FROM OREXIN TO Z-DRUGS: A CLINICAL UPDATE ON INSOMNIA

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Learning Objectives

• Explain the neurobiology of sleep/wake cycles and the role of neurotransmitters in insomnia

• Differentiate the mechanistic and clinical profiles of treatments for insomnia

• Apply current best practices to the treatment of insomnia
Arousal Spectrum of Sleep and Wakefulness

- **Deficient Arousal**
  - Asleep
  - Excessive daytime sleepiness/drowsiness/sedation
  - Cognitive dysfunction (understimulation)

- **Awake**
  - Alert
  - Creative
  - Problem solving

- **Excessive Arousal**
  - Hyper-vigilant/insomnia
  - Panic/fear
  - Hallucinations/psychosis

Stahl and Morrissette. Stahl’s Illustrated sleep and wake disorders, 2016.
The Sleep/Wake Cycle

Suprachiasmatic nucleus (SCN)

Retinohypothalamic tract
Suprachiasmatic nucleus (SCN)

Retinohypothalamic tract

Pineal gland

melatonin
Distinct hypothalamic neurons control the sleep/wake cycle.

**SCN:** suprachiasmatic nucleus. **SPZ:** supraventricular zone. **DMN:** dorsomedial nucleus. **PVN:** paraventricular nucleus. **Lateral Hyp:** lateral hypothalamus. **VLPO:** ventrolateral preoptic nucleus.

Circadian Rhythms Regulated at the Molecular Level

- The molecular clock consists of several transcription factors that regulate each other's expression:
  
<table>
<thead>
<tr>
<th>Transcription Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROR</td>
</tr>
<tr>
<td>CLOCK</td>
</tr>
<tr>
<td>BMAL1</td>
</tr>
<tr>
<td>PERIOD</td>
</tr>
<tr>
<td>CRY</td>
</tr>
<tr>
<td>REV-ERBα</td>
</tr>
</tbody>
</table>

- Transcription factors bind to the promoter regions of DNA and, in doing so, turn the expression of a gene on or off.

GABA/Galanin

Hypocretin

Acetylcholine

Dopamine

Norepinephrine

Serotonin

Histamine

LC: locus coeruleus
LH: lateral hypothalamus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

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Acetylcholine
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VTA: ventral tegmental area

Neurotransmitter Levels Throughout the Sleep/Wake Cycle

Espana, Scammell. Sleep 2011;34(7):845-58;
Hypocretin/Orexin Projections


LC: locus coeruleus
LH: lateral hypothalamus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
Raphe: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

Wakefulness
Attention

Feeding
Motivation
Reward

norepinephrine
serotonin
histamine
acetylcholine
GLUTAMATE
dopamine

hypo.png
Cancer and Circadian Rhythms

Sleep and Immunity

Sleep and Obesity

- Decreased leptin
- Increased ghrelin
- Impaired sleep/wake cycle
- Gut microbiota dysbiosis
- Increased risk of obesity, type 2 diabetes, and cardiovascular disease

References:
Insomnia: Excessive Nighttime Arousal

awake
alert
creative
problem solving

insomnia

deficient arousal

excessive arousal

Insomnia: Excessive Nighttime Arousal

• The most common sleep-wake disorder
  • Prevalence: 15% in the adult US population
    (40 million Americans)

• Affected individuals often complain of poor sleep quality or duration, difficulty falling asleep, nighttime awakenings, or wake times that are earlier than desired

• Importantly, the vast majority of the time, insomnia is comorbid with medical and psychiatric disorders

Conditions Associated With Insomnia


- Substance Abuse
  - More likely to develop anxiety
  - More likely to develop depression
  - More likely to develop SUD

- Medication Side Effects

- Medical Conditions

- Psychiatric Conditions
  - More likely to develop anxiety
  - More likely to develop depression
  - More likely to develop SUD

- Behavioral/Psychological Causes

- Sleep/Wake Disorders
Insomnia: DSM-5 Diagnostic Criteria

• Complaint of dissatisfaction with sleep quantity or quality, associated with at least one of the following symptoms:
  • Difficulty initiating sleep
  • Difficulty maintaining sleep
  • Early-morning awakening with inability to return to sleep

• Sleep disturbance causes distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning

• Disturbance occurs at least 3 nights per week and is present for at least 3 months

• Disturbance is not attributable to the physiologic effects of a substance or a coexisting medical or mental disorder

Association AP. Diagnostic and Statistical Manual of Mental Disorders, DSM-V 2013.
# Insomnia Severity Index

Please rate the **CURRENT (i.e., LAST 2 WEEKS) SEVERITY** of your insomnia problem(s).

<table>
<thead>
<tr>
<th>Insomnia problem</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>
</tbody>
</table>

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

<table>
<thead>
<tr>
<th>Very Satisfied</th>
<th>Satisfied</th>
<th>Moderately Satisfied</th>
<th>Dissatisfied</th>
<th>Very Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

<table>
<thead>
<tr>
<th>Not at All Noticeable</th>
<th>A Little</th>
<th>Somewhat</th>
<th>Much</th>
<th>Very Much Noticeable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

6. How WORRIED/DISTRESSED are you about your current sleep problem?

<table>
<thead>
<tr>
<th>Not at All Worried</th>
<th>A Little</th>
<th>Somewhat</th>
<th>Much</th>
<th>Very Much Worried</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g., daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood) CURRENTLY?

<table>
<thead>
<tr>
<th>Not at All Interfering</th>
<th>A Little</th>
<th>Somewhat</th>
<th>Much</th>
<th>Very Much Interfering</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total score categories:
- 0–7 = No clinically significant insomnia
- 8–14 = Subthreshold insomnia
- 15–21 = Clinical insomnia (moderate severity)
- 22–28 = Clinical insomnia (severe)

Sleep-Wake Hygiene

**Sleep Time**
- Dark room
- Cool environment
- No stimulants before bed
- No disturbances

**Wake Time**
- Activity
- Bright Light
Resetting Circadian Rhythms

**Bright Light Therapy**
Suppresses melatonin release

- Treatment with 10,000 lux, bright, blue light for 30 minutes a day may be used to reset circadian rhythms
- Shown to improve performance, alertness, and mood during the night shift can be improved in shift workers

Theoretical Pharmacological Targets

- To promote wakefulness
  - Inhibit
    - GABA
    - Galanin
  - Enhance
    - DA
    - NE
    - 5HT
    - Hcrt
    - ACh
    - HA

- To promote sleep
  - Inhibit
    - DA
    - NE
    - 5HT
    - Hcrt
    - ACh
    - HA
  - Enhance
    - GABA
    - Galanin

Resetting Circadian Rhythms

- **Melatonergic** agents promote sleep by resetting the sleep/wake cycle
- Endogenous melatonin is secreted by the pineal gland during periods of darkness
- Acts on the suprachiasmatic nucleus to regulate circadian rhythms
- Melatonin may help to adjust circadian rhythms if taken 3 hours before dim-light melatonin onset

**Melatonin**
- Acts at MT1 and MT2 receptors as well as at the MT3 site
- Available over the counter

**MT1 and MT2 Receptor Agonists**
- Improve sleep onset
  - *ramelteon*: FDA-approved for the treatment of insomnia
  - *tasimelteon*: FDA-approved for Non-24-Hour Sleep-Wake Disorder

Enhance
- GABA/galanin

Inhibit
- hypocretin/orexin
- acetylcholine
- dopamine
- norepinephrine
- serotonin
- histamine

Promoting Sleep

HA
ACh
5HT
NE

overactivation
normal
baseline
hypoactivation

GABA-A PAMs (Z drugs)
benzos
H1 antagonists
5HT2A/2C antagonists

deficient arousal
asleep

excessive arousal

Pharmacological Treatments for Insomnia

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepine Hypnotics</strong></td>
<td></td>
</tr>
<tr>
<td>Estazolam</td>
<td>✓</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>✓</td>
</tr>
<tr>
<td>Quazepam</td>
<td>✓</td>
</tr>
<tr>
<td>Temazepam</td>
<td>✓</td>
</tr>
<tr>
<td>Triazolam</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Nonbenzodiazepine Hypnotics</strong></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>✓</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>✓</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td>✓</td>
</tr>
<tr>
<td>Trazodone</td>
<td></td>
</tr>
<tr>
<td><strong>Hypocretin/Orexin Antagonist</strong></td>
<td></td>
</tr>
<tr>
<td>Suvorexant</td>
<td>✓</td>
</tr>
<tr>
<td>Lemborexant</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Melatonin Receptor Agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td>✓</td>
</tr>
<tr>
<td>Tasimelteon</td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
</tr>
</tbody>
</table>

# Mechanism of Trazodone and Doxepin as Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Antidepressant dose</th>
<th>Hypnotic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>(150–600 mg)</td>
<td>(1–6 mg)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>(150–600 mg)</td>
<td>(25–150 mg)</td>
</tr>
</tbody>
</table>

Orexin Receptor Antagonist

Single Orexin Receptor Antagonist (SORAs)

SORA1 works selectively at orexin 1 receptor

SORA2 works selectively at orexin 2 receptor

Dual Orexin Receptor Antagonist (DORA)

DORA bind to both orexin 1 and orexin 2 receptors

Blocking Orexin Receptors With Antagonist Agents May Help to Promote Sleep

- Binding of orexin to OXR1 and OXR2 receptors promotes wakefulness; orexin antagonists promote sleep by blocking these receptors.
Lemborexant

The latest FDA-approved treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adults

• Multicenter, randomized, double-blind, parallel-group phase III study
  • Results showed decreases from baseline in patient-reported (subjective) sleep onset latency and subjective wake after sleep onset, and increases from baseline in subjective sleep efficiency, were significantly greater with 5mg lemborexant and 10 mg lemborexant versus placebo
  • FDA approved at both 5 and 10 mg doses for insomnia

Kärppä M et al. Sleep. 2020;43(9)
Nonpharmacological Treatments for Insomnia

• Relaxation training
  • Aimed to reduce somatic tension and intrusive thoughts that interfere with sleep

• Stimulus control therapy
  • Get out of bed if not sleepy; use bed only for sleeping; no napping

• Sleep restriction therapy
  • Limit time spent in bed to produce mild sleep deprivation; results in more consolidated sleep

• Intensive sleep retraining
  • 25-hour sleep deprivation period in which the patient is given 50 sleep onset trials but awoken following 3 minutes of sleep

• Cognitive behavioral therapy
  • Reduce negative attitudes and misconceptions about sleep
Summary

• The neurobiology and molecular underpinnings of sleep are complex

• The quality and quantity of sleep can greatly affect our physical and mental health

• There are numerous pharmacological and nonpharmacological treatment options available that target various components of the sleep/wake circuit to improve sleep/wake
A 30-year-old patient with narcolepsy with cataplexy demonstrates profound loss of hypocretin/orexin (Hcrt/Ox) neurons in the lateral hypothalamus. Hcrt/Ox typically stimulates:

A. Acetylcholine release from the basal forebrain  
B. Acetylcholine release from the pedunculopontine nucleus  
C. Acetylcholine release from the laterodorsal tegmental area  
D. All of the above  
E. None of the above
Sarah is a 19-year-old college student who is interested in using over-the-counter melatonin to help with her sleep/wake cycle while studying for final exams. Which of the following statements is true regarding endogenous melatonin?

A. Melatonin is released from the pineal gland during periods of light
B. Melatonin is released from the pineal gland during periods of darkness
C. Melatonin is released from the suprachiasmatic nucleus during periods of darkness
D. Melatonin is released from the suprachiasmatic nucleus during periods of light
Peggy is a 59-year-old patient who suffers from insomnia. Among the FDA-approved treatments for insomnia are dual orexin receptors antagonists (DORA) suvorexant and lemborexant. The blockade of hypocretin/orexin receptors via hypocretin/orexin antagonists typically:

A. Increases histamine levels
B. Lowers histamine levels
C. Does not effect histamine levels