Identifying and Treating Sleep Disorders in Psychiatric Practice
Learning Objectives

• Understand the neurobiology and molecular basis of sleep

• Recognize and assess sleep/wake disorders

• Educate patients about the consequences of sleep/wake disturbances

• Implement treatment strategies to address sleep/wake disturbances
Fran is a 42-year-old patient with shift work disorder who reports that she is having difficulty in her job as a police officer due to excessive sleepiness during her 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
Pre-Poll Question

What percentage of your patients have sleep/wake problems?

1. 0-20%
2. 20-40%
3. 40-60%
4. 60-80%
5. 80-100%
NEUROBIOLOGY OF SLEEP
Processes Regulating Sleep

- **Awake**
- **Stage 1**
- **Stage 2**
- REM
- REM
- REM
- REM

ultradian (sleep cycle)

Slow wave sleep

Time of Sleep

0
1
2
3
4
5
6
7
8
Zeitgebers

Cues to synchronize circadian rhythms

- Light
- Melatonin
- Eating and drinking patterns
- Social interactions

Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract
Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract

Pineal Gland

melatonin
Distinct hypothalamic neurons control the sleep/wake cycle.


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

**Awake**

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

**Stage 1**

**Stage 2**

**Stage 3**

**Stage 4**

**REM**

**Time of Sleep**

0 1 2 3 4 5 6 7 8

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>Examples</th>
<th>Pharmacologic Effect</th>
<th>Neurobiologic Mechanism</th>
<th>Clinical Effects</th>
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<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Fluoxetine, Fluvoxamine, Citalopram</td>
<td>Increase extracellular levels of 5-HT</td>
<td>5-HT inhibits REM sleep-producing cells</td>
<td>Decreased REM sleep</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, Nortriptyline, Clomipramine, Desipramine</td>
<td>Increase extracellular levels of 5-HT and NE</td>
<td>5-HT and NE inhibit REM sleep-producing cells</td>
<td>Decreased REM sleep</td>
</tr>
<tr>
<td>Traditional, amphetamine-like stimulants</td>
<td>Amphetamine, Dextroamphetamine, Methylphenidate</td>
<td>Increase extracellular levels of 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>Modafinil, Armodafinil</td>
<td>Increase extracellular levels of DA</td>
<td>Increased DA signaling</td>
<td>Increased wakefulness</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam, Clonazepam, Lorazepam, Trazolam</td>
<td>Enhance GABA signaling via GABA&lt;sub&gt;α&lt;/sub&gt; receptors</td>
<td>GABA inhibits the arousal systems</td>
<td>Increased sleep</td>
</tr>
<tr>
<td>Non-benzodiazepine sedative hypnotics</td>
<td>Zolpidem, Zaleplon, Zopiclone</td>
<td>Enhance GABA signaling via GABA&lt;sub&gt;α&lt;/sub&gt; receptors</td>
<td>GABA inhibits the arousal systems</td>
<td>Increased sleep</td>
</tr>
<tr>
<td>Classic antihistamines</td>
<td>Diphenhydramine, Triprolidine</td>
<td>Block HA&lt;sub&gt;1&lt;/sub&gt; receptors</td>
<td>Reduced HA signaling</td>
<td>Increased sleep</td>
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<tr>
<td>Typical antipsychotics</td>
<td>Haloperidol, Chlorpromazine</td>
<td>Block DA receptors</td>
<td>Reduced DA signaling</td>
<td>Increased sleep</td>
</tr>
</tbody>
</table>
negative feedback loops
Transcription Factors

DNA

Promoter/Gene

OFF

Gene
CAUSES AND CONSEQUENCES OF SLEEP/WAKE DISORDERS

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

### Psychiatric Disorders

#### Clock Genes Associated With Psychiatric Disorders

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<thead>
<tr>
<th>Clock Gene</th>
<th>Disorder</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bmal</td>
<td>Bipolar</td>
<td>Mansour et al. 2006;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nievergelt et al. 2006.</td>
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<tr>
<td>Clock (or its homolog, NPAS)</td>
<td>Bipolar</td>
<td>Benedetti et al. 2003;</td>
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<td></td>
<td></td>
<td>Soria et al. 2010.</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Soria et al. 2010.</td>
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<td></td>
<td>Schizophrenia</td>
<td>Takao et al. 2007.</td>
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<td></td>
<td>Seasonal affective disorder</td>
<td>Johansson et al. 2003;</td>
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<td></td>
<td></td>
<td>Partonen et al. 2007.</td>
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<tr>
<td>Cry</td>
<td>Depression</td>
<td>Soria et al. 2010.</td>
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<td>Per</td>
<td>Bipolar</td>
<td>Nievergelt et al. 2006;</td>
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<td></td>
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<td>Artioli et al. 2007;</td>
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<td>Seasonal affective disorder</td>
<td>Partonen et al. 2007.</td>
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<tr>
<td>Rev-erbα</td>
<td>Bipolar</td>
<td>Kripke et al. 2009;</td>
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<tr>
<td></td>
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<td>Severino et al. 2009.</td>
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</tbody>
</table>
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

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 for 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;
SLEEP DISORDERS AND THEIR TREATMENTS
Tools for Assessing Sleep/Wake Disorders (see appendix)

• Polysomnography
  • Electroencephalogram (EEG): brain activity
  • Electrooculogram (EOG): eye movements
  • Electromyogram (EMG): muscle activity
  • Electrocardiogram (ECG): heart rhythm

• Multiple Sleep Latency Testing
  – Uses polysomnography to detect the latency to onset of sleep

• Actigraphy
  – Measures gross motor activity to detect rest/activity cycles

• Sleep/wake diary

• Assessment questionnaires (e.g., Epworth Sleepiness Scale)
Sleep/Wake Hygiene

Sleep Time

- No stimulants before bed
- Dark room
- Cool environment
- No disturbances

Wake Time

Activity
## Insomnia

- The 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>Reduced</td>
<td>Reduced</td>
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<tr>
<td>Reduced</td>
<td>Adequate</td>
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</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

<table>
<thead>
<tr>
<th>Psychiatric Disorders</th>
<th>Medical Conditions</th>
<th>Medications/Substances</th>
</tr>
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<tbody>
<tr>
<td>• Major depression</td>
<td>• Congestive heart failure</td>
<td>• Alcohol</td>
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<tr>
<td>• Dysthymic disorder</td>
<td>• COPD</td>
<td>– Acute use</td>
</tr>
<tr>
<td>• Bipolar affective disorder</td>
<td>• Asthma</td>
<td>– Withdrawal</td>
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<tr>
<td>• Generalized anxiety disorder</td>
<td>• Chronic renal failure</td>
<td>• Caffeine</td>
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<tr>
<td>• Panic disorder</td>
<td>• Prostatic hypertrophy</td>
<td>• Nicotine</td>
</tr>
<tr>
<td>• PTSD</td>
<td>• Gastroesophageal reflux</td>
<td>• Antidepressants</td>
</tr>
<tr>
<td>• Schizophrenia</td>
<td>• Fibromyalgia</td>
<td>• Corticosteroids</td>
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<tr>
<td>• Substance use disorders</td>
<td>• Osteoarthritis</td>
<td>• Decongestants</td>
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<tr>
<td></td>
<td>• Rheumatoid arthritis</td>
<td>• β agonists/antagonists</td>
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<tr>
<td></td>
<td>• Hyperthyroidism</td>
<td>• Theophylline derivatives</td>
</tr>
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<td>• Parkinson's disease</td>
<td>• Statins</td>
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<td></td>
<td>• Cerebrovascular disease</td>
<td>• Stimulants</td>
</tr>
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<td></td>
<td>• Menopause</td>
<td>• Dopamine agonists</td>
</tr>
</tbody>
</table>

### Sleep/Wake Disorders

- Sleep apnea
- Restless leg syndrome
- Circadian rhythm disorders

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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-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

Obstructive Sleep Apnea (OSA)

• 1 out of every 5 adults has mild OSA
• 1 out of every 15 adults has moderate OSA
• Up to 75% of patients with insomnia may have a sleep-related breathing disorder
• OSA is commonly associated with:
  – Hypertension
  – Hypercholesterolemia
  – Type 2 diabetes
  – Ischemic heart conditions
  – Coronary artery disease

Krakow, Ulibarri. Sleep Breathing 2012;Epub ahead of print.
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 (BPAP) or autotitrating (APAP) may be considered for CPAP-intolerant patients
- 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 2,000 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

Restless Leg 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

Diagnosing RLS

- Cambridge-Hopkins Diagnostic Questionnaire for RLS (CH-RLSq) (see appendix)
- Thyroid function testing
- Determine folate, vitamin B12, and sugar levels in blood
- Measure electrolyte status, urea, and creatinine as determinants of liver function
- Immobilization testing
  - Leg activity and EEG are recorded in the period before bedtime
- Polysomnography
- Actigraphy

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, Ca\(^{2+}\) antagonists, and antihypertensives may exacerbate RLS

*FDA-approved for the treatment of RLS*

Circadian Rhythm Disorders

• Circadian alteration in timing of sleep
  – Advanced sleep phase rhythm
    – Sleep pattern is earlier than desired (early to bed, early to rise)
    – Associated with polymorphisms in PER gene
  – Delayed sleep phase rhythm
    – Sleep pattern is later than desired (late to bed, late to rise)
    – Associated with polymorphisms in PER and CLOCK genes
• Shift work disorder (SWD)
  – Present in 44.8% of night shift workers

Diagnosing Circadian Rhythm Disorders

• Sleep/wake diary
• Morningness-Eveningness Questionnaire (MEQ)
• Actigraphy
• Melatonin levels
• Polysomnography to rule out other sleep disorders

Circadian Rhythm Disorders: Treatment Options

• Melatonin
  – Administered 3 hours before dim-light melatonin onset
    ▪ Phase response curve to melatonin advances; advances sleep, temperature, and melatonin rhythms; decreases sleep latency

• Bright light therapy (BLT)
  – Evening BLT phase delays circadian parameters and sleep/wake cycle
  – Shift workers can be completely re-entrained with bright light intermittently for 20 minutes during the night
  – Performance, alertness, and mood during night shift improve

• Modafinil/armodafinil to improve daytime sleepiness

• Hypnotics to improve daytime sleepiness in SWD

• Planned napping and caffeine

TREATING "AWAKE" SLEEP DISORDERS
Non-pharmacological 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-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

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*
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*
Mechanism of Trazodone and Doxepin as Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Antidepressant dose</th>
<th>Hypnotic dose</th>
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<tbody>
<tr>
<td><strong>Trazodone</strong></td>
<td><img src="image" alt="Trazodone Diagram" /></td>
<td><img src="image" alt="Trazodone Hypnotic Diagram" /></td>
</tr>
<tr>
<td><strong>Doxepin</strong></td>
<td><img src="image" alt="Doxepin Diagram" /></td>
<td><img src="image" alt="Doxepin Hypnotic Diagram" /></td>
</tr>
</tbody>
</table>

- **Trazodone**: (150-600 mg) for Antidepressant, (25-150 mg) for Hypnotic dose
- **Doxepin**: (150-600 mg) for Antidepressant, (1-6 mg) for Hypnotic dose

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 with non-pharmacological therapy may have longer-lasting effects and facilitate medication discontinuation.

Optimize treatment for comorbid disorders (e.g., sleep apnea, depression)

Non-pharmacological treatments (e.g., sleep hygiene, CBT)

Zolpidem, eszopiclone, zaleplon, temazepam, or ramelteon

Sedating antidepressant or antipsychotic

Non-benzodiazepine hypnotic or ramelteon + sedating antidepressant

Other sedating agents (e.g., anticonvulsant)

Emerging Treatments: Orexin (Hcrt) Antagonists

- Hypocretin-1 and hypocretin-2 (also known as orexins)
  - The Hcrt-1 receptor is selective for Hcrt-1
  - The Hcrt-2 receptor binds Hcrt-1 and Hcrt-2 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 antagonism
  - Modulates dopamine in addiction/reward centers of the brain
- Hcrt-2 antagonism
  - Decreases histamine in the hypothalamus

Emerging Treatments: Orexin (Hcrt) Antagonists

• May be ideal for treating comorbid insomnia and metabolic disorders

• Dual Hcrt-1/Hcrt-2 receptor antagonists
  – Almorexant
    • Demonstrated dose-dependent improvement in symptoms of insomnia
    • Phase III trials were discontinued due to side effect burden
  – MK-4305 (Suvorexant)
    • In Phase III trials

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

#### Antidepressants
- SSRIs
- SNRIs, atypical
- Mirtazapine
- Trazodone
- Nefazodone

#### Atypical Antipsychotics
- Quetiapine
- Risperidone
- Olanzapine

#### Anticonvulsants
- Riluzole
- Topiramate
- Zonisamide
- Carbamazepine

#### Anticonvulsants

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

*FDA-approved for this indication*
Modafinil vs. Armodafinil

- Both promote wakefulness through activation of hypothalamus, prefrontal cortex, and anterior cingulate cortex

- Modafinil contains both R (long-acting) and S (short-acting) isomers
  
  - Less plasma drug variability than modafinil
  
  - May be more effective in promoting wakefulness toward the end of an 8-hr shift in patients with SWD

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

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.

• 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.
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

---

![Graph showing mean sleep latency (min) vs degree of sleepiness (Normal, Mild, Moderate, Severe)]
Actigraphy
## Sleep/Wake Diary

<table>
<thead>
<tr>
<th></th>
<th>First day</th>
<th>Second day</th>
<th>Third day</th>
<th>Fourth day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete in morning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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</td>
<td>2 hours</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>
<tr>
<td><strong>Complete at bedtime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naps (number, time, and duration)</td>
<td>1 at 3:30 p.m.</td>
<td>45 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks (number and time)</td>
<td>1 drink at 8:00 p.m.</td>
<td>2 drinks at 9:00 p.m.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List stresses of the day</td>
<td>Flat tire</td>
<td>Argued with son</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate how you felt today</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = Very tired/sleepy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Somewhat tired/sleepy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Fairly alert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 = Wide awake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability level</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Some</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 = Fairly high</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 = High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 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>Sitting and reading</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>As a passenger in a car for an hour without a break</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting and taking to someone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
Cambridge-Hopkins Diagnostic Questionnaire for RLS (CH-RLSq)

Table 1. Critical diagnostic questions from the CH-RLSq.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down?</td>
<td>Yes • No</td>
</tr>
<tr>
<td>Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down?</td>
<td>Yes • No</td>
</tr>
<tr>
<td>Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active?</td>
<td>Resting • Active</td>
</tr>
<tr>
<td>If you get up or move around when you have these feelings do these feelings get any better while you actually keep moving?</td>
<td>Yes • No • Don't know</td>
</tr>
<tr>
<td>Which times of day are these feelings in your legs most likely to occur?</td>
<td>Morning • Mid-day • Afternoon • Evening • Night • About equal at all times</td>
</tr>
<tr>
<td>Will simply changing leg position by itself once without continuing to move usually relieve these feelings?</td>
<td>Usually relieves • Does not usually relieve • Don't know</td>
</tr>
<tr>
<td>Are these feelings ever due to muscle cramps?</td>
<td>Yes • No • Don't know</td>
</tr>
<tr>
<td>If so, are they always due to muscle cramps?</td>
<td>Yes • No • Don't know</td>
</tr>
</tbody>
</table>

Scoring: Definite RLS: 1 yes, 2 yes, 3 resting, 4 yes, 5 NOT equal or morning, 6 does not usually relieve, 7a as No OR b as No.

Note: This is not the complete questionnaire.
Contact Richard P. Allen @ richardjhu@mac.com to obtain the full questionnaire.