Pharmacotherapy of Sleep Disorders

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ARS Questions
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Disclosure Statement

- Consultant
  - Pernix, Pfizer, Jazz, Teva, Merck, Xenosports
- Stock Ownership
  - Merck
Insomnia Disorder

A. Dissatisfaction with sleep quantity or quality with one or more of the following:
   1. Difficulty initiating sleep (children: w/o caregiver intervention)
   2. Difficulty maintaining sleep (children: w/o caregiver intervention)
   3. Early morning awakening w/inability to return to sleep

B. Significant distress or impairment

C. > Three nights per week

D. > Three months

E. Adequate opportunity for sleep
   • Specify if:
     – With non–sleep disorder mental comorbidity
     – With other medical comorbidity
     – With other sleep disorder

Criteria F, G, and H not shown; not all specifiers shown
DSM-5, American Psychiatric Association, 2013
Prevalence of Insomnia in the General Adult Population

Insomnia = sleep disturbance every night for 2 weeks or more, or similarly stringent criteria.
Insomnia and Hyperarousal

- HPA axis activation
- Sympathetic activation
- Heightened brain metabolism
- Increased body metabolic rate
- Cognitive arousal
- EEG arousal

Hyperarousal
Impairments Associated with Insomnia

- Diminished ability to enjoy family and social relationships
- Decreased quality of life
- Increased absenteeism and poor job performance
- Motor vehicle crashes
- Increased risk of falls
- Impaired concentration and memory
- Increased incidence of pain
- Enhanced risk of present and future psychiatric disorders
- Hypertension
- Diabetes
- Increased mortality

N=580.
Complex Relationship Between Insomnia and Mood Disorders

Insomnia

- Is a common complaint in MDD
- Is more likely to emerge prior to, than during or after, MDD first episode or recurrence
- Is associated with higher rates of lifetime and current MDD and suicide
- Its presence and persistence predict future MDD
- Predicts poorer outcome in MDD (persistence, chronicity, suicidality)
- Predicts the onset of mania in bipolar depression

The Role of Polysomnography in the Management of Psychiatric Patients with Insomnia

- The American Academy of Sleep Medicine has stated that there is no role for PSG in the routine management of insomnia, but that PSG can be justified if there are specific reasons to suspect a primary sleep disorder, or if the insomnia does not respond to routine care.
- Unsuspected primary sleep disorders occur in about 16% of adults with depressive disorders.

Comorbid Conditions

- Sleep disorders
  - Sleep apnea
  - Restless legs syndrome
  - Periodic limb movement disorder
  - Circadian rhythm disorders
- Alzheimer’s disease
- Arthritis: osteoarthritis and rheumatoid arthritis
- Chronic back pain
- Cancer
- Cardiac disease: congestive heart failure, myocardial infarction, nocturnal angina, dyspnea
- Diabetes mellitus
- End-stage renal disease
- Functional bowel syndromes
- GERD
- Huntington’s disease
- Menopause
- Nocturia
- Nocturnal angina
- Chronic pain
- Parkinson’s disease
- Progressive supranuclear palsy
- Pulmonary disorders (e.g., COPD)
- Thyroid disease

Treatment Approaches for Insomnia

• Address comorbid problems.
• Examples:
  – Antidepressants for major depression
  – Proton pump inhibitors for GERD
  – Mood stabilizers for mania
  – Medication change for iatrogenic insomnia

• Address insomnia directly
  – Effective for a broad range of patients
  – Includes behavioral therapy and hypnotic medications

• Above two approaches may be combined
Depressed Insomniacs Who Receive a Hypnotic in Conjunction with Their SSRI Have Better Acute Outcomes

- Better quality of life and higher overall response rates (eszopiclone)
- Higher overall remission rates
- Superior self-reported sleep

# Psychological and Behavioral Treatments for Primary Insomnia

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus control therapy*</td>
<td>If unable to fall asleep within 20 minutes, get OOB and repeat as necessary</td>
</tr>
<tr>
<td>Relaxation therapies*</td>
<td>Biofeedback, progressive muscle relaxation</td>
</tr>
<tr>
<td>Restriction of time in bed</td>
<td>Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves</td>
</tr>
<tr>
<td>(sleep restriction)</td>
<td></td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Talk therapy to dispel unrealistic and exaggerated notions about sleep</td>
</tr>
<tr>
<td>Paradoxic intention</td>
<td>Try to stay awake</td>
</tr>
<tr>
<td>Sleep hygiene education</td>
<td>Promote habits that help sleep; eliminate habits that interfere with sleep</td>
</tr>
<tr>
<td>Cognitive-Behavioral Therapy*</td>
<td>Combines sleep restriction, stimulus control and sleep hygiene education with cognitive therapy</td>
</tr>
</tbody>
</table>

*Standard Treatment according to American Academy of Sleep Medicine
The Do’s of Sleep Hygiene

- Awaken at the same time every morning
- Increase exposure to bright light during the day
- Establish a daily activity routine
- Exercise regularly in the morning and/or afternoon
- Set aside a worry time
- Establish a comfortable sleep environment
- Do something relaxing prior to bedtime
- Try a warm bath
The Don’ts of Sleep Hygiene

Avoid…

• Alcohol
• Caffeine, nicotine, and other stimulants
• Exposure to bright light during the night
• Exercise within 3 hours of bedtime
• Heavy meals or drinking within 3 hours of bedtime
• Using your bed for things other than sleep (or sex)
• Napping, unless a shiftworker
• Watching the clock
• Trying to sleep
• Noise
• Excessive heat/cold in room
Prescription Agents for Insomnia

• FDA-non-approved for insomnia
  – Sedating antidepressants
  – Antipsychotics
  – Anticonvulsants

• FDA-approved hypnotics
  – Benzodiazepine receptor agonists (BzRA’s)
    • Benzodiazepines
    • Nonbenzodiazepines
  – Melatonin receptor agonist
  – H-1 receptor antagonist
  – Orexin receptor antagonist
Arousal and Sleep-Promoting Systems

Hypocretins and The Sleep Arousal Switch

Waking: Balance is shifted towards greater activity in wake promoting systems

Sleep: Balance is shifted towards greater activity in sleep promoting systems

Sedating Antidepressants

• Advantages
  – Many have sedating side effects
  – At appropriate doses, effective for mood and anxiety disorders
  – Low abuse risk
  – Large dose range

• Disadvantages
  – At low doses, efficacy not well established for insomnia
  – Daytime sedation (most have long half lives), anticholinergic effects, weight gain, and other systemic side effects; drug-drug interactions

These agents are not FDA approved for insomnia.
Atypical Antipsychotics

• Advantages
  – At appropriate doses, effective for psychotic disorders
  – Low abuse potential
  – Sedation

• Disadvantages
  – Not well investigated in primary insomnia
  – Daytime sedation, anticholinergic effects, weight gain
  – Low risk of extrapyramidal symptoms
  – Possible glucose and lipid abnormalities

These agents are not FDA approved for insomnia.
Initiation vs. Maintenance Insomnia

W, wake; S, sleep

11 pm

Initial

Middle

Terminal

7 am
# Benzodiazepine Receptor Agonists: The Benzodiazepines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Range† (mg)</th>
<th>Onset of Action</th>
<th>Half-life (h)</th>
<th>Short-term Limitation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estazolam</td>
<td>0.5 – 2</td>
<td>Rapid</td>
<td>10 - 24</td>
<td>Yes</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15 – 30</td>
<td>Rapid</td>
<td>47 - 100</td>
<td>Yes</td>
</tr>
<tr>
<td>Quazepam</td>
<td>7.5 – 15</td>
<td>Rapid</td>
<td>39 - 100</td>
<td>Yes</td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5 – 15</td>
<td>Slow-Intermediate</td>
<td>9.5 -12.4</td>
<td>Yes</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25 – 0.50</td>
<td>Rapid</td>
<td>1.5 - 5.5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Normal adult dose. Dosage may require individualization.
MICROMEDEX. http://www.micromedex.com
PDR. www.PDR.net
# Selective Benzodiazepine Receptor Agonists

<table>
<thead>
<tr>
<th></th>
<th>Zaleplon</th>
<th>Zolpidem</th>
<th>Zolpidem ER</th>
<th>Eszopiclone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hours)</strong></td>
<td>1</td>
<td>1.6</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Half-life [elderly] (hrs.)</strong></td>
<td>1</td>
<td>2.5 [2.9]</td>
<td>2.8 [2.9]</td>
<td>6 [9]</td>
</tr>
<tr>
<td><strong>Sleep latency</strong></td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Wake After Sleep Onset</strong></td>
<td>--</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Total sleep time</strong></td>
<td>↑ (20 mg)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

# Zolpidem Dosing Recommendations

<table>
<thead>
<tr>
<th>Dosing recommendations in current drug label for zolpidem</th>
<th>FDA’s proposed new dosing recommendations for zolpidem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men and Women:</strong> 10 mg once daily, immediately before bedtime</td>
<td><strong>Women:</strong> 5 mg once daily, immediately before bedtime</td>
</tr>
<tr>
<td><strong>Men:</strong> 5 or 10 mg once daily, immediately before bedtime</td>
<td><strong>Women:</strong> 6.25 mg once daily, immediately before bedtime</td>
</tr>
<tr>
<td><strong>Men and Women:</strong> 12.5 mg once daily, immediately before bedtime</td>
<td><strong>Men:</strong> 6.25 or 12.5 mg once daily, immediately before bedtime</td>
</tr>
</tbody>
</table>
Eszopiclone Dosing Recommendations

• Decrease in starting dose to 1 mg
• Can be increased to 2-3 mg
  – Caution when taking 3 mg for driving, activities that require mental alertness the day after
• Women and men are equally susceptible
• Rationale: 3 mg can cause impairment in driving, memory, and coordination following >11 hours

### Zolpidem Variants

<table>
<thead>
<tr>
<th></th>
<th>Zolpidem</th>
<th>Zolpidem SL</th>
<th>Zolpidem Oral Spray</th>
<th>Zolpidem SL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tmax (hours)</strong></td>
<td>1.6</td>
<td>1.4</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Half-life [elderly] (hrs.)</strong></td>
<td>2.5 [2.9]</td>
<td>2.9</td>
<td>2.7</td>
<td>2.5</td>
</tr>
</tbody>
</table>
# Newer Hypnotics

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Ramelteon</th>
<th>Doxepin</th>
<th>Suvorexant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Melatonin agonist</td>
<td>H1 antagonist</td>
<td>Orexin antagonist</td>
</tr>
<tr>
<td><strong>Dose – mg [elderly]</strong></td>
<td>8</td>
<td>3,6 [3]</td>
<td>10-20</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hours)</strong></td>
<td>0.75</td>
<td>3.5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Half-life [elderly]</strong> (hrs.)</td>
<td>1-2.6</td>
<td>15.3</td>
<td>12</td>
</tr>
<tr>
<td><strong>Sleep latency</strong></td>
<td>↓</td>
<td>--</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Wake After Sleep Onset</strong></td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Total sleep time</strong></td>
<td>--</td>
<td>--</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>None</td>
<td>None</td>
<td>IV</td>
</tr>
</tbody>
</table>
Sleep Pattern: Therapeutic Implications

- **Initial insomnia only**
  - Zaleplon
  - Zolpidem
  - Ramelteon

- **Middle insomnia only**
  - Doxepin low dose
  - Zolpidem SL MOTN

- **Initial and middle insomnia**
  - Zolpidem ER
  - Eszopiclone
  - Suvorexant
Adverse Effects of Hypnotics

- Benzodiazepine receptor agonists
  - Daytime sedation, psychomotor and cognitive impairment (depending on dose and half-life)
  - Rebound insomnia
  - Respiratory depression in vulnerable populations
- Melatonin receptor agonist
  - Headache, somnolence, fatigue, dizziness
  - Not recommended for use with fluvoxamine due to CYP 1A2 interaction
- H1 receptor antagonist
  - Somnolence/sedation
  - Nausea
  - Upper respiratory tract infection
- Orexin receptor antagonist
  - Somnolence
  - Risk of impaired alertness and motor coordination, including impaired driving; increases with dose
  - Contraindicated in narcolepsy

Mitler MM. Sleep. 2000;23:S39-S47.
MICROMEDEX. Available at: www.micromedex.com; Package inserts for various compounds.
Special Issues In Prescribing Hypnotics

• Abuse liability
• Parasomnias and amnestic behavior
• Long term use
• Tolerance and rebound
• Use in vulnerable populations
Long-Term Intermittent Treatment with Zolpidem Extended-Release

Patient Global Impression of Treatment Aid to Sleep

1° endpoint of this 25-week study was the patient global impression of treatment aid to sleep. The difference between treatment groups was P<.0001 for each visit. Similarly, the 2° endpoint, the clinician global impression of treatment aid to sleep, was also P<.0001 for all time points.

Twelve Months of Nightly Zolpidem Does not Lead to Dose Escalation

The percent of participants in the placebo and zolpidem groups that increased (Panel A) or decreased (Panel B) relative to month 1 the number of capsules (i.e., dose) that they self-administered in month 4 and 12. Percents increasing and decreasing within a group do add to 100% as a percent within each group did not change. A greater percentage of zolpidem versus placebo participants decreased dose in month 4 and 12 ($\chi^2 = 11.22, P < 0.001$).
Long-Term Continuous Treatment with Eszopiclone

**P ≤ 0.01 vs. placebo
‡P ≤ 0.0001 vs placebo

Long-Term Continuous Treatment with Ramelteon

![Graph showing latency to persistent sleep over time with placebo and ramelteon treatments. Asterisks indicate statistical significance at p<0.05.](image-url)

*p<0.05  
Parasomnias and Hypnotics

- Limited to spontaneous reports
- Sleep-driving i.e., driving while not fully awake; preparing and eating food, making phone calls, or having sex. Amnesia for events
- FDA label change applies to all manufacturers of sedative hypnotic drugs
Risk Factors for Zolpidem-Induced Parasomnias

- Co-use of alcohol or sedatives
- Use at doses exceeding the maximum recommended dose
- Sleep disorder: OSA or PLMS
- H/O parasomnia
- Ingestion at unusual bedtime
- Ingestion while agitated or not typically asleep
- Ingestion when sleep deprived
- Poor management of pill bottles
- Living alone
Vulnerable Populations

- Respiratory compromise (COPD, OSA)
- Elderly
- Women
- History of D/A use disorders
- Pregnancy
- Multiple medication users (sedation mainly)
- Hepatic impairment
- Depression
- Pediatric patients: Not indicated
Selected Guidelines for Hypnotic Use

- Comprehensive evaluation; specific treatment for comorbidities
- Caution in patients with respiratory and hepatic impairment, substance use disorders, or who are already taking sedatives; avoid alcohol; not approved for children; avoid during pregnancy
- Use lowest effective dose, lower dose in elderly (and in women for certain compounds)
- Take at bedtime (or MOTN for zolpidem SL low dose)
- 7-8 hours in bed (or minimum of 4 hours for zolpidem SL low dose)
- Efficacy may be improved on empty stomach
- Gradual discontinuation
- Follow-up visits

ARS Questions
Q&A
Thank you