Utilizing New Tools to Regulate the Sleep-Wake Mode and Better Treat Insomnia

Supported by an educational grant from Merck & Co., Inc.
Target Audience
This continuing medical education activity is planned to meet the needs of sleep specialists who are involved in the diagnosis, evaluation, and treatment of patients with insomnia. These include physicians, researchers, sleep technologists, and other professionals who specialize in sleep medicine, neurology, psychology, psychiatry, and neurophysiology.

Learning Objectives
Upon completing this activity, participants will be able to:
• Understand the latest advancements in the pathophysiology of sleep disorders
• Recognize the latest non-pharmacologic and pharmacologic approaches in controlling the sleep-wake cycle
• Evaluate the use of orexin receptor antagonists in the management of insomnia
Normal Sleep Physiology and Its Implications in Insomnia Pathophysiology

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Benjamin and Virginia T. Boshes Professor in Neurology
Director Center for Circadian and Sleep Medicine
Northwestern University Feinberg School of Medicine
Chicago, IL
Sleepless Patient

- 34-year-old female with difficulty falling asleep (1‒2 hours) and staying asleep (wakes up for 1‒2 hours) for past 8 months
- She feels tired, down and irritable
- Just can’t seem to shut her mind down at bedtime
- It’s affecting her work and personal life

Sleep-Wake Regulation: Interacting Homeostatic and Circadian Systems

SCN, suprachiasmatic nucleus; REM, rapid eye movement; SWS, slow-wave sleep.
Regulation of Wakefulness

Hypocretin/Orexin

- Maintenance of arousal/wakefulness
- Hypothalamic peptides
  - Localized in the dorsolateral hypothalamus
  - Wide projections throughout the brain
  - Projections found in the spinal column
- Dense, excitatory projections to brain areas that influence
  - Wakefulness
  - Appetite
  - Thermoregulation
  - Autonomic control

Control of NREM Sleep

GABA, $\gamma$-aminobutyrate; VLPO, ventrolateral preoptic area; TMN, tuberomammillary nucleus; VTA, ventral tegmental area; PPT, pedunculopontine nucleus; LDT, laterodorsal tegmental nucleus; LC, locus coeruleus.

Adapted with permission from Espana RA, Scammell TE. Sleep. 2004;27:811-20.
The VLPO is Sleep-active in Mammals

VLPO, ventrolateral preoptic area.

Lesions of the VLPO in Rats Produce Insomnia

The Sleep-Wake Switch

Homeostatic Regulation of Sleep

Activation of Neuronal Activity in the Wake-Promoting Regions of the Brain

Dissipation of Homeostatic Process

Initiation of Sleep (VLPO)

Accumulation of Homeostatic Substrates

Datta S, MacLean RR. *Neurosci Biobehavioral Rev.* 2007;31:775-824.
What Determines Homeostatic Sleep Drive?

Model of Insomnia: Implications for Treatment

Neurobiology of Insomnia

Increased physiological arousal day and night

Physiological Factors
- Autonomic arousal
- HPA dysregulation

Cognitive Factors
- Excessive cognitive activity

Psychological or Physiological Stressors
- Anxiety
- Hypersensitivity
- Tension

Arousal Systems in Insomnia Patients That Deactivate Less from Waking to Sleep Compared to Good Sleepers

ARAS, ascending reticular activating system.
Insomnia: Functional Neuroanatomical Changes

- Cortical thinning of anterior cingulate, precentral, lateral prefrontal regions
- Decreased structural connectivity of anterior and posterior regions of the default mode network

CNS and Peripheral Overactivity in Insomnia

- Significant 24-hour increase in cortisol (Vgontzas. *J Clin Endocrinol Metab.* 2001;86:3787-94.)
- Increased sympathetic activity (Lushington. *Sleep.* 2000;23:504-10.)
Conceptual Model of Sleep-Wake Regulation Relevant to Insomnia Disorder

Insomnia Subtypes?

Sleep-Wake Regulatory System
Homeostatic Sleep Drive
Circadian Timing System

Cognitive-Affective System
Cognitive System ↔ Affective System

Sleep-Wake State Switching System
VLPO → LHA
“Sleep Switch” ↔ “Wake Stabilizer”

Brainstem-Hypothalamic Arousal System
LC, Raphe, LDT/PPT, TMN

Thalamus

Solid arrows indicate direct anatomic or physiologic pathways. Dotted arrows indicate indirect pathways. VLPO, Ventrolateral preoptic area. LHA, Lateral hypothalamus peri-fornical area. LC, locus coeruleus. LDT, Laterodorsal pontine tegmentum. PPT, Pedunculopontine tegmentum. TMN, Tuberomammillary nucleus of the posterior hypothalamus.

Courtesy: D. Buysse (modified)
Evidence for Circadian Disturbance in Insomnia Disorder

Decreased amplitude and earlier phase of melatonin rhythm in older adults with insomnia

Circadian Melatonin and Insomnia in Older Women

• Melatonin level and core body temperature (CBT) were intact in young and older poor sleepers.
• However, older poor sleepers showed:
  o Weaker evening increase in melatonin level
  o DLMO was a significant predictor of SOL in the older women (R(2)=0.64, p<.001), but not in younger women.
• Suggests that amplitude and timing of the circadian rhythm might contribute to disturbances in insomnia of older adults.

Differential Sleep, Sleepiness, and Neurophysiology in the Insomnia Phenotypes of Shift Work Disorder

Figure 2—MSLT scores by SWD phenotype (mean latency ± SD). *SI vs. Controls, P < 0.05. †SI vs. Al, P < 0.05. Al vs. Controls, all n/s.

Figure 1—DLMO times by SWD phenotype, individual and mean ± SD.

MSLT, multiple sleep latency test; Al, alert insomniacs; SI, sleepy insomniacs; DLMO, dim light salivary melatonin onset.

# Circadian Insomnia Subtypes

<table>
<thead>
<tr>
<th>Low levels of melatonin associated with insomnia in middle to older age.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Melatonin deficiency may be marker of risk for insomnia subtype.</td>
</tr>
<tr>
<td>• Represents an insomnia subtype that may be responsive to adjunctive treatment with melatonin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insomnia associated with circadian alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Late chronotype insomnia</td>
</tr>
<tr>
<td>- Sleep-onset insomnia</td>
</tr>
<tr>
<td>- Risk for severity and non-remission of depression</td>
</tr>
<tr>
<td>• Early chronotype, earlier phase</td>
</tr>
<tr>
<td>- Sleep-maintenance insomnia</td>
</tr>
<tr>
<td>• SWD insomnia subtype</td>
</tr>
<tr>
<td>- <strong>Sleepy</strong> vs. alert</td>
</tr>
</tbody>
</table>
Melatonin at Bedtime Improves Sleep in Patients on Beta Blockers (Atenolol or Metoprolol)

Beta blockers can decrease melatonin secretion and are associated with sleep and circadian disruption.
How and Why Orexin-Receptor Antagonists for Insomnia Treatment

Orexin: Central Regulator of Wake-Promoting System

# Distribution of Orexin Receptors and Multiple Other CNS Effects


<table>
<thead>
<tr>
<th>Gene</th>
<th>$OX_1$</th>
<th>$OX_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main ligand</td>
<td>Orexin A (Hcrt1)</td>
<td>Orexin A, Orexin B (Hcrt2)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Prefrontal cortex</td>
<td>Tuberomammillary nucleus</td>
</tr>
<tr>
<td></td>
<td>Insular cortex</td>
<td>Lateral hypothalamus</td>
</tr>
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<td></td>
<td>LDT/PPT</td>
<td>VTA</td>
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<td></td>
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<td></td>
<td>VTA</td>
<td></td>
</tr>
<tr>
<td>Functions</td>
<td>REM sleep modulation?</td>
<td>Arousal</td>
</tr>
<tr>
<td></td>
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<td>Stress responses</td>
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<td>Drug-seeking behavior</td>
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Diurnal Rhythm of Orexin Levels (Rise During Wake and Decline During Sleep)


A temporal pattern of orexin concentration in human CSF samples has also been observed.
Inhibition of Orexin Activity Promotes Sleep

No clear evidence that orexin levels are higher in patients with insomnia but there is evidence for “hyperarousal”

Suppression of the wake-promoting system is considered necessary for sleep onset and maintenance to occur.

Conceptual Model of Treatment Approaches Relevant to Insomnia

- **Homeostatic Sleep Drive**
  - **Circadian Timing System**
  - **Brainstem-Hypothalamic Arousal System**
  - **Sleep-Wake State Switching System (Hypothalamus)**
  - **Cognitive-Affective Circuits (Cortex, Limbic System)**

**Melatonin, receptor agonists**

**Orexin antagonists**

**CBT-I**

**BzRA**

**Antidepressants, antihistamines**

Modified and courtesy of D. Buysse.
Personalization of Insomnia Therapy: Matching Treatment with Patient Needs

Andrew D. Krystal, MD, MS
Ray and Dagmar Dolby Distinguished Professor of Psychiatry and Neurology
Vice Chair of Research
University of California San Francisco School of Medicine
San Francisco, CA
Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine
Durham, NC
Introduction – “One Size Fits All”

• Insomnia therapy has long been a one-size-fits-all endeavor
  – Clinicians have tended to use one medication to treat all of their patients with insomnia
• The opportunity to improve treatment through personalization has been limited to matching the time of night of sleep problem with drug duration of action
  – Example: Zolpidem
• There was no evidence that mechanism of action of insomnia therapy mattered
  – It was assumed that clinical effects were determined only by pharmacokinetics
Introduction – “Mechanism Matters”

• There are several relatively recently emerging insomnia medications with high pharmacologic specificity
  – Mechanism of action affects the nature of clinical effects

• Such agents pave the way for a new paradigm for insomnia therapy where specific interventions are selected to target a specific type of sleep difficulty for each patient
  – Advantage: improved risk/benefit ratio over non-specific agents that have global effects and impact many areas of the brain other than those needed to improve a patient’s particular sleep problem
Introduction – Towards Personalization

• This requires characterizing the specific effects of each of the targeted therapies and identifying key phenotypes of insomnia patients who will optimally benefit from each type of therapy
  – This is a work in progress

• We will review the existing insomnia treatments in this forward-looking context, discussing rationale for patient subtype matching
Overview

• Existing insomnia treatments
• Specificity of insomnia treatments
• Review of each insomnia treatment, identifying considerations for matching mechanism to insomnia subtype
Current Primary Options

• Cognitive Behavioral Therapy (CBT)
• Medications
Insomnia Medications

- **Hypocretin/Orexin Antagonists**
  - Suvorexant
- **Selective H1 Antihistamines**
  - Doxepin 3–6 mg
- **Melatonin Agonists**
  - Ramelteon
- **Antihypertensives**
  - Prazosin
- **Benzodiazepines**
  - Triazolam, flurazepam, temazepam, clonazepam, alprazolam, diazepam, lorazepam

- **“Non-benzodiazepines”**
  - Zolpidem, zaleplon, eszopiclone
- **Antidepressants**
  - Trazodone, doxepin, mirtazapine, amitriptyline...
- **Antipsychotics**
  - Quetiapine, risperidone, olanzapine...
- **OTC Agents (Antihistamines)**
  - Diphenhydramine, doxylamine, chlorpheniramine

# Treatment Specificity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Specificity</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT-I</td>
<td>Highly Specific</td>
<td>Specific maladaptive behaviors and cognitions that perpetuate insomnia</td>
</tr>
<tr>
<td>Suvorexant</td>
<td>Highly Specific</td>
<td>Antagonism of orexin receptors</td>
</tr>
<tr>
<td>Doxepin 3–6 mg</td>
<td>Highly Specific</td>
<td>Antagonism of H1 histamine receptors</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Highly Specific</td>
<td>Antagonism of $\alpha_1$ adrenergic receptors</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Highly Specific</td>
<td>Agonism of melatonin M1/M2 receptors</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Non-Specific</td>
<td>Binding to benzo binding site on GABA-A receptor complex leads to broad CNS inhibition</td>
</tr>
<tr>
<td>Non-Benzodiazepines</td>
<td>Non-Specific</td>
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<td>Antidepressants</td>
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<td>Antagonism of 5HT and NE transporters, $5HT_2$, $\alpha_1$, adrenergic, H1 histaminergic, and muscarinic cholinergic antagonism</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Non-Specific</td>
<td>Dopamine D2, Dopamine D1, $5HT_2$, $\alpha_1$, adrenergic, H1 histaminergic, and muscarinic cholinergic antagonism</td>
</tr>
<tr>
<td>OTC “Antihistamines”</td>
<td>Non-Specific</td>
<td>Antagonism of H1 histamine receptors and cholinergic receptors</td>
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Cognitive Behavioral Therapy – Insomnia (CBT-I)

• Cognitive/Behavioral Targets
  – Individuals with maladaptive behaviors/cognitions that perpetuate insomnia
    • Spending excessive time in bed, napping, worrying in bed, etc., etc.

• Physiologic Targets
  – Diminished homeostatic sleep drive
  – Elevated arousal
We evaluated the relationship between Spectral Analysis Derived Indices (all night averaged Beta Power and Delta Power Dynamics) in primary insomnia patients treated with CBT-I.

PSG, polysomnography.
Krystal AD, Edinger JD. *Sleep*. 2010;33:669-77.
### Correlations of non-REM Delta Power Indices and Improvement in Sleep with CBT

<table>
<thead>
<tr>
<th>EEG Variable</th>
<th>Correlation with Improvement in Sleep</th>
</tr>
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<tbody>
<tr>
<td>Baseline Peak Delta</td>
<td>-0.57**</td>
</tr>
<tr>
<td>Baseline Peak Slope</td>
<td>0.51**</td>
</tr>
<tr>
<td>Baseline Average Beta</td>
<td>0.56**</td>
</tr>
<tr>
<td>Change in Peak Delta with CBT</td>
<td>0.81**</td>
</tr>
<tr>
<td>Change in Delta Slope with CBT</td>
<td>-0.46**</td>
</tr>
<tr>
<td>Change in Average Beta with CBT</td>
<td>0.76**</td>
</tr>
</tbody>
</table>

**p<0.05
Cognitive Behavioral Therapy – Insomnia

This work supports the hypothesis that individuals with diminished homeostatic sleep drive or elevated arousal are appropriate candidates for CBT-I.
Orexin Antagonists

- Specific effect: they block receptors targeted by only the 10–20,000 neurons in the entire brain that produce orexin.
- Can attempt to infer insomnia subgroups likely to improve with treatment from known anatomy/physiology of orexin system.
Role of Orexin in Sleep-Wake

- Best understood orexin role: maintenance of long, consolidated awake periods. Suggested by:
  - Orexin neuron loss, and deficiencies in OX2R associated with narcolepsy in mice, dogs, and humans
  - Diurnal variation of orexin activity in normal animals, with increased activity during wakefulness and reduced activity during sleep
    - Activity increases over the course of the day counteracting increasing homeostatic drive

Orexin System Pathways Related to Arousal

**Input signals**
- Sleep
- Wake
- Circadian
- Stress
- Emotions
- Autonomic
- Motivation
- Movement
- Hunger

**Afferent nuclei**
- Preoptic area
- Dorsal raphe
- SCN → DMH
- Lateral septum
- Amygdala
- Posterior hypothalamus
- Periaqueductal gray
- Parabrachial nucleus
- Accumbens nucleus
- Substantia nigra
- Ventral tegmental area
- Arcuate nucleus
- Lateral hypothalamus
- ▼ Glucose
- ▲ Ghrelin

**Target nuclei**
- Cortex
- Basal forebrain
- Tuberoventricular nucleus
- Dorsal raphe
- Periaqueductal gray
- Locus coeruleus
- Accumbens nucleus
- Substantia nigra
- Ventral tegmental area
- Solitary tract nucleus
- Ventrolateral medulla
- Preganglionic neurons

**Behavioral effects**
- ▲ Wakefulness
- ▲ Attention
- ▼ REM sleep
- ▲ Motivation
- ▲ Reward
- ▲ Feeding
- ▲ Locomotion
- ▲ Sympathetic tone

Contexts in Which Orexin Antagonists Likely to Be Particularly Effective

• Based on role in maintaining prolonged periods of wakefulness in face of rising sleep drive
  – Those who can’t seem to shut down at bedtime; get “second wind”
  – People attempting to sleep at adverse circadian time?

• Based on Inputs/Outputs of Orexin Neurons
  – Stress/anxiety-related arousal (e.g., trauma-related insomnia)
  – Arousal in setting of loss of rewarding stimuli including substances of abuse
Selective H1 Antagonist

- Doxepin’s strongest effect is H1 antagonism
- At 3–6 mg, it has essentially only H1 antagonism
  - Specificity -> relatively benign adverse effects profile
- Novel effects suggest PK\PD Dissociation
  - Peak blood level in 3–4 hours, but peak sleep effect 7–8 hours after dosing, with minimal effects after waking 9 hours after dosing
  - Decreases WASO but not awakenings

Wake Time by Hour Night 1 in Elderly With Primary Insomnia: Doxepin 1–3 mg

Histamine Overactivity Subtype?

- There appear to be individuals, especially the elderly, who have histamine overactivity underlying their insomnia.
- The hallmark of this problem is sleep disturbance predominantly in the last 3rd of the night or early morning awakening.
- Best treated with selective H1 antagonist.
- Also useful in abuse-prone individuals with sleep maintenance problems.
Selective NE Antagonism

- Norepinephrine (NE) plays an important role in wake promotion
- Blocking NE receptors has the potential to enhance sleep
- Increased peripheral NE activity has been identified in insomnia patients
- Prazosin is a selective alpha-1 antagonist
  - No controlled trials in primary insomnia
  - Improves nightmares and sleep maintenance problems in PTSD in 4 placebo-controlled trials

Animal Model of Insomnia Has Increased NE Activity

• Cage Change Model – Causes acute stress response
  – Associated with longer sleep-onset latency and sleep fragmentation

• Evidence for a role of increased NE release
  – Lesioning locus coeruleus and a pharmacologic intervention that decreases HA and NE release decreased manifestations of disturbed sleep

Elevated Nocturnal Circulating Levels of Norepinephrine in Insomnia


Fig. 1. Circulating levels of norepinephrine during the nocturnal period in insomniacs, depressed patients, and controls. The bars represent the SEM.

Fig. 2. Correlation between average nocturnal level of norepinephrine and sleep efficiency in the insomniacs.
Increased NE Insomnia Subtype?

• There may be some individuals who have NE overactivity underlying their insomnia
  – Serum vs. CNS?
• The hallmark of this problem may be association with Novelty/Stress/Trauma
  – Best evidence in PTSD
• Best treated with agent that specifically blocks NE activity such as prazosin to optimize risk/benefit
  – Relatively benign side effect profile
    • Orthostatic hypotension, sedation
Selective Melatonergic Agonism

- Promote sleep onset by binding to neuronal membrane-bound MT1 receptors
  - Melatonin
    - Very modest effect on sleep-onset latency
    - More consistent effect on sleep phase
  - Ramelteon
    - Effective for sleep-onset insomnia only
    - Consistent effect on PSG
    - Effect on self-reported outcomes less consistent

Target Subtype

- Patients with only sleep-onset difficulty
  - Those who have been treated with benzodiazepines or non-benzodiazepines don’t tend to improve as much
  - Relatively benign adverse effect profile
  - Useful for those with insomnia in setting of substance use disorders or in substance abuse-prone patients
Medications That Enhance GABA-ergic Inhibition: Non-Selective CNS Inhibition

- **Benzodiazepines** (Temazepam, Flurazepam, Triazolam etc.)
  - Group of compounds with related chemical structure
  - Mechanism of action:
    - GABA-A receptor complex is comprised of 5 peptides that form a channel which controls the flow of chloride ions in and out of the neuron.
    - Generally, Cl is greater outside than inside neurons. GABA binding opens the channel and the resulting inward flux of Cl hyperpolarizes the membrane resulting in inhibition.
    - Benzos bind to a site on α subunit of GABA receptor complex and enhance this GABA-mediated inhibition.

- **“Non-Benzodiazepines”** (Zolpidem, Zaleplon, Eszopiclone)
  - A group of compounds not related to benzos
  - Mechanism of action:
    - Same as benzos, though they have relatively greater α subunit binding specificity.
Dose-Dependent Effects of Benzos and Non-Benzos

• Effects are non-specific reflecting global inhibition due to increase in GABA activity in various brain regions
  – Possibly therapeutic
    • Sleep enhancing, myorelaxant, anxiolytic, anti-seizure effect
  – Adverse effects:
    • Cognitive impairment, psychomotor impairment, abuse potential

Target Subtype

- Most efficacious sleep-onset therapies in common use
- Efficacy for maintenance depends on half-life/dose
- Particularly useful where non-specific effects are advantageous:
  - Co-morbidities such as anxiety, pain, treatment-resistant patients, etc.

Antidepressants

- Non-selective agents with varying degrees of antagonism of 5HT and NE transporters, and 5HT2, α1, adrenergic, histaminergic, and muscarinic cholinergic antagonism
  - Trazodone, mirtazapine, amitriptyline, doxepin (>6 mg), etc.
  - Minimal data on efficacy/safety in the treatment of insomnia
  - Side effect profile inferred from use in depression, anxiety, etc.
    - May include sedation, weight gain, orthostatic hypotension, dry mouth, constipation, blurred vision, etc.
Target Subtype

• Particularly useful where non-specific effects are advantageous:
  – Co-morbidities such as depression, anxiety, pain, and treatment-resistant patients where it is advantageous to block multiple wake-promoting systems, etc.
Antipsychotics

- Non-selective agents with varying degrees of antagonism of D1, D2, 5HT2, 5HT7, α1, adrenergic, histaminergic, and muscarinic cholinergic receptors
  - Quetiapine, olanzapine, risperidone, lurasidone
  - Minimal data on efficacy/safety in the treatment of insomnia
  - Side effect profile inferred from use in schizophrenia, mania, depression, etc.

  - May include extrapyramidal side effects, sedation, weight gain, insulin resistance, orthostatic hypotension, dry mouth, constipation, blurred vision, etc.
Target Subtype

• Particularly useful where non-specific effects are advantageous:
  – Co-morbidities such as psychotic conditions, mania, depression, anxiety, pain, and treatment-resistant patients where it is advantageous to block multiple wake-promoting systems, etc.
The Future

- There are now several insomnia medications with high pharmacologic specificity
- Such agents pave the way for a new paradigm for insomnia therapy where specific interventions are selected to target a specific type of sleep difficulty
  - Promises improved risk/benefit
  - Problem: We have only limited understanding about how to best match specific treatments to specific patient subgroups
    - Once “pie in the sky”, this approach is increasingly becoming a reality as new data emerge and new specific agents become available
      - Promising methods for personalization
        » Type/Time of Night Sleep Problem
        » The context in terms of co-occurring conditions
          • Depression, anxiety, substance abuse-prone individual, psychosis, pain, PTSD, etc.
        » Physiologic markers of homeostasis and arousal
        » Genotype?
A 42-year-old with a history of alcohol use disorder with chronic difficulty falling asleep.

A. Doxepin 3-6 mg
B. Eszopiclone
C. Ramelteon
D. Zolpidem
Case Exercise: What would you choose?

A 70-year-old with a history of alcohol use disorder with chronic difficulty waking up too early in the morning and not being able to return to sleep.

A. Doxepin 3-6 mg
B. Eszopiclone
C. Ramelteon
D. Prazosin
Unique Role of Orexin Receptor Antagonists in Insomnia Management: Mechanism and Clinical Implications

Thomas Roth, PhD
Director
Sleep Disorders and Research Center
Henry Ford Hospital
Detroit, MI
Arousal Systems in Insomnia Subjects That Do Not Deactivate from Waking to Sleep

ARAS, ascending reticular activating system
Brain Activity in Wake-Promoting Areas in Patients With 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\(^1, a\).

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\(^a\)Measured in 7 patients with primary insomnia compared with 20 healthy controls.


**PSG: Wake After Persistent Sleep Onset (WASO)**

*(Analysis set: Per protocol; N=100)*

<table>
<thead>
<tr>
<th>Dose</th>
<th>LS mean</th>
<th>95% CL</th>
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<tbody>
<tr>
<td>25 mg</td>
<td>-10.4</td>
<td>-17.0 , -3.9</td>
</tr>
<tr>
<td>50 mg</td>
<td>-19.2</td>
<td>-25.7 , -12.6</td>
</tr>
<tr>
<td>100 mg</td>
<td>-31.4</td>
<td>-38.0 , -24.9</td>
</tr>
<tr>
<td>200 mg</td>
<td>-46.5</td>
<td>-53.0 , -39.9</td>
</tr>
</tbody>
</table>

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PSG, polysomnography.

PSG: Total Sleep Time (TST) and Latency To Persistent Sleep (LPS)

(Analysis set: Per protocol; N=100)

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<tr>
<td></td>
<td></td>
<td>20  40</td>
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<tr>
<td>TST [Min]</td>
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<td>25 mg</td>
<td>14.3</td>
<td>7.4 , 21.2</td>
</tr>
<tr>
<td>50 mg</td>
<td>21.5</td>
<td>14.6 , 28.4</td>
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<tr>
<td>100 mg</td>
<td>34.7</td>
<td>27.8 , 41.6</td>
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<tr>
<td>200 mg</td>
<td>55.1</td>
<td>48.2 , 62.0</td>
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<tr>
<th>Drug</th>
<th>LS Mean</th>
<th>95% CL</th>
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<td>20  40</td>
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<tr>
<td>LPS [Min]</td>
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<tr>
<td>200 mg</td>
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<td>-15.4 , -5.0</td>
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</table>

Almorexant AC-057A201 Study Results. Available at: https://clinicaltrials.gov/ct2/show/NCT00606593.
Dose-Related Improvement in PSG Measures with Suvorexant...

Data from pooled pivotal trials.
LPS, latency to the onset of persistent sleep; WASO, wake after persistent sleep onset; LS, Least-Squares; PSG, polysomnography; HD, high dose (40 mg for non-elderly, 30 mg for elderly); LD, low dose (20 mg for non-elderly, 15 mg for elderly).

...Dose-Related Improvements in Subjective Report Measures

Data from pooled pivotal trials.

sTSO\textsubscript{m}, subjective Time to Sleep Onset mean; sTST\textsubscript{m}, subjective Total Sleep Time mean; sWASO\textsubscript{m}, subjective Wake After Sleep Onset mean; LS, Least-Squares; HD, high dose (40 mg for non-elderly, 30 mg for elderly); LD, low dose (20 mg for non-elderly, 15 mg for elderly).

WASO by Hour of Night


WASO, wake after sleep onset.

<table>
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<th>Treatment</th>
<th>Baseline Mean</th>
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<tr>
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<tr>
<td>Suvorexant HD</td>
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</tr>
<tr>
<td>Suvorexant LD</td>
<td>1.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.5</td>
</tr>
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</table>

Adjusted Mean Change from Baseline WASO with 95% CI (minutes)

Night 1

Month 1

Month 3
Suvorexant Efficacy Persists for 12 Months

Note: Nominal p<0.05 for all endpoints and timepoints. Least-Squares mean changes from baseline and 95% confidence intervals shown in plots. sTSOm, subjective Time to Sleep Onset mean; sWASOm, subjective Wake After Sleep Onset mean; sTSTm, subjective Total Sleep Time mean.; HD, high dose (40 mg for non-elderly, 30 mg for elderly).

Power Spectral Profile of 4 Doses of Suvorexant in Primary Insomnia Patients (NREM)

Bolded segments with triangle markers are the frequency ranges where the difference between drug and placebo are statistically significant ($p<0.05$, adjusted for multiplicity)

Power Spectral Profile of 4 Doses of Suvorexant in Primary Insomnia Patients (REM)

Power Spectral Profile of Suvorexant Compared with Other Hypnotics in Healthy Subjects (NREM)


Bolded segments with triangle markers are the frequency ranges where the difference between drug and placebo are statistically significant (p<0.05, adjusted for multiplicity).
Power Spectral Profile of Suvorexant Compared with Other Hypnotics in Healthy Subjects (REM)

Bolded segments with triangle markers are the frequency ranges where the difference between drug and placebo are statistically significant (p<0.05, adjusted for multiplicity).

Insomnia Returns When Suvorexant Stopped

Subjective Total Sleep Time

Baseline Month 12 RD Wk 1 RD Wk 2 RD Wk 3 RD Wk 4 RD Wk 5 RD Wk 6 RD Wk 7 RD Wk 8

Mean sTSTm (minutes)

MK-4305 / MK-4305
MK-4305 / Placebo
Placebo / Placebo

RD Wk = Randomized Discontinuation Phase Week

MK-4305 = suvorexant
Definition of Sleep

- Sustained behavioral quiescence
- Stereotypic, species-specific, posture
- Elevated arousal thresholds
- Rapid reversibility
- Characteristic electroencephalographic changes
- Stereotypic, species-specific duration
Dose-Related Improvement in PSG Measures with Suvorexant...

Data from pooled pivotal trials.

LPS, latency to the onset of persistent sleep; WASO, wake after persistent sleep onset; LS, Least-Squares; HD, high dose (40 mg for non-elderly, 30 mg for elderly); LD, low dose (20 mg for non-elderly, 15 mg for elderly).

Analysis of Sleep and Wake Bouts with Suvorexant

Mean number of wake bouts on Night 1 of treatment by wake bout duration for suvorexant (SUV 20/15 mg, 40/30 mg) and placebo (PBO). X- and Y-axes use logarithmic scales.

Mean number (±2 SEM) of short (≤2 minutes) and long (>2 minutes) wake bouts at baseline (BL) and Night 1 (N1) by treatment

Analysis of Sleep and Wake Bouts with Suvorexant (cont’d)

Non-Elderly

Elderly

PBO
SUV 20/15mg
SUV 40/30mg

Mean time (±2 SEM) spent in short (≤2 minutes) and long (>2 minutes) wake bouts at baseline (BL) and Night 1 (N1) by treatment.
Analysis of Sleep and Wake Bouts with Suvorexant vs. Zolpidem

Cumulative number of bouts with bout duration ≤ x-axis value for treatment suvorexant (SUV 40/30 mg, 20/15 mg) and zolpidem (ZOL 10 mg) vs. placebo by part of the night.

Legend: — active treatment (SUV (40/30 mg), SUV 20/15 mg, or ZOL 10 mg); — placebo (from suvorexant study or from zolpidem study); bout durations where the differences between cumulative time under treatment and under placebo are statistically significant, p-values < 0.05, are indicated by the black bars.

Analysis of Sleep and Wake Bouts with Suvorexant vs. Zolpidem (cont’d)

Mean cumulative time in bouts with bout duration ≤ x-axis value for treatment suvorexant (SUV 40/30 mg, 20/15 mg) and zolpidem (ZOL 10 mg) vs. placebo by part of the night.

Legend: ── active treatment (SUV (40/30 mg), SUV 20/15 mg, or ZOL 10 mg); ── placebo (from suvorexant study or from zolpidem study); bout durations where the differences between cumulative time under treatment and under placebo are statistically significant, p-values < 0.05, are indicated by the black bars.

Orexin Signaling and Salient Arousability

Tone Exposure & Habituation
- Both Tones
  - Randomly played
  - 0.18x/h
  - 0-8h/day + 0-8h/night
  - 8wks
  - 50dB, 300msec
  - 700 Hz & 1000Hz
- After 8wks:
  - Confirmed no behavioral response or ECoG/EMG/EOG disruption to either acoustic stimuli

Classical Conditioning Training
- Neutral Tone
  - Randomly played
  - 0.18x/h
  - 0-8h/day + 0-8h/night
  - 50dB, 300msec
  - 700 Hz
- Salient Tone
  - Tone immediately followed by 30-s food reward
  - 3-15x/wk
  - Day, Night
  - 1000 Hz

Sleep + Salience Testing
- Neutral Stimulus
  - Tone played 3x/30-s epoch @ DORA-22/Eszopiclone/Diazepam/Vehicle
  - ~Cmax: 2 or 3hr into night sleep
  - ECoG/EMG/EOG
  - Active Wake or Continued Sleep?
- Salient Conditioned Stimulus
  - Tone played 3x/30-s epoch @ DORA-22/Eszopiclone/Diazepam/Vehicle
  - ~Cmax: 2 or 3hr into night sleep
  - ECoG/EMG/EOG
  - Active Wake or Continued Sleep?
Monkey + DORA-22, Eszopiclone, Diazepam: All Increase Sleep / Decrease Active Wake

Monkey + GABA-A Modulator Sleep Architecture: More Light & Slow Wave I, Less Delta II and REM Sleep

Monkeys + Vehicle (Unmedicated) Sleep:
Wake to Salient Conditioned Stimulus, Sleep Through Neutral Stimulus

**Percent Awakened - Vehicle**

<table>
<thead>
<tr>
<th></th>
<th>Percentage Awakened (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral</td>
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</tr>
<tr>
<td>Salient CS</td>
<td>***</td>
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</tbody>
</table>

***p<0.001
Monkeys + DORA-22 Sleep:
Wake to Salient Conditioned Stimulus, Sleep Through Neutral Stimulus

DORAN-22

**p<0.001
Monkeys + GABA-A Receptor Modulator Sleep: Do Not Discriminate Between Neutral and Salient Stimuli

Eszopiclone

Diazepam

*a non-sedating dose

Monkeys + GABA-A Receptor Modulator Sleep:
Do Not Discriminate Between Neutral and Salient Stimuli, Rarely Wake to Salient Conditioned Stimuli

**Eszopiclone**

<table>
<thead>
<tr>
<th>Dose (mg/kg) PO</th>
<th>Percentage Awakened (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral</td>
<td>0</td>
</tr>
<tr>
<td>Salient CS</td>
<td>-0-</td>
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</tbody>
</table>

**Diazepam**

<table>
<thead>
<tr>
<th>Dose (mg/kg) PO</th>
<th>Percentage Awakened (mean ± SEM)</th>
</tr>
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<tbody>
<tr>
<td>Neutral</td>
<td>0</td>
</tr>
<tr>
<td>Salient CS</td>
<td>-0-</td>
</tr>
</tbody>
</table>

Aroussability of Insomnia Patients and Healthy Volunteers: Doxepin (3 and 6 mg) and Zolpidem (10 mg)

Study Design

Arousalability Study Results

Conditions Associated With Arousal From Sleep

Sleep Apnea
COPD
GERD
Cough
Nocturia
Abnormal Behaviors in Sleep
Monkey Psychomotor Vigilance Testing (PVT): Wake from DORA-22 and Perform As Unmedicated If Wake from GABA-A Modulators Performance Impaired

*p<0.05
Summary/Key Messages

▪ Arousal is an important characteristic of sleep
▪ Arousal from sleep is an important homeostatic response in many sleep and wake disorders
▪ WASO as a measure of sleep is determined by both arousability and sleep initiation propensity
▪ Drugs working on wake signaling preserve arousability but improve sleep initiation propensity
▪ Drugs working on sleep signaling blunt arousability but improve sleep imitation propensity
▪ Blunting arousability is associated with impaired function post arousal