Meeting the Challenges of Insomnia in Your Patient Population
Co-Management Strategies, Standards of Care, and Emerging Pharmacotherapeutic Options

Karl Doghramji, MD
Professor of Psychiatry, Neurology, and Medicine
Medical Director, Jefferson Sleep Disorders Center
Thomas Jefferson University
Philadelphia, Pennsylvania

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Faculty Disclosure

• Dr. Doghramji: Consultant—Eisai, Purdue, Merck, Pfizer; Stock—Merck.
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – Dr. Doghramji will be discussing off-label use of medications in this presentation and will identify those medications.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
• This activity has been independently reviewed for balance.
Learning Objectives

• Describe the relationship between insomnia and other psychiatric disorders in terms of bidirectional causality and the challenges of co-treatment
• Discuss current clinical guidelines for the management of chronic insomnia, recommended standards of care, and limitations of available therapies
• Evaluate clinical evidence surrounding emerging insomnia pharmacotherapies, including safety, efficacy, adverse events, and risk-to-benefit ratios
Prevalence of Insomnia
Second Highest Health-Related Complaint Worldwide

- Never: 2%
- Rarely: 4.4%
- A Few Nights per Month: 25%
- A Few Nights per Week: 21%
- Every Night: 33%

Case

- 71-year-old c/o unrefreshing sleep following retirement
- Onset 4 months ago
- Frequency 4 to 5 nights/week
- Mind “spins” at bedtime
- Feels washed out during day; low energy, moody, irritable
- No medical contributors
- MSE: Psychomotor slowing; mood “fine”. Affect restricted, no h/s ideation, sensorium clear. Cognitive functions intact
71-year-old c/o unrefreshing sleep 4 to 5 nights/week after retirement, 4 months ago; washed out, low energy, moody, irritable, meets MDD criteria.

What additional criterion must be met to satisfy criteria for DSM-5 insomnia disorder?

A. Duration of insomnia must be > 6 months
B. Difficulty with insomnia must occur nightly
C. Sleep laboratory confirmation of a sleep latency (time to fall asleep) > 1 hour
D. Must not meet criteria for MDD
E. Meets diagnostic criteria for insomnia disorder

MDD = major depressive disorder.
Insomnia Disorder

A. Dissatisfaction with sleep quantity or quality with ≥ 1 of the following:
   1. Difficulty initiating sleep (children: w/o caregiver intervention)
   2. Difficulty maintaining sleep (children: w/o caregiver intervention)
   3. Early morning awakening w/ inability to return to sleep

B. Significant distress or impairment

C. > 3 nights/week

D. > 3 months

E. Adequate opportunity for sleep

Specify if:
   – With non-sleep disorder mental comorbidity
   – With other medical comorbidity
   – With other sleep disorder

Criteria F, G, and H not shown; not all specifiers shown.

Insomnia and Hyperarousal

**Hyperarousal**

- HPA axis activation
- Sympathetic activation
- Heightened brain metabolism
- EEG arousal
- Increased body metabolic rate
- Cognitive arousal

EEG = electroencephalogram; HPA = hypothalamic pituitary adrenal.
Impairments Associated with Insomnia

- Diminished ability to enjoy family and social relationships
- Decreased quality of life
- Increased absenteeism and poor job performance
- Motor vehicle crashes
- Increased risk of falls
- Increased health care costs
- Impaired concentration and memory
- Increased incidence of pain
- Enhanced risk of present and future psychiatric disorders
- Hypertension
- Diabetes
- Increased mortality
Psychiatric Disorders Comorbid with Insomnia Point Prevalence

- Drug Abuse: 4.2%
- Other Psychiatric Disorders: 5.1%
- Alcohol Abuse: 7.0%
- Dysthymia: 8.6%
- Major Depression: 14.0%
- Anxiety Disorder: 23.9%
- No Psychiatric Disorder: 59.5%

N=580.
Complex Relationship between Insomnia and Mood Disorders

• Insomnia
  – Is a common complaint in MDD
  – Is more likely to emerge prior to, than during or after, MDD first episode or recurrence
  – Is associated with higher rates of lifetime and current MDD and suicide
  – Its presence and persistence predict future MDD
  – Predicts poorer outcome in MDD (persistence, chronicity, suicidality)
  – Predicts the onset of mania in bipolar depression

Sleep Disturbances as Residual Symptoms following Acute MDD Remission

Patients with major depressive disorder (N=215) received fluoxetine 20 mg for 8 weeks. Presence of residual symptoms not predicted by baseline demographic characteristics or Axis I and Axis II coexisting conditions.

Selected Comorbid Conditions and Treatment Examples

- Obstructive sleep apnea
  - CPAP, BIPAP, oral appliances, upper airway surgery
- Restless legs syndrome
  - Alpha 2-delta ligands, dopaminergic agents
- MDD
  - Antidepressants
- GERD
  - Proton pump inhibitors, H2 receptor blocker
- Shift work disorder
  - Bedtime melatonin, modafinil/armodafinil prior to shift, bright light therapy
- Medication-induced insomnia
  - Dosage or medication change

BIPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; GERD = gastroesophageal reflux disease.
Obtain details about course of insomnia

Is insomnia contributing to decreased daytime functioning and quality of life or worsening of chief complaint?

Yes

Is insomnia associated with comorbid medical or psychiatric condition?

Yes

Treat with behavioral therapy

No

Treat with behavioral and/or pharmacologic therapy

No

Does insomnia occur in isolation?

Yes

Treat with behavioral therapy

No

Treat with behavioral and/or pharmacologic therapy

Insomnia Disorder

Possible short sleeper; supportive reassurance

Is insomnia contributing to decreased daytime functioning and quality of life or worsening of chief complaint?

No

Treat comorbid condition first

Is insomnia persistent?

Yes

Is use of insomnia medication unsafe in this patient?

Yes

No further treatment needed

No

Treat with behavioral and/or pharmacologic therapy

Treatments for Insomnia

- Cognitive-behavioral therapy
- Alternative nutraceuticals
- Nonprescription pharmacologic agents (over-the-counter)
- Prescription pharmacologic agents
## Psychological and Behavioral Treatments for Primary Insomnia

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus control therapy*</td>
<td>If unable to fall asleep within 20 minutes, get OOB and repeat as necessary</td>
</tr>
<tr>
<td>Relaxation therapies*</td>
<td>Biofeedback, progressive muscle relaxation</td>
</tr>
<tr>
<td>Restriction of time in bed (sleep restriction)</td>
<td>Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Talk therapy to dispel unrealistic and exaggerated notions about sleep</td>
</tr>
<tr>
<td>Paradoxic intention</td>
<td>Try to stay awake</td>
</tr>
<tr>
<td>Sleep hygiene education</td>
<td>Promote habits that help sleep; eliminate habits that interfere with sleep</td>
</tr>
<tr>
<td>CBT*</td>
<td>Combines sleep restriction, stimulus control, and sleep hygiene education with cognitive therapy</td>
</tr>
</tbody>
</table>

*Standard Treatment according to American Academy of Sleep Medicine.
CBT = cognitive-behavioral therapy; OOB = out of bed.
Meta-analytic Support for Efficacy of CBT-i

• 20 RCTs (1162 participants [64% female; mean age, 56 years])
• Approaches to CBT-i incorporated at least 3 of the following: cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation
• At the posttreatment time point
  – SOL improved by 19.03 (95% CI, 14.12 to 23.93) minutes,
  – WASO improved by 26.00 (CI, 15.48 to 36.52) minutes,
  – TST improved by 7.61 (CI, 0.51 to 15.74) minutes, and
  – SE% improved by 9.91% (CI, 8.09% to 11.73%)
• Changes seemed to be sustained at later time points. No adverse outcomes were reported

CBT-i = cognitive-behavioral therapy for insomnia; RCT = randomized controlled trial; SE% = sleep efficiency; SOL = sleep onset latency; TST = total sleep time; WASO = wake after sleep onset.
The Dos of Sleep Hygiene

- Get OOB at the same time every morning
- Increase exposure to bright light during the day
- Establish a daily activity routine
- Exercise regularly in the morning and/or afternoon
- Set aside a worry time
- Establish a comfortable sleep environment
- Do something relaxing prior to bedtime
- Try a warm bath
The Don’ts of Sleep Hygiene

Avoid…

- Alcohol
- Caffeine, nicotine, and other stimulants
- Exposure to bright light during the night
- Exercise within 3 hours of bedtime
- Heavy meals or drinking within 3 hours of bedtime
- Using your bed for things other than sleep (or sex)
- Napping, unless a shift worker
- Watching the clock
- Trying to sleep
- Noise
- Excessive heat/cold in room
Effect of Blue Light Blocking on Sleep
Factors favoring the initial utilization of CBT over pharmacology in insomnia management include:

A. Need for more rapid clinical improvement
B. No comorbid medical conditions
C. History of, or present, substance use disorder
D. Time limitation
# Pharmacotherapy vs CBT for Insomnia

<table>
<thead>
<tr>
<th>Start with Pharmacotherapy</th>
<th>Start with CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of specific cognitive, or behavioral factors</td>
<td>Need for sustained clinical improvement</td>
</tr>
<tr>
<td>Need for rapid improvement</td>
<td>History of, or present, substance use/abuse</td>
</tr>
<tr>
<td>Time limitations</td>
<td>Multiple comorbid medical conditions</td>
</tr>
<tr>
<td>Limited finances</td>
<td>Hypnotic discontinuation</td>
</tr>
<tr>
<td>Shortage of trained therapists</td>
<td></td>
</tr>
</tbody>
</table>
Dietary Supplements

• Utilized by more than 50% of the US adult population
• Dietary substance
  – Supplements existing diet
  – Contains
    • Vitamin
    • Mineral
    • Herb or other botanical
    • Amino acid
    • Others
  – Taken orally

Nonprescription Agents for Insomnia: Limited Evidence for Hypnotic Efficacy

<table>
<thead>
<tr>
<th>Product</th>
<th>Latin Name (or Generic Name)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valerian root</td>
<td>V. officinalis L.</td>
<td>Restless sleep, gastrointestinal upset, headache, contact allergies, mydriasis, possible carcinogen, possible hepatotoxicity</td>
</tr>
<tr>
<td>First-generation histamine-1-receptor antagonists</td>
<td>Diphenhydramine hydrochloride, diphenhydramine citrate, doxylamine succinate</td>
<td>Vomiting, depression, malaise, drowsiness, impaired mentation, extrapyramidal reactions, rhabdomyolysis, dry mouth, weakness, gastrointestinal upset, headache, impotence, urinary retention, increased intraocular pressure</td>
</tr>
</tbody>
</table>
Nonprescription Agents for Insomnia: Insufficient Evidence for Hypnotic Efficacy

<table>
<thead>
<tr>
<th>Product</th>
<th>Latin Name</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hops</td>
<td><em>Humulus lupulus</em></td>
<td>Unknown</td>
</tr>
<tr>
<td>Chamomile</td>
<td><em>Matricaria recutita</em></td>
<td>Vomiting, allergic reactions</td>
</tr>
<tr>
<td>Lemon balm</td>
<td><em>Melissa officinalis</em></td>
<td>Unknown</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td><em>Hypericum perforatum</em></td>
<td>Fatigue, gastrointestinal upset, dizziness, anxiety, headache, photosensitivity, phototoxicity</td>
</tr>
<tr>
<td>Patrinia root</td>
<td><em>Patrinia Scabiosaefolia Fisch</em></td>
<td>Nausea</td>
</tr>
<tr>
<td>Niacin</td>
<td>Niacin, niacinamide, vitamin $B_3$</td>
<td>None known at recommended daily allowances</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium</td>
<td>None known at recommended daily allowances</td>
</tr>
<tr>
<td>Vitamin $B_{12}$</td>
<td>Vitamin $B_{12}$, cyanocobalamin, hydroxocobalamin, methylcobalamin</td>
<td>None known at recommended hydroxocobalamin, daily allowances</td>
</tr>
<tr>
<td>Diet changes</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Yoku-kan-san-ka chimpi-hange</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Nonprescription Agents for Insomnia:
No Evidence of Hypnotic Efficacy or Significant Safety Concerns

<table>
<thead>
<tr>
<th>Product</th>
<th>Latin or Scientific Name</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passionflower</td>
<td><em>Passiflora incarnata</em></td>
<td>Dizziness, confusion, ataxia, possible prolonged QT</td>
</tr>
<tr>
<td>Californian poppy</td>
<td><em>Eschscholzia californica</em></td>
<td>Unknown</td>
</tr>
<tr>
<td>Wild lettuce</td>
<td><em>Lactuca virosa</em></td>
<td>Possible hallucinogenic</td>
</tr>
<tr>
<td>Scullcap</td>
<td></td>
<td>Seizures, possible hepatotoxicity</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>None known at recommended daily allowances</td>
</tr>
<tr>
<td>Vitamin A</td>
<td></td>
<td>None known at recommended daily allowances</td>
</tr>
<tr>
<td>5-hydroxytryptophan</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Natrum muriaticum</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Jamaican dogwood</td>
<td><em>Piscidia piscipula</em></td>
<td>Toxicity to humans</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td>Dependence, neurotoxicity, cardiotoxicity, myelosuppression, hepatotoxicity,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>respiratory depression, sedation, depression</td>
</tr>
<tr>
<td>L-tryptophan</td>
<td>L-2-amino-3-(indole-3-yl) propionic acid</td>
<td>Eosinophilia myalgia syndrome</td>
</tr>
<tr>
<td>Kava kava</td>
<td><em>Piper methysticum</em></td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>

Melatonin Meta-analysis in Primary Sleep Disorders

- 19 placebo-controlled studies, 1683 participants
- Melatonin demonstrated efficacy in
  - Reducing sleep latency (WMD = 7.06 minutes)
  - Increasing total sleep time (WMD = 8.25 minutes)
    - Effects magnified with longer duration and higher doses
  - Improved sleep quality (standardized mean difference = 0.22)
    - No significant effects of trial duration and melatonin dose

WMD = weighted mean difference.
Melatonin Impairs Glucose Tolerance

Comparison between the effects of placebo and melatonin administrations on plasma glucose and insulin concentrations in response to an oral load of glucose (75 g) performed in the morning (09:00) and evening (21:00). TF = time fasting; T30, 60, 90, 120, and 180, time after OGTT (min); AUC_{120}, paired t-test for AUC (melatonin and placebo) calculated with 120 min; ANOVArm, two-way ANOVA for time and treatment effects with repeated measurements. When ANOVA was significant, paired t-test was used to evaluate times in which variations were different. *Different from placebo at that time, P<.05.

Prescription Agents for Insomnia

- FDA-non-approved for insomnia
  - Sedating antidepressants
  - Antipsychotics
  - Anticonvulsants
- FDA-approved hypnotics
  - Benzodiazepine receptor agonists
    - Benzodiazepines
    - Nonbenzodiazepines
  - Melatonin receptor agonist
  - H1 receptor antagonist
  - Orexin receptor antagonist
Low Dose Sedating Antidepressants for Insomnia

- Trazodone, doxepin, mirtazapine, paroxetine
- Advantages
  - Sedating side effects
  - Low abuse risk
  - Large dose range
- Disadvantages
  - Efficacy not well established for insomnia
  - Side effects include daytime sedation, anticholinergic effects, weight gain, drug-drug interactions

These agents are not FDA approved for insomnia.

Low Dose Atypical Antipsychotics for Insomnia

• Quetiapine, olanzapine
• Advantages
  – At appropriate doses, effective for psychotic disorders
  – Low abuse potential
  – Sedation
• Disadvantages
  – Not well investigated in insomnia disorder
  – Daytime sedation, anticholinergic effects, weight gain
  – Risk of extrapyramidal symptoms, possible tardive dyskinesia
  – Glucose and lipid abnormalities

These agents are not FDA approved for insomnia.
Which of the following brain neurotransmitters is involved in sleep generation?

A. Histamine
B. GABA
C. Serotonin
D. Norepinephrine
E. Epinephrine
Arousal and Sleep-Promoting Systems

Arousal

Sleep

5-HT = serotonin; Ach = acetylcholine; BF = basal forebrain; DA = dopamine; DR = dorsal raphe nucleus; GABA = gamma-aminobutyric acid; Gal = galanin; LC = locus coeruleus; LH = lateral hypothalamic; MCH = melanin-concentrating hormone; NE = norepinephrine; ORX = orexin; PPT/LDT = pedunculopontine and laterodorsal tegmental; TMN = tuberomammillary nucleus; VLPO = ventrolateral preoptic nucleus; vPAG = ventral periaqueductal gray matter.

Orexins/Hypocretins

• Hypothalamic peptides
  – Localized in the dorsolateral hypothalamus
  – Wide projections throughout the brain
  – Projections found in the spinal column

• Peptide neurotransmitters
  – Arousal
  – Locomotion
  – Metabolism
  – Increase blood pressure/heart rate

Elevated Plasma Orexin-A Levels in Insomnia Disorder

228 patients with insomnia disorder vs 282 normal sleepers.
## Benzodiazepine Receptor Agonists: Benzodiazepines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Range† (mg)</th>
<th>Onset of Action</th>
<th>Half-life (h)</th>
<th>Short-term Limitation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estazolam</td>
<td>0.5–2</td>
<td>Rapid</td>
<td>10–24</td>
<td>Yes</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15–30</td>
<td>Rapid</td>
<td>47–100</td>
<td>Yes</td>
</tr>
<tr>
<td>Quazepam</td>
<td>7.5–15</td>
<td>Rapid</td>
<td>39–100</td>
<td>Yes</td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5–15</td>
<td>Slow–Intermediate</td>
<td>9.5–12.4</td>
<td>Yes</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25–0.50</td>
<td>Rapid</td>
<td>1.5–5.5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

A 60-year-old man complains of insomnia; he falls asleep rapidly after going to bed, but wakes up repeatedly starting at 1 AM, feeling fatigued the next day.

What is the least appropriate medication?

A. Zolpidem ER
B. Ramelteon
C. Eszopiclone
D. Doxepin low dose
E. Suvorexant
## Selective Benzodiazepine Receptor Agonists

<table>
<thead>
<tr>
<th></th>
<th>Zaleplon</th>
<th>Zolpidem</th>
<th>Zolpidem ER</th>
<th>Eszopiclone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hours)</strong></td>
<td>1</td>
<td>1.6</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Half-life (hours) [elderly]</strong></td>
<td>1</td>
<td>2.5 [2.9]</td>
<td>2.8 [2.9]</td>
<td>6 [9]</td>
</tr>
<tr>
<td><strong>Sleep Latency</strong></td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Wake after Sleep Onset</strong></td>
<td>--</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Total Sleep Time</strong></td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

## Newer Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Ramelteon</th>
<th>Doxepin</th>
<th>Suvorexant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Melatonin receptor agonist</td>
<td>H1 receptor antagonist</td>
<td>Dual orexin receptor antagonist</td>
</tr>
<tr>
<td>Dose (mg) [elderly]</td>
<td>8</td>
<td>3, 6 [3]</td>
<td>10–20</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hours)</td>
<td>0.75</td>
<td>3.5</td>
<td>2</td>
</tr>
<tr>
<td>Half-life (hours) [elderly]</td>
<td>1–2.6</td>
<td>15.3</td>
<td>12</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>↓</td>
<td>--</td>
<td>↓</td>
</tr>
<tr>
<td>Wake after Sleep Onset</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>--</td>
<td>--</td>
<td>↑</td>
</tr>
<tr>
<td>Schedule</td>
<td>None</td>
<td>None</td>
<td>IV</td>
</tr>
</tbody>
</table>

# Zolpidem Variants

<table>
<thead>
<tr>
<th></th>
<th>Zolpidem</th>
<th>Zolpidem SL</th>
<th>Zolpidem SL</th>
<th>Zolpidem Oral Spray</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (mg) [elderly]</strong></td>
<td>5,10 [5]</td>
<td>5,10 [5]</td>
<td>Men: 3.5; Women: 1.75 [1.75]</td>
<td>5,10 [5]</td>
</tr>
<tr>
<td>MOTN, 4 hours remaining until AM awakening</td>
<td></td>
<td></td>
<td>MOTN, 4 hours remaining until AM awakening</td>
<td></td>
</tr>
<tr>
<td><strong>$T_{max}$ (hours)</strong></td>
<td>1.6</td>
<td>1.4</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Half-life (hours) [elderly]</strong></td>
<td>2.5 [2.9]</td>
<td>2.9</td>
<td>2.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

MOTN = middle-of-the-night; SL = sublingual.
Adverse Effects of Hypnotics

- Benzodiazepine receptor agonists
  - Daytime sedation, psychomotor and cognitive impairment (depending on dose and half-life)
  - Rebound insomnia
  - Respiratory depression in vulnerable populations
  - DEA Schedule IV
- Melatonin receptor agonist
  - Headache, somnolence, fatigue, dizziness
  - Not recommended for use with fluvoxamine due to CYP 1A2 interaction
- H1 receptor antagonist
  - Somnolence/sedation
  - Nausea
  - Upper respiratory tract infection
- Orexin receptor antagonist
  - Somnolence
  - Risk of impaired alertness and motor coordination, including impaired driving; increases with dose
  - Contraindicated in narcolepsy
  - DEA Schedule IV

Driving Safety:
MOTN Low-Dose Zolpidem SL

SDLP = standard deviation of lateral position; SL = sublingual; ZOP = zopiclone; ZST = zolpidem sublingual tablet.
The risk of parasomnias during hypnotic use is enhanced by:

A. Co-administration with sedating agents
B. MDD
C. Younger age
D. Female gender
E. Lower socioeconomic status
Zolpidem-Induced Parasomnias

- Spontaneous reports
- Sleep-driving; preparing and eating food, making phone calls, or having sex
- Amnesia for events
- Risk factors
  - Co-use of alcohol or sedatives
  - Use at doses exceeding the maximum recommended dose
  - Sleep disorder: OSA or PLMS
  - H/O parasomnia
  - Ingestion at unusual bedtime
  - Ingestion while agitated or not typically asleep
  - Ingestion when sleep deprived
  - Poor management of pill bottles
  - Living alone

PLMS = periodic limb movements of sleep; OSA = obstructive sleep apnea.
Selected Considerations in Choosing a Hypnotic Agent

- Initiation or maintenance insomnia
  - Initiation: Zaleplon, zolpidem, ramelteon
  - Maintenance: Doxepin low dose, zolpidem SL MOTN
  - Initiation and maintenance: Zolpidem ER, eszopiclone, suvorexant
- Respiratory compromise; safety in mild to moderate OSA/COPD
  - Ramelteon, suvorexant
- Abuse potential
  - Lowest: Ramelteon, doxepin
- Prior failure of selected medication
- Patient preference

COPD = chronic obstructive pulmonary disease.
Insomnia Complaints in MDD

- 80% inpatients
- 40% outpatients
- Reduced quantity
  - Initial
  - Middle
  - Early morning awakening
- Reduced quality
- Unrefreshing sleep

RCTs of Hypnotic Agents in Conjunction with SSRI in MDD

- Zolpidem 10 mg vs PBO for persistent insomnia following SSRI (fluoxetine, sertraline, paroxetine) Rx for MDD or dysthymia
  - Improvement in subjective sleep measures
- Zolpidem ER 12.5 mg plus escitalopram vs PBO plus escitalopram in MDD patients with insomnia
  - Improvement in subjective sleep measures
  - Improvement in next day functioning
- Eszopiclone 3 mg plus fluoxetine vs PBO plus fluoxetine in MDD patients with insomnia
  - Improved subjective sleep measures
  - Improved quality of life
  - Higher overall MDD remission rates
- Suvorexant 10 to 20 mg vs PBO for persistent insomnia following stable antidepressant management for MDD
  - Study in progress at 3 sites

Hypnotics are not FDA indicated for treatment of MDD.

PBO = placebo; SSRI = selective serotonin reuptake inhibitor.

Hypnotics Under Development

- Dual and single orexin receptor antagonists
  - Lemborexant
  - TCS-OX2-29
  - Seltorexant

- Benzodiazepine receptor agonists
  - Controlled release zaleplon
  - Inhaled zaleplon
  - Lorediplon
  - EVT-201

- Melatonin receptor agonists
  - Controlled release melatonin for elderly (Circadin®)
  - Piromelatine
  - Others

- Beta-blockers
- Histamine H1 antagonists
- 5-HT$_{2A}$ receptor antagonists
- Adenosine receptor agonists
- Angiotensin II receptor 1 antagonist
- Cannabinoid agonist
Lemborexant

- Dual orexin receptor antagonist; is thought to regulate sleep and wake by dampening wakefulness without hindering the ability to awaken to external stimuli
- Controlled study in insomnia disorder demonstrated improvement in sleep latency and continuity
- Phase 2 study under way for irregular sleep-wake rhythm disorder and mild to moderate Alzheimer’s dementia
- New drug application (NDA) submitted to FDA for insomnia disorder January 15, 2019
  - SUNRISE 1 and SUNRISE 2; N=~2000
  - SUNRISE 1: 1-month, double-blind, placebo-controlled study; Phase 3 head-to-head comparison vs zolpidem ER; objectively assessed sleep parameters (time to sleep onset, sleep efficiency, and wake after sleep onset)
  - SUNRISE 2: 12-month study; subjectively assessed for ability to fall asleep and stay asleep based on patient self reports (sleep diaries)
- Adverse effects: Somnolence, headache, sleep paralysis, rapid eye movements abnormal sleep, nightmare, abnormal dreams, dizziness, back pain, hypnagogic hallucinations, myalgia, feeling drunk

Lemborexant Morning Driving Performance and MOTN Body Sway

*A unit of body sway is defined as 1/3 degree angle of arc movement of the ataxiameter. Dashed horizontal line indicates threshold for clinically meaningful change from baseline.

The Future in Insomnia Treatments

- Refining pharmacotherapy
  - Higher efficacy, remission (cure?)
  - Fewer side effects
  - Novel mechanisms
  - Selection of hypnotic based on receptor profile or comorbid conditions
- Development of hypnotic devices
  - Mobile electronics to stratify and treat insomnia
  - Thermal devices
- Online CBT
- Improving health outcomes through insomnia treatment
Conclusions

• Insomnia is highly prevalent in psychiatric patients
• It is associated with psychological and physical impairments and enhances the risk of psychiatric conditions
• Management begins with a systematic evaluation followed by treatment of comorbidities
• Whenever possible, treat the comorbid disorder
• Insomnia can be directly managed by CBT and pharmacologic agents