10 mg) or formulation (IR, SR/CR, PD, sublingual)
- Low potency, rare side effects

**Ramelteon**
- Approved for insomnia in 7/22/05
- Improves sleep latency only
- No withdrawal
- Side effects mild (headache, dizziness, GI upset, taste disturbance)

Melatonin - an Unregulated Dietary Supplement

- Analysis of 31 supplements from 30 commercial sources.
- 72% of products did not meet label claim.
- 26% of products contained serotonin.
- Other ingredients may include lavender, chamomile, lemon balm, valerian, passion flower, skullcap, hops.

What Time to Take Melatonin?

**DLMO = dim light melatonin onset (occurs 2-3 hours prior to sleep)**

Dosing strategies:
- For sedation: take 3 to 6 mg 30 minutes before ready to sleep.
- For adjusting sleep rhythm: take 0.3 to 1 mg 2-3 hours before desired bedtime.
Sedating Antihistamines

- Widely available as OTC or prescription
- Centrally acting agents on Beers criteria
- Little data to support use
- Anticholinergic side effects most profound in older patients

Avoid in patients ≥ 65 years old

Diphenhydramine, doxylamine, dimenhydrinate, hydroxyzine, meclizine, etc.

What’s Not Recommended

Chamomile (common tea preparations)
- Kava kava (significant risk of liver toxicity)
- Alcohol (acute use reduces sleep latency, chronic use without benefits, resp. depression)
- Opioids (addiction, resp. depression, drug interactions, disrupts sleep architecture)

Valerian root (liver toxicity, withdrawal)

Marijuana

Cannabinoids
- Cannabidiol (CBD) promotes relaxation
- Cannabinol (CBN) has sedative effects
- Tetrahydrocannabinol (THC) is psychoactive

Terpenes
- Give cannabis its smell and taste
- Ubiquitous in natural plants and fruits
- May enhance effects of cannabinoids and sleep

Strains
- Sativa stimulates and energizes
- Indica relaxes and promotes sleep
- Hybrid strains

Formulations
- Vaporized
- Edibles & beverages
- Oils & tinctures
- Pills & topicals

Images from: livescience.com; vectorstock.com

Final words

Treatment Decision Pathway

- Consider combination therapy (behavioral + drug), switch drug classes, combine drug classes

Images from: NCCIH; Seed Corner; Salembotanicals.com; mumbaimirror.indiatimes.com; Pilot Online

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Clinical Pearls

For insomnia
- Very common diagnosis
- Sleep diary and trackers are very useful
- Effective treatment takes a concerted effort from patient and provider
- Do NOT forget to address secondary or comorbid conditions

For medications
- Tailor to patient preference, timing of symptoms, comorbidities
- Strive for shortest duration, lowest dose, shorter half-life drug
- OK for sustained use (acute insomnia), intermittent use (if chronic user)
- Low dose combination therapy is OK
- Be cognizant of side effects

For CBT-I/BBT-I
- First line intervention with most robust evidence
- Consider concurrent CBT-I with drug therapy
- Taper drugs during or after CBT-I
- CBT-I may simultaneously improve comorbid mood disorders

Final Thoughts...
- Reduce time in bed
- Go to bed only when sleepy
- Get out of bed when awake
- Get up at the same time every day regardless of how much sleep the night before
- Avoid long naps
- Only use the bed for sleeping
- Keep a consistent sleep-wake schedule

You will be the first point of contact!
Behavioral sleep medicine specialist are very limited.
Self-guided programs are effective and available.

Provider & Patient Education Materials

<table>
<thead>
<tr>
<th>Resource</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASM Clinical Review of Insomnia Diagnosis and Treatment (2013)</td>
<td><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632369/#R49">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632369/#R49</a></td>
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<tr>
<td>CBT-I Slide Set (from Anxiety and Depression Association of America)</td>
<td><a href="https://adaa.org/sites/default/files/Runko_177.pdf">https://adaa.org/sites/default/files/Runko_177.pdf</a></td>
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<td>CBT-I coach (phone based application)</td>
<td><a href="https://mobile.va.gov/app/cbt-i-coach">https://mobile.va.gov/app/cbt-i-coach</a></td>
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Thank You & Questions?