Handout for the Neuroscience Education Institute (NEI) online activity:

Sleep-Wake Disorders in Psychiatric Practice
Learning Objectives

• Apply differential diagnostic assessment of patients with sleep-wake problems according to established best practices

• Educate patients about the consequences of sleep-wake disturbances

• Implement treatment strategies to address sleep-wake disorders
Mitchell is a 42-year-old patient with shift work disorder who reports that he is having difficulty in his job as a police officer due to excessive sleepiness during his shift. Which of the following is a potential therapeutic mechanism to promote wakefulness?

1. Inhibit hypocretin activity
2. Promote GABA activity
3. Promote histamine activity
4. All of the above
5. None of the above
A 26-year-old woman presents with complaints of recent-onset depression. Upon further examination, this patient also mentions that she is often unable to fall asleep and that she wakes many times during the night; these symptoms have been occurring for the past 3 years. Emerging data indicate that individuals with insomnia are:

1. No more likely to develop depression than individuals without insomnia
2. 2X more likely to develop depression
3. 4X more likely to develop depression
4. 8X more likely to develop depression
Justin is a 51-year-old overweight man who presents with complaints of excessive sleepiness. Recent laboratory testing of this patient has indicated an apnea-hypopnea index (AHI) score of 22, indicating:

1. Severe sleep apnea
2. Moderate sleep apnea
3. Mild sleep apnea
4. No or minimal sleep apnea
NEUROBIOLOGY OF SLEEP
Processes Regulating Sleep

- **Awake**
- **Stage 1**
- **Stage 2**
- **Stage 3**
- **Stage 4**

**REM**

**Time of Sleep**
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8

**7 am**

**11 pm**

**7 am**

**11 pm**

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Distinct hypothalamic neurons control the sleep-wake cycle


Stahl SM. Diagnosis and Treatment of Sleep/Wake Disorders. 2007.
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  

Sleep Cycle

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

Time of Sleep

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

## Effects of Commonly Used Drugs on Sleep and Waking

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Pharmacological Effect</th>
<th>Neurobiological Mechanism</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td>Increase 5HT</td>
<td>5HT inhibits REM sleep</td>
<td>Decreased REM sleep</td>
</tr>
<tr>
<td><strong>TCAs</strong></td>
<td>Increase 5HT and NE</td>
<td>5HT and NE inhibit REM</td>
<td>Decreased REM sleep</td>
</tr>
<tr>
<td>Traditional amphetamine-like stimulants</td>
<td>Increase DA and NE</td>
<td>Increased DA and NE signaling</td>
<td>Increased wakefulness</td>
</tr>
<tr>
<td>Wake-promoting, non-traditional stimulants</td>
<td>Increase DA</td>
<td>Increased DA signaling</td>
<td>Increased wakefulness</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Enhance GABA signaling GABA-A receptors</td>
<td>GABA inhibits the arousal systems</td>
<td>Increased sleep</td>
</tr>
<tr>
<td>Non-benzodiazepine sedatives</td>
<td>Enhance GABA signaling GABA-A receptors</td>
<td>GABA inhibits the arousal systems</td>
<td>Increased sleep</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>Block HA H1 receptors</td>
<td>Reduced HA signaling</td>
<td>Increased sleep</td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>Block DA receptors</td>
<td>Reduced DA signaling</td>
<td>Increased sleep</td>
</tr>
</tbody>
</table>

CAUSES AND CONSEQUENCES OF SLEEP-WAKE DISORDERS
Sleep-Wake Disturbances Increase Risk of Work-Related Injury

• Sleep-wake disorders affect up to 70 million people in the USA

• Workers with sleep-wake problems have a 1.62-fold 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 (OSA) 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 use disorder

• Many psychotropic agents can affect sleep-wake cycles

Sleep Deprivation Heightens Limbic Response to Negative Emotional Stimuli

- Police officers with sleep disorders report more instances of uncontrolled anger
  - fMRI studies show that the amygdala is less able to govern behavioral responses to negative emotional stimuli following sleep deprivation

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

SLEEP DISORDERS AND THEIR TREATMENTS
Sleep-Wake Hygiene

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

**Wake Time**
- Activity
Insomnia

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

- Insomnia ≠ sleep deprivation

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

Symptoms of Insomnia

- Subjective complaints of poor sleep quality or duration
  - Possibly a marker of 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) >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
- PTSD
- Schizophrenia
- Substance use disorders

Sleep-Wake Disorders
- Sleep apnea
- Restless legs syndrome
- Circadian rhythm disorders

Medical Conditions
- Congestive heart failure
- COPD
- 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

Sleep-Related Biological Abnormalities Associated With Insomnia

- Elevated heart rate
- Heart rate variability
- Abnormal body temperature
- Abnormal HPA activity
- Abnormal norepinephrine secretion
- Elevated brain glucose metabolism
- Reduced gray matter volume in cortex and hippocampus
- Greater frequency of the 5HTTLPR short allele
  - Regulatory region of the serotonin transporter gene
  - Also associated with depression

Insomnia: Differential Diagnosis

• Evaluate sleep quality and sleepiness
  – e.g., Epworth Sleepiness Scale
  – 24-hour sleep-wake diary maintained for 2 weeks

• 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 (eg, apnea, RLS), when initial diagnosis is uncertain, when treatment fails, or if arousals occur with violent or injurious behavior

Features of Obstructive Sleep Apnea

- Repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep
- Episodes result in decreased blood oxygen saturation and are terminated by arousal

Clinical Features
- Loud snoring
- Obesity
- Hypertension
- Neck >17"
- Enlarged tonsils
- Loss of interest
- Excessive daytime sleepiness
- Fatigue
- Depression

Pathophysiology
- Partial/full collapse of upper airway
- Narrowing may occur at different levels
- Muscle tone, airway reflexes
- Metabolic abnormalities in frontal lobe white matter and hippocampus

Diagnosing Obstructive Sleep Apnea

• Polysomnography (PSG)

• Portable monitor
  – Can be used at home without a technician in attendance
  – May be more cost effective than in-lab PSG but perhaps less accurate

• Frequency of obstructive events reported as either:
  – Apnea-hypopnea index (AHI)
    • AHI 5-15 = mild sleep apnea
    • AHI 15-30 = moderate sleep apnea
    • AHI >30 = severe sleep apnea
  – Respiratory disturbance index (RDI)

• Multiple Sleep Latency Test (MSLT) is not routinely indicated unless symptoms persist despite treatment
Continuous Positive Airway Pressure (CPAP): First-Line Therapy for Sleep Apnea

- Bilevel (BiPAP) or autotitrating (APAP) may be considered for CPAP-intolerant patients
- CPAP has lower hospitalization rates and healthcare costs
- Adherence rates with CPAP are poor (54%)

Additional Treatment Options

• Oral appliance therapies (OATs)
  – Mandibular advancement devices
    • Stabilize mandible in protruded position during sleep
  – Tongue retaining devices
    • Hold tongue in forward position to open upper airway

• Devices that combine OAT with CPAP are in development

• Surgery
  – Adenotonsillectomy
    • First-line for pediatric OSA
  – Upper airway surgery
  – Plastic rod soft palate implant
  – Genioglossus advancement
  – Hyoid suspension
  – Maxillomandibular advancement

• Topical nasal corticosteroids
  – For patients with rhinitis

Behavioral Interventions

• Weight loss to BMI <25

• Exercise

• Avoidance of alcohol or sedatives at bedtime

• Positional therapy
  – Keeps patient in non-supine position
  – Actually, typically involves the use of a tennis ball or backpack
  – Some disgruntled spouses may contemplate using a sharp tack!

Narcolepsy

• Neurological disorder characterized by severe excessive sleepiness and inability to maintain stable sleep-wake states

• Sleep episodes occur ~3-5 times/day and last minutes to hours

• Affects 1 in 2000 people in the USA

Clinical Features
• Sleepiness and insomnia
• Cataplexy: muscle weakness with strong emotion
• Sleep paralysis
• Sleep hallucinations
• Disrupted sleep

Pathophysiology
• Loss of hypocretin-containing neurons in lateral hypothalamus

• May be an autoimmune disorder
  – Several polymorphisms in immunity-related genes have been described

Diagnosing Narcolepsy

• Polysomnography for differential diagnosis
  – OSA is often comorbid with narcolepsy
    • There is an increased prevalence of obesity in patients with narcolepsy
  – Diagnosis and treatment of OSA should be done before confirming diagnosis of narcolepsy

• Multiple Sleep Latency Testing to confirm narcolepsy diagnosis

• A low CSF hypocretin level (<110 pg/mL) is also diagnostic

Treatment Options for Narcolepsy

• Excessive sleepiness (ES) can be treated with modafinil, armodafinil, or stimulants

• Sodium oxybate
  – Approved for the treatment of both ES and cataplexy in narcolepsy

• Antidepressants are not FDA-approved for ES in narcolepsy but may be beneficial
  – SSRIs, NRIs, SNRIs, TCAs, MAOIs

• Scheduled naps

Mechanism of Action of Sodium Oxybate

GABA

Xyrem

GABA_A

GABA_B

GHB

cataplexy

slow-wave sleep

excessive daytime sleepiness

Restless Legs Syndrome (RLS)

- Affects 2-3% of the population and is twice as common in females; prevalence is 27% in pregnant females
- Urge to move limbs is usually associated with paresthesias or dysesthesias
- Symptoms start or become worse with rest
- Physical activity often provides some relief
- Associated with dopamine or iron deficiency
- Patients often experience excessive daytime sleepiness and impaired sleep onset and maintenance

Treatment Options for RLS

- **Dopamine agonists**
  - Ropinirole, pramipexole, carbidopa-levodopa
  - Dopamine agonists may increase the risk of impulsive behaviors and lead to augmentation (worsening of symptoms beyond baseline)

- **Iron supplementation**

- **Gabapentin/pregabalin**
  - GABAergic agents
  - Gabapentin enacarbil is a newly approved prodrug with once-daily dosing

- **Low potency opiates**

- **Benzodiazepines**

  *Note: antipsychotics, antiemetics, SSRIs, TCAs, lithium, antihistamines, Ca²⁺ antagonists, and antihypertensives may exacerbate RLS*

*FDA-approved for the treatment of RLS*

TREATING "AWAKE" SLEEP DISORDERS
Nonpharmacological Treatments

• Sleep hygiene education
• 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 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-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

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

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>Total (95% CI)</td>
<td>0.26 [0.08, 0.43]</td>
</tr>
</tbody>
</table>
Benzodiazepine Hypnotics

- Bind with equal affinity to α1, α2, α3, and α5 subunits of the GABA-A receptor
  - Alpha subunit expression differs throughout the brain
  - The selectivity of a hypnotic for different α 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

• The FDA recently recommended that bedtime doses be lowered
  – Zolpidem
    • From 10 mg to 5 mg for immediate-release formulation
    • From 12.5 mg to 6.25 mg for extended-release formulation
  – Eszopiclone
    • From 3 mg to 1 mg

http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm
http://www.fda.gov/Drugs/DrugSafety/ucm397260.htm
Additional Treatments

- **Antidepressants**
  - Doxepin
  - Trazodone
  - Amitriptyline
  - Trimipramine
  - Mirtazapine
  - Agomelatine

- **Antipsychotics**
  - Olanzapine
  - Quetiapine
  - Asenapine

- **Anticonvulsants**
  - Clonazepam
  - Gabapentin
  - Tiagabine

- **Melatonin receptor agonists**
  - Ramelteon
  - Melatonin
  - Tasimelteon

- **Sodium oxybate**
  - *FDA-approved for the treatment of insomnia or non-24*
# 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><img src="image1" alt="Trazodone Diagram" /></td>
<td><img src="image2" alt="Hypnotic Trazodone 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="Doxepin Diagram" /></td>
<td><img src="image4" alt="Hypnotic Doxepin 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

- 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.

Optimize treatment for comorbid disorders (eg, sleep apnea, depression)

Nonpharmacological treatments (eg, sleep hygiene, CBT)

Ramelteon, doxepin
Zolpidem, eszopiclone, zaleplon, temazepam

Sedating antidepressant or antipsychotic

Non-benzodiazepine hypnotic or ramelteon + sedating antidepressant

Other sedating agents (eg, anticonvulsant)

TREATING "SLEEPY" SLEEP DISORDERS
# Medications and Substances Associated With Hypersomnia

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Anticonvulsants</th>
</tr>
</thead>
<tbody>
<tr>
<td>– SSRIs</td>
<td>– Riluzole</td>
</tr>
<tr>
<td>– SNRIs, atypicals</td>
<td>– Topiramate</td>
</tr>
<tr>
<td>– Mirtazapine</td>
<td>– Zonisamide</td>
</tr>
<tr>
<td>– Trazodone</td>
<td>– Carbamazepine</td>
</tr>
<tr>
<td>– Nefazodone</td>
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</tbody>
</table>

## Atypical Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Benzodiazepines</th>
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</thead>
<tbody>
<tr>
<td>– Quetiapine</td>
<td></td>
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<tr>
<td>– Risperidone</td>
<td></td>
</tr>
<tr>
<td>– Olanzapine</td>
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</tbody>
</table>

Any drug that crosses the blood-brain barrier and affects a neurotransmitter system may be associated with hypersomnia.
# Pharmacological Treatments for Hypersomnia

<table>
<thead>
<tr>
<th></th>
<th>Modafinil</th>
<th>Armodafinil</th>
<th>Stimulants</th>
<th>Caffeine</th>
<th>Melatonin</th>
<th>Sleep aids</th>
<th>Antidepressants</th>
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<tbody>
<tr>
<td>Narcolepsy</td>
<td>✓</td>
<td>X</td>
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<td></td>
<td>X</td>
<td></td>
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<td>Idiopathic hypersomnia</td>
<td>X</td>
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<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>OSA</td>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>RLS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Circadian rhythm disorders</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*FDA-approved for this indication*
Modafinil's MOA: Alpha-Adrenergic Stimulation via DAT Inhibition?

Downstream: Increase in HA, Glu
Activation of wake-related circuitry

Off-Label Treatments for Excessive Sleepiness

• Stimulants
  – Low dose (5–10 mg) of methamphetamine
    • Potential for abuse
    • Adverse effects at higher doses (10–20 mg) are not uncommon
  – Caffeine
    • 300 mg has been shown to increase performance and alertness in shift workers
  – Energy drinks: no evidence supports their use

• Avoid stimulants during the second half of the work shift

• A person who relies on stimulants may experience insomnia and subsequent excessive sleepiness on the next shift

Emerging Treatments: Histamine Receptor Antagonists

- Histamine H3 receptors are autoreceptors
  - Blockade of these receptors promotes histamine activity and wakefulness

- Several H3 antagonists are under investigation as potential treatments for excessive daytime sleepiness
Emerging Treatments: Orexin (Hcrt) Antagonists

• Hypocretin-1 and hypocretin-2 (also known as orexins)
  – The Hcrt-1 (OxR1) receptor is selective for Hcrt-1
  – The Hcrt-2 (OxR2) receptor binds Hcrt-1 (OxR1) and Hcrt-2 (OxR2) with equal affinity

• Sustain wakefulness and increase arousal in motivating conditions

• The 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

Emerging Treatments: Orexin (Hcrt) Antagonists

- May be ideal for treating comorbid insomnia and metabolic disorders

- Dual OxR1/OxR2 receptor antagonists
  - Almorexant
    - Demonstrated dose-dependent improvement in symptoms of insomnia
    - Phase III trials were discontinued due to side effect burden
  - Suvorexant

from hypothalamus (LHA/PA)

orexin A

orexin B

Ca++

Na+

OX1R

OX2R

OX2R

NMDA

GIRK

awake
OX1R  OX1R  OX2R  OX2R
DORA  SORA1  SORA2  DORA

Ca++  NMDA  GIRK

asleep
Suvorexant

- Most common side effects in clinical trials: somnolence, headache, dizziness, abnormal dreams
- Label contains warning for risk of next-day impaired alertness and motor coordination
- Starting dose: 10 mg, no more than once per night and within 30 minutes of bedtime; requires 7 hours remaining of sleep time; 20 mg is the maximum recommended dose
- Patients who tolerate but do not respond to 10 mg may receive 15 mg or 20 mg doses
- Not recommended in patients taking concomitant strong CYP450 3A4 inhibitors; patients taking moderate CYP3A4 inhibitors should receive a 5 mg dose
- Contraindicated in narcolepsy

4 Weeks of Suvorexant Treatment Compared to Placebo

Sleep Efficiency

Mean Change Compared to Placebo (min)

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

4 Weeks of Suvorexant Treatment Compared to Placebo

**Wake After Sleep Onset (WASO)**

Mean Change Compared to Placebo (min)

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

*** 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

10 mg
20 mg
40 mg
80 mg

*** p<0.001

4 Weeks of Suvorexant Treatment Compared to Placebo

**Total Sleep Time (TST)**

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

**Hoyer et al. Neuropeptides 2013;47:477-88.**

**p<0.01**

**p<0.001**
Summary

• One of the easiest and earliest ways to try to help a patient with excessive sleepiness is to investigate if poor sleep-wake hygiene is contributing to excessive sleepiness or if there is a bona fide underlying medical cause.

• Sleep-wake disorders may have severe negative consequences on both physical and mental health.

• Medications can be used to treat excessive sleepiness during waking hours and help alleviate sleep problems that can lead to excessive sleepiness.

• Treatment regimens differ for the various sleep-wake disorders; thus, proper recognition and assessment are vital.