FROM OREXIN TO Z-DRUGS: A CLINICAL UPDATE ON INSOMNIA
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
  - Inattentive
  - Cognitive dysfunction (understimulation)
  - Excessive daytime sleepiness/drowsiness/sedation

- Excessive arousal:
  - Hyper-vigilant/insomnia
  - Insomnia
  - Cognitive dysfunction (overstimulation)
  - Panic/fear
  - Hallucinations/psychosis

- Awake:
  - Alert
  - Creative
  - Problem solving

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

homeostatic (sleep drive)

circadian (wake drive)
Suprachiasmatic nucleus (SCN)

Retinohypothalamic tract
Suprachiasmatic nucleus (SCN)

Pineal gland

Retinohypothalamic tract

melatonin
The Hypothalamus and Control

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

![Transcription Factors](image)

- ROR
- CLOCK
- BMAL1
- PERIOD
- CRY
- REV-ERBα

• 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
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

Neurotransmitter Levels Throughout the Sleep/Wake Cycle

Neurotransmitter Levels Throughout the Sleep/Wake Cycle

GABA/Galanin

Espana, Scammell. Sleep 2011;34(7):845-58;
Neurotransmitter Levels Throughout the Sleep/Wake Cycle

Espana, Scammell. Sleep 2011;34(7):845-58;
Neurotransmitter Levels Throughout the Sleep/Wake Cycle

Espana, Scammell. Sleep 2011;34(7):845-58;
Neurotransmitter Levels Throughout the Sleep/Wake Cycle

- GABA/Galanin
- Hypocretin
- Acetylcholine
- Dopamine
- Norepinephrine
- Serotonin
- Histamine

Graph showing neurotransmitter levels throughout stages 1 to 4 of sleep and REM sleep periods. Source: Espana, Scammell. Sleep 2011;34(7):845-58; Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders 2016.
Hypocretin/Orexin Projections

Cancer and Circadian Rhythms

Sleep and Immunity

Sleep and Obesity

- Impaired sleep/wake cycle
- Decreased leptin
- Increased ghrelin
- 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

- Medication Side Effects
- Substance Abuse
- Behavioral/Psychological Causes
- Sleep/Wake Disorders
- Medical Conditions
- Psychiatric Conditions
  - 2x more likely to develop anxiety
  - 4x more likely to develop depression
  - 7x more likely to develop SUD

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></th>
<th>Very Satisfied</th>
<th>Satisfied</th>
<th>Moderately Satisfied</th>
<th>Dissatisfied</th>
<th>Very Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 How satisfied you are</td>
<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></th>
<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>5.1 Noticeable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<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>6.1 Worried</td>
<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></th>
<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>7.1 Interfering</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</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.

Promoting Sleep

Enhance
- GABA/galanin

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

Overactivation
- HA
- ACh
- NE
- 5HT

Normal Baseline
- Hypoactivation

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

Asleep
- deficient arousal

Sleep
- excessive arousal

## Pharmacological Treatments for Insomnia

### Benzodiazepine Hypnotics

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

### Nonbenzodiazepine Hypnotics

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone</td>
<td>✓</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>✓</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Antidepressants

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>✓</td>
</tr>
<tr>
<td>Trazodone</td>
<td></td>
</tr>
</tbody>
</table>

### Antipsychotics

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
</tbody>
</table>

### Anticonvulsants

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
</tr>
</tbody>
</table>

### Hypocretin/Orexin Antagonist

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suvorexant</td>
<td>✓</td>
</tr>
<tr>
<td>Lemborexant</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Melatonin Receptor Agonists

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>FDA-Approved for Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td>✓</td>
</tr>
<tr>
<td>Tasimelteon</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><strong>Trazodone</strong></td>
<td>(150–600 mg)</td>
<td>(25–150 mg)</td>
</tr>
<tr>
<td><strong>Doxepin</strong></td>
<td>(150–600 mg)</td>
<td>(1–6 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

• Binding of orexin to OXRx1 and OXRx2 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
APPENDIX
Polysomnography

- Electroencephalogram (EEG) determines sleep stages
- Electrooculogram (EOG) measures eye movement to identify rapid eye movement (REM) sleep
- Electromyogram (EMG) measures muscle activity via electrodes on the chin, jawbone, and calf muscles
- Electrocardiogram (ECG) is used to measure heart rate and rhythm
- Breathing is measured with a piezo crystal effort sensor, which utilizes 2 Velcro bands around the chest and abdomen to measure movements and effort
- Airflow is measured with a thermistor secured under the nose, and oxygen saturation can be measured by a pulse oximeter on the finger or ear lobe
- The patient may be videotaped
Polysomnography

- Eye movements
- Muscle activity
- Brain activity
- Muscle activity
- Respiration
- Heart activity
- Oxygen level
Multiple Sleep Latency Testing

**Method**
- Nocturnal polysomnogram
- 5 daytime nap opportunities
  - Quiet, dark room
  - 2-hour intervals
- Score time to sleep onset
  - Max time: 20 min
- Wake patient 15 min from sleep onset

<table>
<thead>
<tr>
<th>Degree of sleepiness</th>
<th>Mean sleep latency (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>5</td>
</tr>
<tr>
<td>Moderate</td>
<td>10</td>
</tr>
<tr>
<td>Severe</td>
<td>20</td>
</tr>
</tbody>
</table>

Degree of sleepiness
Actigraphy
# Sleep-Wake Diary

<table>
<thead>
<tr>
<th>Complete in morning</th>
<th>First day</th>
<th>Second day</th>
<th>Third day</th>
<th>Fourth day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedtime (date/time)</td>
<td>10:45 p.m. (4/10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise time (date/time)</td>
<td>7:00 a.m. (4/11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated time to fall asleep</td>
<td>30 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated number of awakenings and total time awake</td>
<td>5 times 2 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated amount of sleep obtained</td>
<td>4 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Complete at bedtime                      |           |            |           |            |
| Naps (number, time, and duration)        | 1 at 3:30 p.m. 45 minutes |            |           |            |
| Alcoholic drinks (number and time)       | 1 drink at 8:00 p.m. 2 drinks at 5:00 p.m. |            |           |            |
| List stresses of the day                 | Flat tire Argued with son |            |           |            |
| Rate how you felt today                  | 2         |            |           |            |
| 1 = Very tired/Sleepy                    |           |            |           |            |
| 2 = Somewhat tired/sleepy                |           |            |           |            |
| 3 = Fairly alert                         |           |            |           |            |
| 4 = Wide awake                           |           |            |           |            |
| Irritability level                       | 5         |            |           |            |
| 1 = None                                 |           |            |           |            |
| 2 = Some                                 |           |            |           |            |
| 3 = Moderate                             |           |            |           |            |
| 4 = Fairly high                          |           |            |           |            |
| 5 = High                                 |           |            |           |            |
| Medications                              |           |            |           |            |
Epworth Sleepiness Scale

<table>
<thead>
<tr>
<th>Situation</th>
<th>would never doze (0)</th>
<th>slight chance of dozing (1)</th>
<th>moderate chance of dozing (2)</th>
<th>high chance of dozing (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sitting and reading</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Watching TV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Sitting, inactive in a public place (e.g., a theatre or a meeting)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. As a passenger in a car for an hour without a break</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Sitting and talking to someone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Sitting quietly after a lunch without alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. In a car, while stopped for a few minutes in traffic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Calculate Total Score]

Interpretation:

<table>
<thead>
<tr>
<th>Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>Normal (a low score does not exclude significant daytime sleepiness)</td>
</tr>
<tr>
<td>10-11</td>
<td>Borderline</td>
</tr>
<tr>
<td>12-24</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>