Insomnia in Patients with Psychiatric Disorders: Causes, Consequences, Best Practices, and Emerging Treatments

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Faculty Disclosure

• **Dr. Chepke**: Consultant—Janssen, Neurocrine Biosciences, Otsuka; Grant/Research Support—Acadia, Harmony, Neurocrine Biosciences; Speakers Bureau—Acadia, Allergan, Eisai, Intracellular, Ironshore, Janssen, Jazz, Neurocrine Biosciences, Otsuka, Sunovion, Takeda, Teva.

• **Dr. Doghramji**: Consultant—Eisai, Harmony, Jazz, Merck, Pfizer; Educational/Research Grant—Eisai, Harmony, Inspire, Jazz; Stock—Merck; Stock (Spouse)—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).
  – The off-label use of diphenhydramine, tiagabine, melatonin, tryptophan, valerian, trazodone, and quetiapine; and the investigational use of daridorexant and seltorexant for the treatment of insomnia will be discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.

• Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.
Learning Objectives

• Evaluate common root causes and the link between insomnia and psychiatric disorders

• Review guideline-directed best practices for treatment of primary insomnia

• Discuss current and emerging agents for the treatment of insomnia, including their pharmacodynamics and safety/efficacy data
The Burden of Insomnia: An Overview

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Philadelphia, Pennsylvania
Insomnia Disorder

A. Dissatisfaction with sleep quantity or quality with $\geq 1$ 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.
Prevalence of Insomnia

Insomnia is the second most common health-related complaint worldwide

54% of the population reports at least 1 insomnia symptom a few nights per week or more often

- 21% Every Night
- 33% A Few Nights Per Week
- 25% A Few Nights Per Month
- 19% Rarely
- 2% Never

Influences on Sleep

- Genetic and Epigenetic
- Personality Features
- Life Circumstances
- Daily Behaviors and Routines
- Bedroom Environment
- Substances and Medications
- Comorbid Health Conditions
- Thoughts, Attitudes, and Beliefs about Sleep

Prevalence of Medical Disorders in Individuals with Insomnia

Community-based population of 772 adults.
GI = gastrointestinal.
Negative Outcomes 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

Impaired Driving in Insomnia

SDLP throughout the driving task. Significant effects of the dummy variable are indicated on the graph. The dummy variable represents the comparison between the period of the first 20 minutes and the period of the last 30 minutes of driving for each group. $P<.05$ was considered significant between periods.

SDLP = standard deviation of lateral position.

Insomnia Predicts Future Hypertension

N=9237 males. Followed for 4 years or until developed HTN. Adjusted for BMI, tobacco, alcohol, and job stress.

BMI = body mass index; HTN = hypertension.


![Bar chart showing incidence of HTN and 95% CI for individuals with and without insomnia.](chart.png)
Enhanced Brain Activity in Wake-Promoting Areas in Insomnia

Brain structures did not show the expected decreased metabolic activity in wake-promoting areas of the brain during the transition from wake to sleep.

BF = basal forebrain; LC = locus coeruleus; LDT = laterodorsal tegmental nuclei; ORX = orexin; PPT = pedunculopontine; TMN = tuberomammillary nucleus; vPAG = ventral periaqueductal gray.

Exploring the Relationship between Insomnia and Psychiatric Disorders
Psychiatric Disorders Comorbid with Insomnia Point Prevalence

N=580.
## Sleep Impairments are Relevant across Many Psychiatric Disorders

<table>
<thead>
<tr>
<th>Sleep Impairment</th>
<th>Psychiatric Disorder</th>
</tr>
</thead>
</table>
| **Depressive Disorders** | • 90% of patients with depression complain about sleep quality  
  • Awake ruminating about perceived problems/deficiencies |
| **Anxiety Disorders** | • Anxiety about consequences of poor sleep $\rightarrow$ worsening anxiety $\rightarrow$ worsening insomnia  
  • Physiological symptoms of anxiety “just can’t settle down” |
| **Posttraumatic Stress Disorder** | • Nightmares  
  • Fear/avoidance of nightmares  
  • Hypervigilance  
  – Fear of being unsafe while asleep  
  – May be reluctant to take hypnotic |
| **Bipolar Disorder** | • A symptom and a trigger  
  – Sleep deprivation can trigger mania in a stable patient  
  – Restoration of regular sleep is an essential part of treatment |
| **Psychotic Disorders** | • Often driven by paranoia/fear |
| **ADHD** | • Difficulty stopping tasks and going to sleep  
  • Sleep deprivation can then worsen concentration $\rightarrow$ more disorganization $\rightarrow$ less sleep |

ADHD = attention-deficit/hyperactivity disorder.  
Insomnia and Depression

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
• predicts future MDD
• predicts worse outcomes in MDD (persistence, chronicity, suicidality)
• or sleep loss may trigger a manic episode in patients with bipolar disorder

MDD = major depressive disorder.
Insomnia Predicts Future Depression

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Odds Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Z-value</th>
<th>P-value</th>
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<td>1.86</td>
<td>2.38</td>
<td>11.96</td>
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</table>

Meta-analysis of 21 studies, OR 2.6 (CI 1.98–3.42).
Insomnia is a Risk Factor for Suicide

- Insomnia is strongly associated with suicidal ideation cross-sectionally and longitudinally, even when controlling for hopelessness and depression.
- Insomnia is linked to death by suicide among adolescents, adults, and older adults.
- Mediators may be thwarted belongingness and hopelessness.

Sleep Disturbances as Residual Symptoms following Acute MDD Remission

Patients with MDD (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.

Sleep Disturbance Predicts Recurrence of Depression

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
  - Results pending

Hypnotics are not FDA indicated for treatment of MDD.

PBO = placebo; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.

Hypnotic Cotreatment in MDD Reduces Suicidal Ideation

Least square mean scores on the Scale for Suicide Ideation for participants in the Reducing Suicidal Ideation Through Insomnia Treatment study

<table>
<thead>
<tr>
<th>Weeks since Randomization</th>
<th>Controlled-Release Zolpidem</th>
<th>Placebo</th>
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<tr>
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Study Medication Withdrawal

Least square mean scores for suicidal ideation on the Columbia–Suicide Severity Rating Scale for participants in the Reducing Suicidal Ideation Through Insomnia Treatment study

<table>
<thead>
<tr>
<th>Weeks since Randomization</th>
<th>Study Medication Withdrawal</th>
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<tr>
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<td>7</td>
<td>5</td>
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<tr>
<td>8</td>
<td>4</td>
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</table>

N= 51 50 49 47 46 44 41 39
N= 52 51 47 43 40 39 38 37

aError bars indicate standard errors.
Treating Insomnia:
Following Guideline-Recommended Best Practices

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Adjunct Assistant Professor of Psychiatry
University of North Carolina School of Medicine
Medical Director, Excel Psychiatric Associates
Huntersville, North Carolina
CBT-I and Other Behavioral Therapies

• Cognitive-Behavioral Therapy for Insomnia (CBT-I)
  – Gold standard for behavioral treatment of insomnia
  – 6 to 8 in-person visits over 8 weeks

• Unguided CBT-I via smartphone
  – Somryst™ (a/k/a “SHUTi”)
  – Validated, with durability for 18 months
  – Cleared by FDA as a prescription digital therapeutic March 2020

• Brief Behavioral Therapy for Insomnia (BBTI)
  – Created in 2011 to increase access to behavioral treatments for insomnia
  – Initial efficacy study performed by an NP with no prior experience in sleep medicine or behavioral interventions for insomnia
  – 2 in-person visits, 2 telephone sessions over 4 weeks
  – Currently ongoing trial of BBTI delivered entirely via telehealth

SHUTi = Sleep Healthy Using the Internet.
Don’t Forget Exercise!

- Meta-analysis of 14 studies (6 RCTs) assessing effects of exercise on sleep outcomes in adults 60+ years
  - Moderate intensity exercise 3×/week produced the highest number of significant improvements
  - Session duration range 20–70 minutes
  - Examples: Qi Gong, Tai chi, Silver Yoga

- Significant effects in:
  - Subjective sleep quantity, difficulty falling back to sleep (100% of studies)
  - Sleep latency, wake after sleep onset, total sleep time (50% of studies)
  - Reduction in sleep medication use (40% of studies)

- Large standardized effect size (Cohen’s $d \geq 0.8$) in 40% of studies

Approved Pharmacotherapies for Insomnia Disorder

• Benzodiazepine Receptor Agonists (BzRA)
  – Estazolam, flurazepam, quazepam, temazepam, triazolam
• Nonbenzodiazepine BzRA ("Z-drugs")
  – Eszopiclone, zaleplon, zolpidem
• Melatonin Agonist
  – Ramelteon
• H1 Antagonist
  – Doxepin low dose
• Dual Orexin Receptor Antagonists (DORAs)
  – Lemborexant, suvorexant

Limitations of Current Therapies

- Benzodiazepine Receptor Agonists (BzRA)
  - Abuse/dependence, respiratory depression, rebound insomnia, daytime cognitive and psychomotor impairment (agent/dose-dependent), Schedule IV
- Nonbenzodiazepine BzRA (“Z-drugs”)
  - Conceptually similar to those of the benzodiazepines, also Schedule IV
  - As of April 2019, boxed warning of complex sleep behaviors

WARNING: COMPLEX SLEEP BEHAVIORS

Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of AMBIEN. Some of these events may result in serious injuries, including death. Discontinue AMBIEN immediately if a patient experiences a complex sleep behavior [see Contraindications (4) and Warnings and Precautions (5.1)].
2017 AASM Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults

Recommendations

• Difficulties with sleep onset
  – Ramelteon, triazolam, zaleplon
• Difficulties with sleep maintenance
  – Doxepin low dose, suvorexant
• Difficulties with onset and maintenance
  – Eszopiclone, temazepam, zolpidem

NOT Recommended

• Diphenhydramine
• Tiagabine
• Melatonin, tryptophan, valerian
• Suvorexant for sleep-onset insomnia
• Trazodone

Evaluated but no formal statement

• Quetiapine

AASM = American Academy of Sleep Medicine.
Limitations of Off-Label Therapies

**Trazodone**
- Insufficient evidence of efficacy
- Retrospective study of 348,449 Veterans: Suicide attempt hazard 61% higher with trazodone (< 200 mg) than zolpidem
  - Boxed warning for suicidality < 25 years
- The primary metabolite of trazodone (mCPP) is anxiogenic, pro-migraine
  - Metabolized by CYP450 2D6
  - Genetic polymorphism or those on 2D6 inhibitors (eg, fluoxetine, paroxetine, bupropion) may have adverse effects

**Melatonin**
- Insufficient evidence of efficacy
- Physiologic dose is 0.1–0.3 mg
  - Unclear effect of chronic supraphysiologic dosing
- May impair glucose tolerance

**Quetiapine**
- Insufficient evidence of efficacy
- Anticholinergic, risk of weight gain, metabolic syndrome, tardive dyskinesia

These agents are not FDA approved for insomnia.

mCPP = m-Chlorophenylpiperazine.

Orexin Antagonism for the Treatment of Insomnia

Mechanism of Action and Clinical Data
Neurobiology of the Orexin System

- In 1998, 2 research groups discovered a group of neurons that released a peptide neurotransmitter they called orexin (or hypocretin)
- Orexin neurons originate in the hypothalamus and project widely to areas of the brain that regulate sleep and wake states
- ~ 86 billion neurons in the human brain
  - Only 20,000 to 50,000 orexin neurons
  - 20% to 50% are GABA

ACh = acetylcholine; GABA = gamma-aminobutyric acid.
• Orexin stabilizes the wake-promoting systems of the brain
  – LC (norepinephrine), Raphe (serotonin), TMN (histamine)
  – “Pressing on the gas petal”

• When orexin is inactive (or blocked), sleep-promoting systems predominate
  – VLPO (GABA, galanin)
  – “Pressing on the brake petal”

VLPO = ventrolateral preoptic nucleus; eVLPO = extended VLPO.
Suvorexant Clinical Data

- Approved 2014 for insomnia (Schedule IV)
  - Onset and/or maintenance of sleep
  - 40% of patients ≥ 65 years in trials
- Antagonist of both orexin receptors
- Most Common AE
  - Somnolence: 7% vs 3% with PBO
  - AEs with ≥ 2:1 ratio women over men
    - Somnolence, headache, dry mouth, abnormal dreams, cough, upper respiratory tract infection
- No difference vs PBO
  - Morning driving performance
  - Psychomotor performance
  - Rebound insomnia

- Label update January 2020
  - 4-week study of patients with insomnia who had mild-to-moderate Alzheimer’s disease
  - Significant improvements in total sleep time, wake after sleep onset compared to PBO
  - Nonsignificant reduction in sleep latency
  - Most common AEs
    - Somnolence (4% vs 1% PBO), falls (2% vs 0% PBO)

AE = adverse effect.

Lemborexant Clinical Data

- Approved December 2019 for insomnia (Schedule IV)
  - Onset and/or maintenance of sleep
- Antagonist of both orexin receptors

- 2 positive trials for insomnia
  - 1-month trial vs PBO and zolpidem CR in women ≥ 55 years and men ≥ 65 years
  - 6-month placebo-controlled phase, followed by 6-month open-label extension in adults ≥ 18 years

- Most common AE
  - Somnolence or fatigue
    - PBO 1.3%, 5 mg 6.9%, 10 mg 9.6%
- No difference vs PBO in
  - Morning cognitive performance, driving performance, or body sway
  - Auditory awakening threshold
  - Rebound insomnia

- Demonstrated safety in mild OSA
  - Safety in COPD and moderate-to-severe OSA not yet studied

COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnea.
Lemborexant Short-Term Sleep Onset Efficacy

Objective Latency to Persistent Sleep
Mean change from baseline LPS (primary end point)

Subjective Sleep Onset Latency
Mean change from baseline sSOL

Left: \( P < .01 \) vs placebo. \( P < .05 \) vs zolpidem. \( P < .001 \) vs placebo. \( P \leq .001 \) vs zolpidem.

Right: \( P < .05 \) vs placebo. \( P < .01 \) vs placebo. \( P < .001 \) vs placebo. \( P \leq .01 \) vs zolpidem. \( P < .05 \) vs zolpidem. \( P < .001 \) vs zolpidem.

Lemborexant Sleep Maintenance Efficacy

LSM change from baseline in WASO (key secondary end point)

LSM change from baseline in WASO2H (key secondary end point)

LSM = least squares mean; WASO = wake-after sleep onset; WASO2H = WASO in the second half of the night.

\( ^a P < .01 \) vs placebo. \( ^b P < .05 \) vs zolpidem. \( ^c P < .001 \) vs placebo. \( ^d P \leq .001 \) vs zolpidem. \( ^e P < .01 \) vs zolpidem.

Lemborexant Long-Term Data

Subjective Sleep Onset Latency

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<thead>
<tr>
<th>Median (1st and 3rd quartiles)</th>
<th>SSOL (min)</th>
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<tr>
<td>BL First 7 Nights</td>
<td>70</td>
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<td>Month 2</td>
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<table>
<thead>
<tr>
<th>Treatment Period 1</th>
<th>Treatment Period 2</th>
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<tbody>
<tr>
<td>Improvement</td>
<td>Improvement</td>
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ISI = Insomnia Severity Index.

Yardley J, et al. Presented at: Advances in Sleep and Circadian Science/Sleep Research Society; February 1–4, 2019; Clearwater, FL.

Moline M, et al. Presented at: Neuroscience Education Institute Congress; November 7–10, 2019; Colorado Springs, CO.
Emerging Orexin Antagonists

**Daridorexant**
- Dual orexin receptor antagonist
- Half-life 6 hours (shorter than currently approved DORAs)
- Currently in Phase 3 trials, adults and aging patients being studied

**Seltorexant**
- Selective orexin-2 receptor antagonist
  - Orexin-2 receptor hypothesized to be more important than OxR-1 in insomnia
- Clinical trials
  - Positive Phase 2b trial in insomnia
  - Also being investigated for treatment of MDD adjunctive to antidepressants
    - Positive Phase 2b trial vs placebo
    - Second Phase 2b trial compared to adjunctive quetiapine XR
    - Better results in both MDD trials for patients with insomnia symptoms

These agents are investigational and not FDA approved for any indication.

Using Patient and Disease Characteristics to Inform Treatment Decisions

- Patient age
  - Some therapies are better studied than others in aging populations

- Onset-predominant?
  - Consider ramelteon, zolpidem, zaleplon

- Maintenance-predominant?
  - Most nights: doxepin low dose
  - Infrequent: zolpidem low dose SL PRN MOTN awakening

- Onset and Maintenance?
  - Consider eszopiclone, lemborexant, suvorexant, zolpidem ER

- Need to awaken to auditory stimulus? eg, parent with a baby, or job requiring overnight call
  - Consider doxepin low dose, lemborexant, suvorexant

- Comorbid mild-to-moderate OSA or COPD?
  - Consider ramelteon, suvorexant, (lemborexant in mild OSA)

- Need for lowest abuse potential?
  - Consider ramelteon, doxepin

- Patient preference
  - May refuse controlled agents or have other choices we must consider

Summary

• Behavioral therapies are first-line, but access may be limited
• There are still many unmet needs in insomnia pharmacotherapy
  – Especially in the aging (≥ 55 years) population
• Current guidelines do not recommend most popular off-label treatments
• Orexin antagonists may play a role for patients with insomnia
  – Suvorexant recently showed efficacy and safety in patients with Alzheimer’s disease
  – Lemborexant recently showed superiority to placebo for aging patients in a trial with a zolpidem active control
• Above all, take the time to listen to what your patient’s goals are, solicit their preferences, and fully educate them so you can share the decision-making and create a personalized treatment plan for their needs
Q&A