## Treatment of Insomnia

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## Presentation Objectives:
- Briefly review function of sleep and neurotransmitters associated with promotion of sleep
- Review current and newly approved therapies for the treatment of insomnia – including mechanisms of action and pharmacology
- Discuss agents in clinical development for the potential treatment of insomnia and their mechanisms of action

## Function of Sleep

<table>
<thead>
<tr>
<th>“If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process ever made.”</th>
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<tbody>
<tr>
<td>A. Rechtschaffen</td>
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## Function of Sleep

<table>
<thead>
<tr>
<th>Restoration and recovery</th>
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<tbody>
<tr>
<td>Sleep serves to reverse and/or restore biochemical and/or physiological processes degraded during prior wakefulness</td>
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<thead>
<tr>
<th>Energy conservation</th>
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<tr>
<td>10% reduction of metabolic rate below basal level</td>
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<tr>
<th>Memory consolidation</th>
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<tr>
<th>Thermoregulation</th>
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<tr>
<th>Homeostasis</th>
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</table>
The Sleep Cycle

Alternating states and stages of sleep that occur over an 8-hour time period:
- **NREM**: Non-Rapid Eye Movement; Stages 1-4; 75% of the night
- **REM**: Rapid Eye Movement; Dreams occur; 25% of the night

During the Sleep Cycle

- Brain waves represent different stages of sleep.

### NREM Stages of Sleep

### REM Sleep

During the Sleep Cycle (cont.)

- Body temperature lowers
- Hormone levels rise and fall

Sleep needs vary over the life cycle.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age Range</th>
<th>Sleep Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns/Infants</td>
<td>0 - 2 months; 2 - 12 months</td>
<td>10.5-18 hours; 14-15 hours</td>
</tr>
<tr>
<td>Toddlers/Children</td>
<td>12 mo - 18 mo; 18 mo - 3 years; 3 - 5 years; 5 - 12 years</td>
<td>13-15 hours; 12-14 hours; 11-13 hours; 10-11 hours</td>
</tr>
<tr>
<td>Adolescents</td>
<td>On Average:</td>
<td>9.25 hours</td>
</tr>
<tr>
<td>Adults/Older Persons</td>
<td>On Average:</td>
<td>7-9 hours</td>
</tr>
</tbody>
</table>
Sleep patterns and characteristics change over the life cycle.

| Newborns/Infants | Sleep begins at 20-30 min; sleep cycles are short and frequent |
| Toddlers         | Sleep begins to resemble adult pattern |
| Children         | Experience more deep sleep |
| Adolescents      | Shift to later sleep-wake cycle; experience daytime sleepiness |
| Adults           | More likely to have medical problems; sleep disruptions & disorders; sleep loss efficiency |
| Older Adults     | More likely to have medical problems; sleep disruptions & disorders; sleep loss efficiency |

Sleep Promoting CNS Neurotransmitters

- **GABA (inhibitory amino acid)**
  - Ventral Lateral Pre-Optic Nucleus (VLPO) within anterior hypothalamus – "command & control center" for sleep
  - Inhibitory connections to thalamus, descending projections inhibit cell bodies and dendrites of serotonin, norepinephrine, histamine, acetylcholine-producing inter-neurons
  - Role: Initiation and maintenance of sleep spindles and SWS

- **Melatonin (hormone of darkness)**
  - Secreted from pineal gland during darkness/ indirectly feedbacks to SCN
  - High levels secreted prior to sleep
  - Levels low during wakefulness

Conditions of Insomnia:

- **Primary Insomnia**: Insomnia that is not a result of another condition -hyper-arousal disorder
- **Secondary Insomnia**: Insomnia resulting from:
  - Psychiatric: depression, anxiety
  - Medical conditions: pain, CV, neurological or GI illnesses
  - Substance abuse
  - Behavior
  - Another primary sleep disorder
  - RLS/PLMS
  - Apnea
  - Narcolepsy
  - Circadian rhythm disorders
Over 30% of American adults experience occasional insomnia; 10% on a chronic basis.

Those most at risk:
- Women
- Older adults
- Patients with psychiatric disorders
- Patients with medical disorders (pain syndromes, asthma, CV)
- Shift workers

Reduced Total Sleep Time Impacts Health & Next-day Functioning

- Increased number (4.5-fold) of serious accidents or injuries
  - 200,000 MVA each year caused by drowsiness (US DOT)
- Impaired alertness & memory
- Impaired psychomotor performance
- Increased healthcare utilization and absenteeism

Treatment of Insomnia

- Behavioral Interventions – CBT (Cognitive Behavioral Therapy)
- Pharmacological
  - OTCs (Over-The-Counter)
    - Diphenhydramine
    - Doxylamine
    - L-Tryptophan
    - Melatonin
    - Alcohol
    - Plant-based herbs – Valerian, Chamomile, Hops, Lemon Balm, Lavender, Ylang Ylang, Melissa, Passion Flower, Kava Kava
  - Barbiturates
  - Chloral Hydrate
  - Antidepressants
  - GABA-A Receptor Allosteric Modulators
    - Benzodiazepines
    - Non-Benzodiazepines
  - Melatonin Receptor Agonists
### Antidepressants

- Tricyclic Antidepressants (TCAs)
- SSRIs/SNRIs
- Trazodone

### TCAs (Not FDA approved for hypnotic use)

- Tertiary amines (amitriptyline, doxepin, imipramine...) greater sedation than secondary amines (desipramine, nortriptyline, protriptyline)
- TCAs decrease REM sleep & prolong REM latency
- May increase TST but may worsen periodic limb movements (PLMs); specific agents may prolong SWS
- MOA: Block 5-HT and NE reuptake/anticholinergic and antihistaminic activity
- Weak alpha-1 blockade results in orthostatic hypotension
- TCAs have poor sleep onset activity
- Acute withdrawal can cause REM rebound

### SSRIs/SNRIs (Not FDA approved for hypnotic use)

- Antidepressant drugs can both improve and disturb sleep, as well as have effects on waking function.
- Evaluation of the effects of these drugs on sleep and wakefulness is complicated by the fact that many individuals with depression typically have:
  - disturbed sleep
  - daytime fatigue
  - sleepiness
  - somatic complaints
  - decreased cognitive and psychomotor functioning
- PSG (polysomnogram) and subjective patient reports of sleep do not always correlate

### Effects of Newer Antidepressants on Sleep and Waking Behavior

- Most SSRIs ↑ wakefulness, ↓ TST (no data on sertraline and no change in TST or W with citalopram)
- Insomnia incidence in SSRI treated patients ranges from 5-16%
- Daytime sedation incidence in SSRI treated patients ranges from 2-26%
- Venlafaxine (5HT/NE reuptake inhibitor): similar to SSRIs, insomnia 8%, sedation 3-31%
- Bupropion (DE/NE reuptake inhibitor): insomnia 5-19%
Trazodone (Not FDA approved for hypnotic use)

- Produces sedating effects via antagonistic effects at H1 & 5-HT2 receptors
- Low doses (50-100mg) often used as adjunct to SSRI treatment
- Men must be counseled about priapism (persistent and painful erections)
- Severe postural hypotension can occur due to antagonism of alpha-1 receptors
- Long T1/2 may lead to daytime sedation
- Recent concerns about administration with strong inhibitors of CYP3A4 (i.e., itra-, ketoconazole)

Select Benzodiazepines*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual adult oral dose (mg)</th>
<th>Tp (hrs)</th>
<th>T1/2 (hrs)</th>
<th>Protein binding (%)</th>
<th>Urinary excretion, unchanged (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estazolam (Prosom®)</td>
<td>1-2</td>
<td>2</td>
<td>8-28</td>
<td>93</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Flurazepam (Dalmane®)</td>
<td>15-30</td>
<td>0.5-1</td>
<td>2-3</td>
<td>97</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Guazepam (Donall®)</td>
<td>7.5-15</td>
<td>2 (1-2)</td>
<td>41 (47-100)</td>
<td>&gt; 95</td>
<td>Trace</td>
</tr>
<tr>
<td>Temazepam (Restoril®)</td>
<td>15-30</td>
<td>1.2-1.6</td>
<td>3.5-18.4 (9-15)</td>
<td>96</td>
<td>0.2</td>
</tr>
<tr>
<td>Triazolam (Halcion®)</td>
<td>0.125-0.5</td>
<td>1-2</td>
<td>1.5-5.5</td>
<td>78-89</td>
<td>2</td>
</tr>
</tbody>
</table>

(BZDs have long elimination half-life of up to 100 hours)

MOA of BZDs and Non-BZDs: The Role of GABA_A Receptors

- The GABA_A receptor is a pentameric complex
- Currently, there have been 7 subunit families comprising at least 18 subunits in the CNS:
  - α_1, β_1-3, γ_1-3, δ, ε, θ, ρ_1-3
- The major subtype combination (60% of all GABA-A receptors) consist of α_1β_2γ_2

Benzodiazepines

- BZDs suppress SWS and REM sleep as well as prolong REM latency
- Stage 2 sleep is prolonged with an increase in spindle density, sleep latency is shortened, TST is increased
- Flurazepam has long elimination half-life of up to 100 hours
- Shortest acting is triazolam with half-life of 1-5.5 hours
- Acute withdrawal is associated with decreased TST as well as REM & SWS rebound

### Non-Benzodiazepines (GABA-A Receptor Allosteric Modulators)

<table>
<thead>
<tr>
<th>Drug &amp; class</th>
<th>Half Life (hr)</th>
<th>Dose (mg)</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Contraindications and Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone (Lunesta) pyrazolopyrimidine</td>
<td>5-7</td>
<td>1-3</td>
<td>Tx of insomnia</td>
<td>Peppleasing taste, dry mouth, drowsiness, dizziness</td>
<td>Drugs that inhibit CYP3A4, etoh, alprazolam</td>
</tr>
<tr>
<td>Zolpidem (Ambien, Ambien CR) imidazopyridine</td>
<td>3</td>
<td>5-10; 6.25-12.5 (CR)</td>
<td>Short term Tx of insomnia – CR</td>
<td>Drowsiness, dizziness, occasionally amnesia</td>
<td>Possibly drugs that inhibit CYP3A4, etoh</td>
</tr>
<tr>
<td>Zaleplon (Sonata) pyrazolopyrimidine</td>
<td>1</td>
<td>5-20</td>
<td>Short term Tx of insomnia (SL)</td>
<td>Drowsiness</td>
<td>Possibly drugs that inhibit CYP3A4, etoh</td>
</tr>
</tbody>
</table>

Adapted from Silber M, NEJM 353;8: 806.

### Non-benzodiazepines, cont.

- **Zolpidem (Ambien®) / Zaleplon (Sonata®)**
  - Approved for short term use (7-10 days)
  - Reassess in 2-3 weeks
  - Decrease sleep latency and increase TST (zolpidem)
- **PK**
  - T ½ = 2.5 hrs for 10 mg Zolpidem; inactive metabolites
  - CYP3A4 main route of metabolism; minor renal elimination
  - T ½ = 1 hr for 10 mg Zaleplon; elderly dose = 5 mg
- **Efficacy**
  - Zolpidem: longest nightly use 5 weeks/ 8-12 weeks intermittent use
  - Zaleplon: 30 days nightly use
  - Can be taken late at night without next-day effects

- **Safety: Minimal changes in sleep architecture**
  - Minimal next-day effects
  - No improvement in middle insomnia (sleep maintenance).
- **Adverse Events**
  - Zolpidem: common ADR's: drowsiness, headache, dizziness
    - Amnesia more common at doses > 10mg
    - No significant rebound insomnia (5 week study)
    - Reports of abuse in those with hx of substance abuse
    - Rare reports of hallucinations at recommended doses
### Non-benzodiazepines (cont)

- **Ambien CR™** (zolpidem tartrate extended release tablets)
  - Approved Sept 6, 2005 – indicated for the treatment of insomnia (sleep onset/maintenance)
  - Zolpidem CR consists of a coated two-layer tablet:
    - One layer releases drug immediately
    - Another layer that allows slower release of additional drug
  - Available in 6.25 mg and 12.5 mg strengths
  - The clinical trials were both 3 weeks in duration (assessment of SL and maintenance were performed after 2 weeks of treatment)

- **Eszopiclone (Lunesta™)**: non-benzodiazepine cyclopyrrolone
  - Indications: Sleep onset and sleep maintenance insomnia – Approved for long term use
  - Eszopiclone = (S)-Zopiclone, contains pharmacologic activity of racemate
    - Available since 1987
    - Racemic (R,S)-zopiclone (Imovane, Zimovan, Zimovane)
    - Currently marketed in over 85 countries at doses of 5-10 mg

- **Eszopiclone**: PK
  - **T ½ = 5-7 hrs for 3 mg eszopiclone; active metabolite, but to lesser degree than parent compound**
    - CYP3A4 main route of metabolism, 2E1 minor path
  - **Tmax = 1 hr for 3 mg; elderly dose = 1-2 mg**

- **Efficacy**
  - Longest study was 2-6 month double blind randomized studies of eszopiclone 3 mg vs. placebo with a 6 mo open label extension
    - Decrease in sleep latency, increase in TST
  - Minimal changes to sleep architecture
  - Adverse Events & Safety
    - Unpleasant taste, dry mouth, dizziness and drowsiness
    - No significant PSG rebound after 44 nights of therapy nor after 180 nights with 3 mg dose
    - Abuse study performed with s-isomer

- **Ramelteon (Rozerem™)**
  - Ramelteon was approved by the FDA in July 2005 for the treatment of insomnia characterized by difficulty with sleep onset
  - Ramelteon specifically targets the MT1 and MT2 receptors in the brain, believed to be critical in the regulation of the body’s sleep-wake cycle
  - **PK**
    - T ½ = 2-5 hours, dose is 8 mg 30 minutes before going to bed
    - Metabolized by CYP1A2, CYP2C and CYP3A4 minor paths
    - Should not be used in severe hepatic impairment or with fluvoxamine, and used with caution in patients with moderate hepatic impairment
    - Do not take with a high fat meal
Ramelteon MOA

Suprachiasmatic Nucleus

Ramelteon (Rozerem™)

- Efficacy
  - Significant decrease in LPS w/ treatment vs. placebo:
    - Adult chronic insomnia 35 night trial
    - Elderly chronic insomnia 3 period crossover trial
    - Healthy adults first night effect model of transient insomnia

- Adverse Events & Safety
  - Drowsiness, dizziness, increased prolactin levels
    - Patients should be advised to consult their healthcare provider if they experience 1 of the following: cessation of menses or galactorrhea in women, decreased libido, or problems with fertility.
  - No abuse potential

New Insomnia Research
**Indiplon** (Not FDA approved for hypnotic use)

- MOA: GABA-A Receptor Allosteric Modulator
- In development for insomnia (Neurocrine)
- IR and modified release (MR) indiplon are under investigation for both adults and elderly
- Indiplon is a pyrazolopyrimidine (same class as zaleplon)
- In a 35-day DB, parallel trial: 194 patients diagnosed w/ primary insomnia randomized to either 10 mg or 20 mg IR indiplon or placebo
- Primary end point: latency to persistent sleep (LPS) confirmed via PSG
- Results: 10-mg dose significantly reduced LPS by 28 minutes, compared with a mean latency of 37 minutes for placebo ($P < .002$). The 20-mg dose reduced LPS by 27 minutes ($P < .05$)
- Adverse events reported higher than placebo: somnolence and headache

APSS 2005 Abstract #0683; APA 2005 Abstract #551

**Gaboxadol** (Not FDA approved for hypnotic use)

- MOA: GABA-A Receptor Allosteric Modulator - affinity for the $\alpha_4\beta$ GABA$_A$ extrasynaptic receptors (located in cortex, thalamus, and limbic system)
- In development for insomnia (Merck & Lundbeck)
- Several phase III studies are currently underway.
  - 8 week to 12 month chronic insomnia duration studies

**Low Dose Doxepin – SO-101** (Not FDA approved for hypnotic use)

- MOA: Inhibits serotonin and norepinephrine reuptake, anticholinergic and antihistaminergic (Tertiary amine TCA)
- In development for insomnia (Somaxon)
- Several phase III studies are currently underway.
  - 8 week to 12 month chronic insomnia studies

**Other Compounds/Mechanisms** (Not FDA approved for hypnotic use)

- Other GABA-A Receptor Allosteric Modulators
  - Higher selectivity for different alpha subtypes
  - GABA Transport Inhibitor (GAT-1 antagonist/GABA reuptake inhibitor)
  - Tiagabine (Gabitril®) (Cephalon) – in phase II development
- Partial GABA agonists
- Other M1-M2 agonists
- Hypocretin/orexin receptor antagonists
- Selective Serotonin subtype receptor antagonists (5HT2A)
- Substance P antagonists
- Neurosteroids
Other Compounds/Mechanisms, cont. (Not FDA approved for hypnotic use)

- $H_3$ receptor agonists
  - $H_3$ receptor agonists have a sedative effect
  - $H_3$ autoreceptors modulate activity of histaminergic neurons

- Selective $H_1$ receptor antagonists
  - Could induce sedative effect without side effects associated with OTC antihistamines

Conclusions

- The function and mechanisms of sleep are complex
- Insomnia may be a symptom of another illness, may co-exist with another illness or exist alone
- Insomnia impacts psychiatric and medical illness and next-day functioning
- Sleep hygiene should always be cornerstone of treatment

Conclusions

- Barbiturates & BZDs change sleep architecture; withdrawal can ppt rebound effects
- Non-BZDS are safer, minimal next-day effects, but most are approved for short term use and best for sleep onset insomnia
- The wide array of compounds in current development appear promising for the treatment of chronic insomnia

Information on sleep and sleep disorders

- American sleep disorders association (http://www.asda.org)
- The national sleep foundation (http://sleepfoundation.org)
- Sleep home pages (http://www.sleephomepages.org)
- American academy of sleep medicine (AASM) (http://www.aasmnet.org)
- Associated professional sleep societies (APSS) (http://www.apss.org)