Insomnia Pharmacologic Treatments: When is it Appropriate?

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Objectives

• Achieve a basic understanding of the neurophysiology underlying sleep/wake cycles and the benzodiazepine receptor site.

• Become familiar with the different classes of agents used to address insomnia.

• Be able to differentiate among sedative hypnotics and gain perspective on when they should be utilized.
CBT-I vs. Pharmacotherapy

- CBT-I is a “standard of treatment” given its significantly favorable benefit : risk ratio
- All patients with chronic insomnia (at least 3x/week, > 3 months) should be offered CBT-I as a primary intervention
- CBT-I helps to avoid polypharmacy
- While comparable effects may be seen from medications in the short-term, CBT-I typically has been shown to have greater sustained benefit in the long-term

Sateia et al. Journal of Clinical Sleep Medicine, 2017

CBT-I vs. Pharmacotherapy

TST = total sleep time

Indications for Pharmacotherapy

- Acute stressor/short-term use (bereavement, loss of job, divorce, etc.)
- Unable to access CBT-I
- Inability to utilize CBT-I
- Inadequate response to CBT-I
- Adjunct to CBT-I

Indications for Pharmacotherapy

- Specific comorbidities
  - Depression, anxiety, pain/neuropathy
  - Bipolar disorder, epilepsy
- Patient preference
- Cost
- Potentially avoid patient self-medication with alcohol
  - 2005 National Sleep Foundation survey: 11% of patients reported using alcohol for this purpose
Neurotransmitters in Wake

<table>
<thead>
<tr>
<th>Neurotransmitter (Activating/Arousal Promoting)</th>
<th>Location</th>
</tr>
</thead>
</table>
| Acetylcholine                                 | - Basal forebrain  
|                                               | - Pedunculopontine tegmentum (PPT)/laterodorsal tegmentum (LDT) |
| Dopamine                                      | - Ventral periaqueductal gray matter  
|                                               | - Substantia nigra |
| Glutamate                                     | - Ascending reticular activating system  
|                                               | - Thalamocortical system |
| Histamine                                     | - Tuberomammillary nucleus (TMN)/posterior hypothalamus |
| Hypocretin/Orexin                             | - Lateral hypothalamus |
| Norepinephrine                               | - Locus ceruleus (LC) |
| Serotonin                                     | - Dorsal raphe nuclei (DR), thalamus |

The Wake “Switch”

Neurotransmitters in Sleep

<table>
<thead>
<tr>
<th>Neurotransmitter (Sleep Promoting)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Basal forebrain</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Pineal gland</td>
</tr>
<tr>
<td>GABA (located in 30% of all brain synapses)</td>
<td>Ventrolateral preoptic nucleus (VLPO)</td>
</tr>
<tr>
<td>Galanin</td>
<td>Ventrolateral preoptic nucleus (VLPO)</td>
</tr>
</tbody>
</table>

The Sleep “Switch”

“Flip-Flop Switch”

Insomnia Medication History

Prior to 20th century: Opioids, herbal preparations, bromide salts

First half of 20th century: Barbiturates

Second half of 20th century:
- Benzodiazepines (Chlordiazepoxide 1963; Flurazepam 1970)
- Benzodiazepine Receptor Agonist (Zolpidem 1992)

21st century:
- Melatonin Receptor Agonist (Ramelteon 2005)
- Tricyclic Antidepressant (Doxepin–Silenor 2010)
- Orexin Receptor Antagonist (Suvorexant 2014)
Classes of Insomnia Medications

- Benzodiazepines (BZ)
- Benzodiazepine Receptor Agonists (BzRAs)
- Antidepressants
- Antipsychotics
- Antihistamines
- Anticonvulsants
- Melatonin Receptor Agonist
- Orexin Receptor Antagonist
- “Natural” supplements/OTC Agents

FDA-Indicated Sedative Hypnotics

- Benzodiazepines
  - Estazolam (ProSom)
  - Flurazepam (Dalmame)
  - Quazepam (Doral)
  - Temazepam (Restoril)
  - Triazolam (Halcion)

- Benzodiazepine Receptor Agonists (BzRAs)
  - Eszopiclone (Lunesta)
  - Zaleplon (Sonata)
  - Zolpidem (Ambien)
  - Zolpidem Extended Release (Ambien CR)
  - Zolpidem Sublingual (Intermezzo)

- Tricyclic Antidepressant: Doxepin (Silenor)

- Melatonin Receptor Agonist: Rozerem (Ramelteon)

- Orexin Receptor Antagonist: Suvorexant (Belsomra)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage (mg)</th>
<th>Onset (min)</th>
<th>Half-life (hr)</th>
<th>Active metabolite</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam (ProSom)</td>
<td>0.5 – 2.0</td>
<td>15 – 30</td>
<td>8 – 24</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>15 – 30</td>
<td>30 – 60</td>
<td>2 – 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>SMI</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>7.5 – 30</td>
<td>20 – 45</td>
<td>15 – 40&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
<td>SMI</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>7.5 – 30</td>
<td>45 – 60</td>
<td>6 – 20</td>
<td>No</td>
<td>SOI</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>0.125 – 0.25</td>
<td>15 – 30</td>
<td>1.5 – 5</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td><strong>Benzodiazepine Receptor Agonists (BzRAs)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>1 – 3</td>
<td>60</td>
<td>6.0</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>5 – 10</td>
<td>15</td>
<td>1.0</td>
<td>No</td>
<td>SOI, SMI</td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>5 – 10</td>
<td>30</td>
<td>1.5 – 4.5</td>
<td>No</td>
<td>SOI</td>
</tr>
<tr>
<td>Zolpidem ER (Ambien CR)</td>
<td>6.25 – 12.5</td>
<td>90</td>
<td>1.6 – 4.0</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td>Zolpidem SL (Intermezzo)</td>
<td>1.75 – 3.5</td>
<td>35</td>
<td>1.4 – 3.6</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td><strong>Tricyclic Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin (Silenor)</td>
<td>3 – 6</td>
<td>210</td>
<td>15.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>SMI</td>
</tr>
<tr>
<td><strong>Melatonin Receptor Agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelteon (Rozerem)</td>
<td>8</td>
<td>30 – 90</td>
<td>1 – 2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>SOI</td>
</tr>
<tr>
<td><strong>Orexin Receptor Antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suvorexant (Belsomra)</td>
<td>10 – 20</td>
<td>120</td>
<td>12</td>
<td>No</td>
<td>SOI, SMI</td>
</tr>
</tbody>
</table>

<sup>* = parent compound; <sup>a</sup> = active metabolite; SMI = sleep maintenance insomnia; SOI = sleep onset insomnia</sup>
**GABA<sub>A</sub> Receptor Complex**

![Diagram of GABA<sub>A</sub> receptor complex](image)

*Berry, Fundamental Sleep Medicine, 2012*

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**BZ & BzRAs: Effects on Sleep**

- Improved sleep continuity
  - Decreased sleep latency (SL)
  - Increased total sleep time (TST)
  - Decreased wake after sleep onset (WASO)
- PSG changes
  - Decreased stage N3 (less with BzRAs)
  - Reduced amplitude of slow waves
  - Increased sleep spindles (BZ)
- Decreased REM sleep (less with BzRAs)
- Decreased periodic limb movements (BzRAs)
BZ & BzRAs: Side Effects

- Residual daytime sedation
- Dose-related anterograde amnesia
- Discontinuation phenomenon:
  - Rebound insomnia (worsening symptoms)
  - Withdrawal (new symptoms)
  - Insomnia recurrence
- Respiratory suppression (minor effect, more with long-acting BZ)

BZ & BzRAs: Side Effects

- Older adults with increased sensitivity to BZ’s and decreased metabolism
- “Increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults”
- American Geriatric Society Beers Criteria (potentially inappropriate medication use in older adults) recommended avoiding BZs for insomnia and BzRAs being limited to < 90 days

BzRAs: Warnings

- In March 2007, FDA required all manufacturers of BzRA hypnotics to list complex sleep-related behaviors (walking, eating, driving, sexual behaviors) in labeling.
- Zolpidem (Ambien) is the BzRA most often associated with sleepwalking and the sleep-related eating disorder, but these manifestations can happen with other BzRAs.
- Risk factors:
  - Higher doses (2-3 times the indicated clinical dose)
  - Prior history of parasomnias
  - Prior history of brain injury
  - Concurrent use with alcohol

Berry, *Fundamental Sleep Medicine*, 2012

Hypnotics and Suicidality

- In 2006, FDA mandated warnings of suicidal thoughts in primarily depressed patients be included in prescribing information for BzRAs.
- Hypnotics subsequently approved have included the warning (ramelteon, doxepin, suvorexant).
- None of the studies reviewed adequately controlled for depression or possible substance abuse.
- Suicidal ideation ≠ suicide deaths

Hypnotics and Mortality

- Several studies noting association with mortality or cancer
- Kripke 2012: “Patients with prescriptions for hypnotics had approximately 4.6 times the hazard of dying over an average observation period of 2.5 years …”
- Dose-response effect was seen
- Even in lowest category of hypnotic use (< 18 hypnotic pills per year)
- Zolpidem and Temazepam were most prescribed

Survival Curves

Kripke, BMJ Open, Feb 2012
Hypnotics-Mortality: Limitations

- Co-morbidities
- 2012 study: Unable to control for depression, anxiety, and emotional factors
- Epidemiologic vs. controlled trials
- Medications have changed from study to study
- Unknown whether controls/non-controls prescribed other medications for insomnia, or whether taking OTC meds for this purpose

BzRAs: General Considerations

- Use lowest dose for shortest time possible
- Take BzRAs on an empty stomach
- BzRAs are not recommended in pregnant or nursing women
- BzRAs are not recommended in advanced liver disease
- Rapid reduction in dose or withdrawal can cause withdrawal symptoms including rebound insomnia
- Use long-acting BZ with caution in patients with OSA or lung disease (COPD)
- Potential for abuse or dependence thought to be low for BzRAs

Berry, Fundamental Sleep Medicine, 2012
Antidepressants

- Hypnotic properties most strongly related to antagonism of serotonin 5-HT₂, histamine H₁, and α1 adrenergic receptors
- Commonly used medications include trazodone (Desyrel), mirtazapine (Remeron), amitriptyline (Elavil), and doxepin (Silenor)
- Doses used for insomnia are much lower than those used for depression
- Doxepin (Silenor) was FDA-approved in 2010 for maintenance insomnia at low doses (3 and 6 mg—histamine selective)

Antidepressants

- Few studies—strongest evidence for efficacy is for tricyclics (doxepin, amitriptyline, trimipramine)
- Specific adverse effects need to be considered:
  - Tricyclics: anticholinergic side effects
  - Trazodone (Desyrel): hypotension, rare priapism
  - Mirtazapine (Remeron): weight gain
  - SSRIs: insomnia, exacerbate RLS
Antipsychotics

- Atypical antipsychotics such as quetiapine (Seroquel) and olanzapine (Zyprexa) have indications for psychotic disorders and mania
- Antagonize dopamine, histamine (H₁), serotonin (5HT₂A), muscarinic, cholinergic, and α₁ receptors
- Similar to antidepressants, used at lower doses for treating insomnia: quetiapine 25-200 mg; olanzapine 2.5-20 mg
- Olanzapine (Zyprexa) has longer half-life than quetiapine (Seroquel): 21-54 hours versus 6-7 hours

Antipsychotics

- Studies in patient populations other than primary insomnia:
  - Decreased sleep latency
  - Olanzapine may increase deeper NREM sleep
  - Quetiapine may reduce REM sleep
- Significant potential risks:
  - Akathisia
  - Weight gain
  - Orthostatic hypotension
  - Contribution to metabolic syndrome
- Antipsychotics should generally be reserved for cases with primary psychiatric disorders
Antihistamines

- Diphenhydramine (Benadryl), Doxylamine (Nyquil), and Hydroxyzine (Vistaril) are the most commonly used for insomnia.

- Tolerance to daytime sedation and similar decrease in effectiveness as a hypnotic can develop in four days.\(^1\)

- Anticholinergic activity needs to be considered, especially in the elderly.


Anticonvulsants

- Pregabalin (Lyrica) and gabapentin (Neurontin) bind to voltage-gated calcium channels—diminish release of glutamate and norepinephrine.

- Tiagabine (Gabatril) inhibits GABA re-uptake, increasing extracellular GABA.

- Carry FDA indications for partial seizures, pain, fibromyalgia (pregabalin).

- Gabapentin (Neurontin) commonly used at doses of 100-900 mg for insomnia.

- Common adverse effects include sedation, dizziness, ataxia.

Krystal, *Principles and Practice of Sleep Medicine, 5th ed.*, Chapter 82.
Melatonin

- 3.1 million U.S. individuals (1.3%) reported using melatonin in 2012
- Adverse effects: headaches, nightmares
- OTC melatonin banned in UK, EU, Japan, Australia, and most recently Canada
- A recent study found that melatonin content ranged from -83% to +478% of what was noted on the label; content did not meet 10% margin label claim in more than 71% of supplements
- 26% of supplements tested found to contain serotonin
- Best used as a chronobiotic for circadian rhythm disorders

Grigg-Damberger M, Ianakieva D. Journal of Clinical Sleep Medicine, 2017

Melatonin Receptor Agonist

- **Ramelteon (Rozerem)** became first melatonin receptor agonist approved for treating insomnia (2005)
- 17 x more potent at melatonin type I (decreased waking signal) and type II (circadian rhythms) receptors
- Primary benefit on sleep latency
- Non-scheduled medication—lacks potential for abuse or dependence
- Adverse effects: nausea, headache, fatigue
Orexin Receptor Antagonist

- **Suvorexant (Belsomra)** became first orexin receptor antagonist approved for treating insomnia (August 2014)
- Highly selective, antagonizes two G-protein-coupled orexin receptors
- Indicated for both sleep latency and maintenance
- Metabolism may be affected by sex and body mass index
- Adverse effects: somnolence, sleep paralysis, sleep-related hallucinations, cataplexy-like symptoms, suicidal ideation (dose-dependent)

Sedative Hypnotics: General Considerations

- Consider pharmacokinetic and pharmacodynamic properties, cost, side effects, past treatment response, and duration of use
- Do not combine with alcohol; use caution with other sedatives
- Consider patient preference for treatment modality
- Evaluate contributions to insomnia from other medications
- Make sure patients have dedicated an adequate amount of time to sleep
- Discuss specific side effects (for example, bitter aftertaste with eszopiclone)
- Always attempt to supplement or transition to CBT-I for chronic insomnia
Comorbid Conditions

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Medication Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Mirtazapine, SSRI</td>
</tr>
<tr>
<td>Anxiety/Panic</td>
<td>Mirtazapine, SSRI, benzodiazepine, Gabapentin</td>
</tr>
<tr>
<td>Pain/Neuropathy</td>
<td>Gabapentin, Pregabalin</td>
</tr>
<tr>
<td>Substance Addiction/Dependence</td>
<td>Ramelteon, Doxepin, Gabapentin</td>
</tr>
</tbody>
</table>

Sedative Hypnotics: Selection

- Evaluate symptom pattern: sleep onset insomnia, sleep maintenance insomnia, or both?
- Choose among recommendations from the AASM February 2017 clinical practice guideline for pharmacologic treatment of chronic insomnia
AASM Recommendations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sleep onset insomnia (Mean reduction)</th>
<th>Sleep maintenance insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone</td>
<td>X (14 minutes)</td>
<td>X (28-57 min longer TST; 10-14 min less WASO)</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>X (5-12 minutes)</td>
<td>X (29 min longer TST; 25 min less WASO)</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>X (10 minutes)</td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>X (37 minutes)</td>
<td>X (99 min longer TST)</td>
</tr>
<tr>
<td>Triazolam</td>
<td>X (9 minutes)</td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td>X (9 minutes)</td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td></td>
<td>X (26-32 min longer TST; 22.5 min less WASO)</td>
</tr>
<tr>
<td>Suvorexant</td>
<td></td>
<td>X (10 min longer TST; 16-28 min less WASO)</td>
</tr>
</tbody>
</table>

Sateia et al. *Journal of Clinical Sleep Medicine, 2017*  
TST = total sleep time; WASO = wake after sleep onset

AASM Recommendations

- The following were not recommended for treating either sleep onset or sleep maintenance insomnia:
  - Diphenhydramine
  - Melatonin
  - L-tryptophan
  - Valerian
  - Tiagabine
  - Trazodone
Sedative Hypnotics: Selection

- Gauge efficacy as well as side effects within one month by monitoring change in patient report and if possible an objective measure such as ISI (insomnia severity index)
- If patient reports improvement and/or ISI score has decreased by 50%, assess whether there is an ongoing need for the use of medication, or if there is an opportunity to begin weaning medication and/or to begin implementing CBT-I
  - If the patient notes a continued desire for a hypnotic, revisit this need at least every 3 months to assess whether tapering is feasible
  - Tapering should be gradual and flexible

Sedative Hypnotics: ISI

**Insomnia Severity Index Test**

The Insomnia Severity Index is a self-reported questionnaire that consists of seven items to measure subjective perceptions of sleep disturbance.

<table>
<thead>
<tr>
<th>Item</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty falling asleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Difficulty staying asleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Problem waking up too early</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. How satisfied/dissatisfied are you with your current sleep pattern?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5. In what aspect do you consider your sleep problem to interfere with your daily functioning (e.g., daytime fatigue, mood, memory, etc.)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. How satisfied are you with your current sleep problem?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


Sedative Hypnotics: Selection

- If improvement is not noted in the first month (either via patient report or less than 50% decrease in ISI), consider an increase in dose of the patient’s current medication, or a switch to an alternate hypnotic.
- If improvement is still not noted within another 2-4 weeks, consideration could be given to the possibility of combination therapy.
- CBT-I should especially be encouraged throughout, but especially emphasized in the case of multiple medication failures.