Watching the Clock:
An Update on the Causes, Consequences, and Treatment of Insomnia
Learning Objectives

• Describe the neurobiological and molecular bases of sleep/wake cycles

• Apply differential diagnostic assessment of patients with insomnia according to established best practices

• Implement treatment strategies to address insomnia in patients with sleep/wake disorders
I feel competent **diagnosing** patients with insomnia.

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
Pre-Poll Question 2

I feel competent optimizing treatment for patients with insomnia.

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
Pretest Question 1

Which of the following statements regarding the suprachiasmatic nucleus (SCN) is most accurate?

1. The dorsomedial shell contains cells that release the neuropeptides vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP)
2. The ventrolateral core contains cells that release arginine vasopressin (AVP) and prokineticin 2 (PK2)
3. The ventrolateral core receives the majority of the light input coming through the retinohypothalamic tract
4. All of the above
5. None of the above
Pretest Question 2

Genetic testing of a 35-year-old woman who complains of sleep onset insomnia reveals a polymorphism in the clock gene circadian locomotor output cycles kaput (CLOCK). Polymorphisms in the CLOCK gene have been associated with:

1. Increased risk of obesity
2. Increases risk of seasonal affective disorder
3. Increased risk of insomnia
4. 1 and 3 only
5. 2 and 3 only
6. All of the above
A 45-year-old man complains of difficulty falling asleep and excessive daytime sleepiness. Data from a 2-week sleep/wake diary and polysomnography reveal that the patient wakes several times during the night and has difficulty falling back to sleep. The recently developed dual orexin receptor antagonist suvorexant is FDA-approved for the treatment of:

1. Initial insomnia
2. Maintenance insomnia
3. Both initial and maintenance insomnia
4. Excessive daytime sleepiness associated with insomnia
Arousal Spectrum

Zeitgebers

External cues to synchronize circadian rhythms

• Light

• Melatonin

• Eating and drinking patterns

• Social interactions

Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract
Processes Regulating Sleep

Molecular Clock Genes

- **CLOCK** (circadian locomotor output cycles kaput)
- **BMAL1** (brain and muscle ARNT-like-1)
- **PER** (period)
- **CRY** (cryptochrome)
- **REV-ERBα**
- **ROR** (retinoic acid-related orphan receptor)

- Code for proteins that act as transcription factors
- Expression waxes/wanes approximately every 24 hours
- Turn on/off expression of other genes, including those involved in sleep, metabolism, and mood

Buhr ED, Takahashi JS. Handbook of Experimental Pharmacology 2013;217:3-27.
Transcription Factors Involved in the Molecular Clock

ROR 9 3 CLOCK Per Cry REV-ERBα

Bmal1

Heterodimers

DNA

Promoter Gene
CLOCK (circadian locomotor output cycles kaput)

BMAL1 (brain and muscle ARNT-like-1)

PER (period)

CRY (cryptochrome)

REV-ERBα

ROR (retinoic acid-related orphan receptor)

E Box response element

ROR/REV-ERBα response element
CLOCK (circadian locomotor output cycles kaput)

BMAL1 (brain and muscle ARNT-like-1)

PER (period)

CRY (cryptochrome)

REV-ERBα

ROR (retinoic acid-related orphan receptor)

E Box response element

ROR/REV-ERBα response element
CLOCK (circadian locomotor output cycles kaput)
BMAL1 (brain and muscle ARNT-like-1)
PER (period)
CRY (cryptochrome)
REV-ERBα
ROR (retinoic acid-related orphan receptor)
E Box response element
ROR/REV-ERBα response element
Light Control of the Molecular Clock

Suprachiasmatic Nucleus Control of Sleep

VIP: vasoactive intestinal peptide
GRP: gastrin-releasing peptide
AVP: arginine vasopressin
PK2: prokineticin 2

Brancaccio et al, 2014; Colwell, 2011.
Misalignment Between Central and Peripheral Clocks

Green et al, 2008; Oosterman et al, 2014
Cost and Consequences of Sleep/Wake Disorders

Sleep: How Much Is Too Much? Too Little?

Sleep/Wake Disturbances Increase Risk of Work-Related Injury

• Sleep/wake disorders affect up to 70 million people in the US

• Workers with sleep/wake problems have a 1.62 times increased risk of being injured

Psychiatric Disorders

• Sleep/wake disorders may be a contributing cause or consequence of mood disorders
  – High rates of depression have been reported in shift workers
  – As many as 63% of patients with obstructive sleep apnea have a mood disorder

• Individuals with insomnia
  – 2X more likely to develop anxiety
  – 4X more likely to develop depression
  – 7X more likely to develop substance abuse disorder

• Many psychotropic agents can affect sleep/wake cycles

## Clock Genes Associated With Psychiatric Disorders

<table>
<thead>
<tr>
<th>Clock Gene</th>
<th>Disorder</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clock (or its homolog, NPAS)</td>
<td>Bipolar disorder</td>
<td>Benedetti et al, 2003; Soria et al, 2010.</td>
</tr>
</tbody>
</table>
Synaptic Plasticity

• REM sleep may be essential for hippocampal-dependent cognitive function and synaptic plasticity

• Sleep deprivation (specifically REM sleep deprivation) affects the expression of genes involved in synaptic plasticity

• Consequences of 1 night of sleep deprivation
  – Similar effects to those seen with 1% blood alcohol level
  – 32% increase in number of errors by surgeons on a simulated surgery

Synaptic Plasticity

Orzel-Gryglewska, 2010; Dresler et al, 2014; Golombek et al, 2013
Cardiometabolic Consequences

• Sleep deprivation is associated with:
  – Obesity and diabetes
  – Decreased levels of leptin (anorectic hormone)
  – Impaired ability to lose weight

• Shift work is associated with cardiovascular disease, obesity, and type 2 diabetes

• The prevalence of cardiovascular disease is higher in patients with restless leg syndrome

• 83% of patients with drug-resistant hypertension have obstructive sleep apnea (OSA)

• 28% of patients with type 2 diabetes have OSA

• 77% of obese patients have OSA

• Obesity is a risk factor for insomnia to become chronic

Cardiometabolic Consequences (cont)

- Many hormones involved in metabolism (e.g., ghrelin, leptin) exhibit circadian oscillation
  - The expression of these hormones is regulated by molecular clock genes/transcription factors
  - Many of these hormones also regulate the expression of molecular clock genes/transcription factors
- CLOCK polymorphisms are associated with an increased risk of obesity and metabolic syndrome
- BMAL1 polymorphisms are associated with susceptibility to hypertension and type 2 diabetes
- Chronic misalignment of feeding cycles and sleep cycles results in metabolic disorders and DNA damage

Cancer

- Shift workers have a higher incidence of cancer
- Several cell cycle genes (e.g., MYC, WEE1) are regulated by molecular clock genes/transcription factors
- PER interacts with proteins involved in the DNA damage response
- PER expression is deregulated in breast cancer cells
- DNA damage can also act as a zeitgeber (reset the molecular clock)
- Circadian rhythm/cell cycle synchronization may prevent DNA replication during times of high exposure to damaging UV rays or byproducts of intense metabolism

Walsh et al. Sleep Med 2009;10:859-64;
Cancer and Circadian Rhythms

Takahashi et al, 2008; Masri et al, 2015; Sahar and Sassone-Corsi, 2009.
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:
Froy, 2010; Orzel-Gryglewska, 2010; Golombek et al, 2013; Thaiss et al, 2014
ASSESSMENT OF INSOMNIA
Insomnia: Excessive Nighttime Arousal

## Insomnia

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

<table>
<thead>
<tr>
<th></th>
<th>Insomnia</th>
<th>Sleep Deprivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Opportunity</td>
<td>Adequate</td>
<td>Reduced</td>
</tr>
<tr>
<td>Sleep Ability</td>
<td>Reduced</td>
<td>Adequate</td>
</tr>
</tbody>
</table>

Symptoms of Insomnia

- Subjective complaints of poor sleep quality or duration
  - Possibly a marker for the biological severity of insomnia
- Difficulty falling asleep at bedtime
- Waking in the middle of the night or too early in the morning
- Daytime fatigue
- Cognitive deficits
- Mood disturbances

- Suggested criteria include:
  - Average sleep latency >30 min
  - Wakefulness after sleep onset (WASO) of >30 min
  - Sleep efficiency <85%
  - Total sleep time <6.5 hr

## Associated With Insomnia

**Psychiatric Disorders**
- Major depression
- Dysthymic disorder
- Bipolar affective disorder
- Generalized anxiety disorder
- Panic disorder
- Posttraumatic stress disorder
- Schizophrenia
- Substance use disorders

**Medical Conditions**
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Asthma
- Chronic renal failure
- Prostatic hypertrophy
- Gastroesophageal reflux
- Fibromyalgia
- Osteoarthritis
- Rheumatoid arthritis
- Hyperthyroidism
- Parkinson's disease
- Cerebrovascular disease
- Menopause

**Medications/Substances**
- Alcohol
  - Acute use
  - Withdrawal
- Caffeine
- Nicotine
- Antidepressants
- Corticosteroids
- Decongestants
- β-agonists/antagonists
- Theophylline derivatives
- Statins
- Stimulants
- Dopamine agonists

---

Insomnia and Psychiatric Illness

- 3-5 Years
  - 2X more likely to develop anxiety
  - 4X more likely to develop depression
  - 7X more likely to develop SUD

Biology of Insomnia

- **Neuroanatomical Abnormalities**
  - Reduced gray matter in left orbitofrontal cortex and hippocampus

- **Neurobiological Abnormalities**
  - Decreased GABA levels in occipital and anterior cingulate cortices
  - Reduced nocturnal melatonin secretion
  - Increased glucose metabolism
  - Attenuated sleep-related reduction in glucose metabolism in wake-promoting regions
  - Decreased serum BDNF

- **Autonomic Nervous System Abnormalities**
  - Heart rate elevations and variability
  - Increased metabolic rate
  - Increased body temp
  - HPA axis activation
  - Increased NE

- **Systemic Inflammation**

- **Genetic Factors**
  - CLOCK gene polymorphisms
  - GABA-A receptor gene polymorphisms
  - Serotonin reuptake transporter (SERT) gene polymorphisms
  - Human leukocyte antigen (HLA) gene polymorphisms
  - Epigenetic modifications affecting genes involved in the response to stress

**Insomnia: Differential Diagnosis**

- Evaluate sleep quality and sleepiness
  - e.g., Epworth Sleepiness Scale
  - 24-hr sleep/wake diary maintained for 2 wks

- Complete history and both physical and psychiatric exams
  - Evaluate risk factors for sleep apnea (neck circumference, BMI, etc.)
  - Evaluate comorbid medical conditions and medication use
  - Psychiatric evaluation should focus on mood, anxiety, and memory

- Actigraphy is indicated to rule out circadian rhythm disorders

- Polysomnography
  - Not indicated in the routine evaluation of insomnia
  - May be useful for patients with comorbid sleep disorders (e.g., apnea, RLS), when initial diagnosis is uncertain, when treatment fails, or if arousals occur with violent or injurious behavior

Diagnosing Insomnia

Suggested criteria for defining insomnia:
- Average sleep latency >30 min
- Wakefulness after sleep onset (WASO) >30 min
- Sleep efficiency <85%
- Total sleep time <6.5 hours

New DSM-5 Diagnostic Criteria for Insomnia

- Insomnia has traditionally been categorized as either:
  - Secondary: a symptom of psychiatric or medical illness
  - Primary: not associated with a psychiatric or medical illness; not a result of substance abuse or withdrawal
- However, insomnia is now understood as a potential comorbidity rather than a symptom of a psychiatric or medical illness
- Newly revised DSM-5 diagnostic criteria for insomnia
  - Omits the distinction between secondary and primary
  - Recognizes the intricate, 2-way, perpetuating relationship between insomnia and psychiatric and medical conditions

TREATING INSOMNIA
Nonpharmacological Treatments

- Sleep hygiene education
- Relaxation training
  - Aimed at reducing somatic tension and intrusive thoughts that interfere with sleep
- Stimulus control therapy
  - Get out of bed if not sleepy; use bed only for sleep; no napping
- Sleep restriction therapy
  - Limit time spent in bed to produce mild sleep deprivation; results in more consolidated sleep
- Intensive sleep retraining
  - 25-hr 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

Sleep Hygiene

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

**Wake Time**
- Activity
Promoting Sleep

To Promote Sleep

Inhibit
DA
NE
5HT
Hcrt
ACh
HA

Enhance
GABA
Galanin

Meta-analysis of CBT for Insomnia

Sleep Efficiency

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currie et al. [30]</td>
<td>0.99 [0.60, 1.38]</td>
</tr>
<tr>
<td>Epstein &amp; Dirksen [31]</td>
<td>1.65 [1.15, 2.14]</td>
</tr>
<tr>
<td>Espie et al. [32]</td>
<td>0.52 [0.34, 0.71]</td>
</tr>
<tr>
<td>Morin et al. [34]</td>
<td>1.14 [0.46, 1.83]</td>
</tr>
<tr>
<td>Rybarczyk et al. [35]</td>
<td>1.51 [0.69, 2.34]</td>
</tr>
<tr>
<td>Vitiello et al. [19]</td>
<td>1.25 [0.73, 1.76]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1.13 [0.70, 1.56]</strong></td>
</tr>
</tbody>
</table>

Meta-analysis of CBT for Insomnia

Sleep Quality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currie et al. [30]</td>
<td>1.33 [0.96, 1.70]</td>
</tr>
<tr>
<td>Epstein &amp; Dirksen [31]</td>
<td>0.39 [0.08, 0.71]</td>
</tr>
<tr>
<td>Espie et al. [32]</td>
<td>0.72 [0.58, 0.86]</td>
</tr>
<tr>
<td>Miro et al. [31]</td>
<td>0.91 [0.55, 1.26]</td>
</tr>
<tr>
<td>Rybarczyk et al. [35]</td>
<td>1.07 [0.53, 1.62]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.85 [0.57, 1.14]</td>
</tr>
</tbody>
</table>


Copyright © 2015 Neuroscience Education Institute. All rights reserved.
# Meta-analysis of CBT for Insomnia

## Depression

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currie et al. [30]</td>
<td>0.39 [0.23, 0.55]</td>
</tr>
<tr>
<td>Miro et al. [31]</td>
<td>0.21 [-0.04, 0.46]</td>
</tr>
<tr>
<td>Vitiello et al. [19]</td>
<td>0.12 [-0.11, 0.34]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>0.26 [0.08, 0.43]</strong></td>
</tr>
</tbody>
</table>

Benzodiazepine Hypnotics

- Bind with equal affinity to $\alpha_1$, $\alpha_2$, $\alpha_3$, and $\alpha_5$ subunits of the GABA-A receptor
  - Alpha subunit expression differs throughout the brain
  - The selectivity of a hypnotic for different $\alpha$ subunits will induce effects in addition to sedation (e.g., anxiolytic, anti-pain, tolerance)

- Higher risk of tolerance and withdrawal effects compared to non-benzodiazepine hypnotics
  - Estazolam
  - Flurazepam
  - Quazepam
  - Temazepam
  - Triazolam

*FDA-approved for the treatment of insomnia*
Non-benzodiazepine Hypnotics

- Bind selectively to 1 or 2 $\alpha$ subunits of the GABA-A receptor
  - The selectivity of a hypnotic for different $\alpha$ subunits will induce effects in addition to sedation (e.g., $\alpha_2$ and $\alpha_3$ subunits may have anxiolytic, antidepressant, and anti-pain effects)

- **Eszopiclone**
  - Selective for $\alpha_2$ and $\alpha_3$ subunits
  - The only hypnotic approved for use over 35 days

- **Zaleplon**
  - Selective for $\alpha_1$ subunits
  - Can be used for awakening during the night without residual daytime effects

- **Zolpidem**
  - Selective for $\alpha_1$ subunits
  - Sublingual form approved for middle of the night awakening

*FDA-approved for the treatment of insomnia*
Z-Drug Label Changes

- Due to risk of next morning impairment
- FDA recently recommended that bedtime doses be lowered
  - Zolpidem
    - From 10 mg to 5 mg for immediate release formulations
    - From 12.5 mg to 6.25 mg for extended release formulations
  - Eszopiclone
    - From 3 mg to 1 mg

http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm
http://www.fda.gov/Drugs/DrugSafety/ucm397260.htm
Hypocretin/Orexin Antagonists

- Hypocretin-1 and hypocretin-2 (also known as orexins)
  - Hcrt-1 (OxR1) receptor is selective for Hcrt-1
  - Hcrt-2 (OxR2) receptor binds Hcrt-1 (OxR1) and Hcrt-2 (OxR2) with equal affinity
- Sustain wakefulness and increase arousal in motivating conditions
- Lateral hypothalamus is also thought to be the "feeding center" of the brain
  - Hcrt increases appetite
    - Hcrt activity is modulated by glucose, leptin, and ghrelin
- Hcrt-1 (OxR1) antagonism
  - Modulates dopamine in addiction/reward centers of the brain
- Hcrt-2 (OxR2) antagonism
  - Decreases histamine in the hypothalamus

Suvorexant

- FDA approved: August 2014
- Dual orexin receptor antagonist (DORA)
- Recommended dose: 10 mg once per night
  - Increase to 20 mg as needed/tolerated
- Peak plasma concentration in 2 hrs
- Very well tolerated with no rebound insomnia or risk of dependence
  - Inactivates wake circuit rather than promoting sleep circuit
  - Most common adverse effect: somnolence
  - Residual daytime drowsiness and REM sleep abnormalities seem to be dose dependent

4 Weeks of Suvorexant Treatment Compared to Placebo

Mean Change Compared to Placebo (min)

Sleep Efficiency

** p<0.01
*** p<0.001

4 Weeks of Suvorexant Treatment Compared to Placebo

**Wake After Sleep Onset (WASO)**

- **10 mg**
- **20 mg**
- **40 mg**
- **80 mg**

*p<0.01*  
***p<0.001***

4 Weeks of Suvorexant Treatment Compared to Placebo

Latency to Persistent Sleep (LPS)

Mean Change Compared to Placebo (min)

-25 -20 -15 -10 -5 0

***

** p<0.01

*** p<0.001

4 Weeks of Suvorexant Treatment Compared to Placebo

** Total Sleep Time (TST)**

- **10 mg**
- **20 mg**
- **40 mg**
- **80 mg**

-axis mean change compared to placebo (min)

- **p<0.01**
- **p<0.001**

Additional Treatments

• Antidepressants
  – Doxepin
  – Trazodone
  – Amitriptyline
  – Trimipramine
  – Mirtazapine
  – Agomelatine

• Antipsychotics
  – Olanzapine
  – Quetiapine

• Anticonvulsants
  – Clonazepam
  – Gabapentin
  – Tiagabine

• Melatonin receptor agonists
  – Ramelteon
  – Melatonin

• Sodium oxybate

*FDA-approved for the treatment of insomnia*
# Mechanisms 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><img src="image1" alt="Diagram" /></td>
<td><img src="image2" alt="Diagram" /></td>
</tr>
<tr>
<td></td>
<td>(150-600 mg)</td>
<td>(25-150 mg)</td>
</tr>
<tr>
<td><strong>Doxepin</strong></td>
<td><img src="image3" alt="Diagram" /></td>
<td><img src="image4" alt="Diagram" /></td>
</tr>
<tr>
<td></td>
<td>(150-600 mg)</td>
<td>(1-6 mg)</td>
</tr>
</tbody>
</table>

Algorithm for the Treatment of Insomnia

1. **Optimize treatment for comorbid disorders** (e.g., sleep apnea, depression)
2. **Nonpharmacological treatments** (e.g., sleep hygiene, CBT)
3. **Zolpidem, eszopiclone, zaleplon, temazepam, suvorexant, or ramelteon**
4. **Sedating antidepressant or antipsychotic**
5. **Non-benzodiazepine hypnotic or ramelteon + sedating antidepressant**
6. **Other sedating agents (e.g., anticonvulsant)**

- Routine assessment should be done at least every 6 months to monitor efficacy, side effects, tolerance, and abuse/misuse of medications.
- A combination of pharmacological treatment and nonpharmacological therapy may have longer-lasting effects and may facilitate medication discontinuation.

Summary

• Insomnia is highly prevalent, with various causes and numerous consequences for mental and physical health

• There are several treatment options available for the management of insomnia, including the recently approved dual orexin antagonist suvorexant