Outcomes and Multidisciplinary Treatment of Insomnia

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Insomnia as a Disorder

INSOMNIA
More than 1 type of disturbance may be present
Symptoms may vary over time

- Difficulty Falling Asleep
- Difficulty Staying Asleep (eg, inability to return to sleep after awakening)
- Waking Too Early
- Poor Quality of Sleep

Next-Day Consequences

*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*
Insomnia Epidemiology

• Prevalence
  – approximately 30% of general population
  – 10% of population has associated symptoms of daytime functional impairment
  – up to 50% prevalence in clinical practices

NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. (June 15, 2005)
Insomnia Consequences

- Nighttime experience
- Daytime complaints
- Quality of life
- Absenteeism and decreased productivity
- Increased healthcare costs
- Societal burden
- Future health risks
- Increased fall risk
Insomnia – Daytime Complaints

- Fatigue, exhaustion, tiredness
- Poor concentration and memory
- Irritability, moodiness
- Relationship problems
- Decreased enjoyment
Insomnia and Quality of Life

Axes represent subscales of the SF-36. All P values <.05 (range .000-.023).
SF-36: Short Form Health Survey of the Medical Outcomes Study (36 item).
Insomnia Etiology

• Causes and comorbidities
  – Situational disturbances
  – Psychological conditioning – hyperarousal
  – Poor sleep habits
  – Psychiatric disorders
  – Medical disorders
  – Sleep disorders
  – Medication effects

• Often multifactorial

Insomnia: Two General Types

- **Primary**  
  - Insomnia independent from other disorders

- **Comorbid**  
  - Most common category  
  - Presumably associated with co-occurring medical, psychiatric, or sleep disorders  
  - Promotes independent treatment of insomnia and associated disorders  
  - Replaces *secondary insomnia* attribution

NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. (June 15, 2005)
Models of Primary Insomnia

• Psychophysiological
• Hyperarousal
  – EEG activation
  – Cortisol and cytokine abnormalities
  – Thermoregulation
  – Neuroimaging

Neubauer, David N. and Kelleen N. Flaherty
Pathophysiology, Associations, and Consequences of Insomnia
Handbook of Sleep Disorders. Edited by Kushida, C. Taylor and Francis Group, LLC
New York, NY. 2010
Common Insomnia Comorbidities

• Medical
  – Cardiac, pulmonary, rheumatologic, neurologic, endocrine, genitourinary, pain syndromes

• Psychiatric
  – Mood disorders, anxiety disorders, substance abuse

• Sleep
  – Circadian rhythm disorders, RLS
  – Sleep disordered breathing
    • Obstructive
    • Central
More health problems $\rightarrow$ Worse sleep

Percent of community-dwelling subjects (ages 55 – 84 years) with any symptom of insomnia by number of medical conditions

Percent of Individuals With and Without Health Conditions Having Insomnia

Insomnia Increases Future Health Risks

• Medical
  – Hypertension (Japan)
  – Coronary artery disease mortality (Sweden)
  – Diabetes mellitus type II (Sweden, Germany)

• Psychiatric
  – Mood disorders
  – Anxiety disorders
  – Substance abuse
  – Suicide
Insomnia: Evaluation and Treatment
Evaluating Insomnia

• Screen patients for sleep-related symptoms
  – Routine history
  – Review of systems
• Recognize patients with increased risk for insomnia and other sleep disorders
• “Do you feel that you are sleeping well at nighttime and are fully alert throughout the daytime?”
Sleep Logs and Diaries

• Helpful in revealing patterns of sleep disturbance
  – Sleep onset
  – Sleep maintenance
  – Advanced or delayed sleep phase tendencies
  – Insufficient time in bed
• Helpful to monitor effects of treatment strategies
• Daily chart vs. graph approaches
Insomnia Treatment Approaches

- Education
- Sleep hygiene measures
- Behavioral and cognitive therapy techniques
- Pharmacotherapy
- Phototherapy and circadian manipulations
- Sleep medicine specialist consultation and sleep laboratory testing
Who Treats Insomnia

• Physicians
  – Primary care
  – Psychiatrist
  – Multiple specialties
• Sleep medicine MDs
• Behavior sleep medicine specialists

• Nurses
• Nurse practitioners
• Physician assistants
• Therapists

• Collaborative efforts of all providers
Principles of Sleep Hygiene

– Regular sleep/wake cycle
– Regular exercise morning/afternoon
– Increase exposure to bright light during day
– Avoid exposure to bright light during night
– Avoid heavy meals/drinking <3 hrs of bedtime
– Enhance sleep environment
– Avoid caffeine, alcohol, nicotine
– Relaxing routine

## Behavioral Strategies for Treating Insomnia

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive therapy</td>
<td>Challenge patient’s dysfunctional beliefs and misconceptions about sleep and insomnia</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>Reduce physiologic and cognitive arousal at bedtime. Techniques include progression muscular relaxation, transcendental meditation, yoga, biofeedback</td>
</tr>
<tr>
<td>Sleep restriction</td>
<td>Improve sleep continuity by limiting time spent in bed</td>
</tr>
<tr>
<td>Stimulus control</td>
<td>Relate to the bed/bedroom solely as a place for sleep or sexual activity</td>
</tr>
</tbody>
</table>

Cognitive-Behavioral Therapy (CBT)

- Multicomponent approach
  - Sleep education and sleep hygiene advice
  - Stimulus control and sleep restriction
  - Cognitive psychotherapy

- Individual or group format
- Manualized or unstructured
- Numerous studies and meta-analyses demonstrate efficacy and long-term benefits
Cognitive-Behavioral Therapy (CBT)

**Advantages**
- Efficacy and durability
- May address key psychological issues
- Appealing for some

**Disadvantages**
- Availability of qualified therapists
- Cost in time and money
- Lack of immediate results
- Unappealing for others
CBT vs RT vs Placebo in 75 Chronic Primary Insomnia Patients
Objective Measures of Efficacy Following 6 Weeks of Treatment

*RT vs placebo was nonsignificant.
Cognitive-behavioral therapy (CBT) outcomes showing a significant improvement in sleep onset latency, wake after sleep onset, and total sleep time. The improvement is statistically significant with a p-value less than 0.001.

- **Sleep Onset Latency**: Pretreatment 64 minutes, Posttreatment 37 minutes
- **Wake After Sleep Onset**: Pretreatment 70 minutes, Posttreatment 38 minutes
- **Total Sleep Time**: Pretreatment 349 minutes, Posttreatment 378 minutes

Recent Insomnia Behavioral Treatment Reports

- Self-help therapy
- Internet-based interventions
- CBT with and without pharmacotherapy
- CBT for specific comorbid insomnia populations (depression, cancer)
- CBT and mindfulness medication
- Brief behavioral treatment
- Primary care nurses trained as sleep therapists
- Intensive sleep retraining
TINCTURE

OPIUM, U. S. P.

(LAUDANUM)

Tincture of Opium, U. S. P. (Tenth Revision) is identical with the product which was formerly supplied as Tincture No. 22, Opium Deodorised.

Each fluid ounce contains:

- Alcohol 18 per cent.
- Morphine, anhydrous 4 1/2 grains.

POISON

Standard—100 cc contains 0.95 to 1.05 Gm. anhydrous morphine.

NARCOTIC, SEDATIVE AND HYPNOTIC

Arrests.—Belladonna or atropine, strong tea or coffee, stimulants, artificial respiration.

Average dose, 10 minims (0.6 cc).

PARKE, DAVIS & CO.

DETROIT, MICH., U. S. A.
Substances Used for Sleep: Past to Present

– Fermented beverages
– Plant preparations
– Laudanum (opium/alcohol)
– Chloral hydrate
– Barbiturate and related compounds
– Antihistamines
– Benzodiazepine hypnotics
– Nonbenzodiazepine hypnotics
– Selective melatonin receptor agonist
Insomnia: Recent Highlights

**Pharmacologic Developments**

- Pharmacodynamic innovations
  - New mechanism of action medications
- Pharmacokinetic innovations
  - Extended release hypnotics
- FDA insomnia treatment indications
  - Duration of use
  - Differentiating sleep onset and maintenance
- DEA scheduling for hypnotics
Insomnia Treatment Medications (FDA-Approved)

- Benzodiazepine receptor agonist hypnotics
  - Benzodiazepine structure
  - Nonbenzodiazepine
- Selective melatonin receptor agonist
Benzodiazepine Mechanisms

• Gamma aminobutyric acid (GABA)
  – Predominant inhibitory neurotransmitter in CNS
  – A primary inhibitory neurotransmitter in the ventrolateral preoptic nucleus (VLPO)
• Benzodiazepine receptor agonists (BZRA) bind to BZ receptor site on $\mathrm{GABA}_A$ receptor complex
  – Enhance GABA activation of chloride ion channel
  – Hyperpolarizes GABAergic neurons

GABA<sub>A</sub> Receptor Complex

Möhler H et al. (2002), J Pharmacol Exp Ther 300(1):2-8;
Rowlett JK et al. (2005), CNS Spectr 10(1):40-48
Benzodiazepine Receptor Agonist Hypnotics

• Positive allosteric modulators of GABA responses at $\text{GABA}_A$ receptors
• Benzodiazepine and nonbenzodiazepine
• All promote rapid sleep onset
• Duration of action promoting sleep maintenance or causing residual sedation depends upon the dose and elimination half-life
Selective Melatonin Receptor Agonist

- Ramelteon (Rozerem)
- Selective melatonin receptor agonist
  - $\text{MT}_1$: attenuation of circadian alerting signal
  - $\text{MT}_2$: circadian phase reinforcement or shifting
- Acts on the suprachiasmatic nucleus
- Influences the circadian rhythm effects on the sleep-wake cycle
- No abuse liability, not a DEA controlled substance
Circadian and Homeostatic Regulation of Sleep

# FDA-Approved Insomnia Medications as of February, 2010

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Available doses (mg)</th>
<th>Elimination half-life (hr)</th>
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<tbody>
<tr>
<td><strong>Benzodiazepine receptor agonists</strong></td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Immediate release</td>
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<tr>
<td>Estazolam</td>
<td>ProSom</td>
<td>1, 2</td>
<td>8 – 24</td>
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<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>15, 30</td>
<td>48 – 120</td>
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<tr>
<td>Quazepam</td>
<td>Doral</td>
<td>7.5, 15</td>
<td>48 – 120</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>7.5, 15, 22.5, 30</td>
<td>8 – 20</td>
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<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>0.125, 0.25</td>
<td>2 – 4</td>
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<tr>
<td><strong>Nonbenzodiazepines</strong></td>
<td></td>
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<tr>
<td>Immediate release</td>
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<tr>
<td>Eszopiclone</td>
<td>Lunesta</td>
<td>1, 2, 3</td>
<td>5 – 7</td>
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<tr>
<td>Zaleplon</td>
<td>Sonata</td>
<td>5, 10</td>
<td>1</td>
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<tr>
<td>Zolpidem</td>
<td>Ambien</td>
<td>5, 10</td>
<td>1.5 – 2.4</td>
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<tr>
<td><strong>Nonbenzodiazepines</strong></td>
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<tr>
<td>Extended release</td>
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<tr>
<td>Zolpidem ER</td>
<td>Ambien CR</td>
<td>6.25, 12.5</td>
<td>2.8 – 2.9</td>
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<tr>
<td><strong>Nonbenzodiazepines</strong></td>
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<tr>
<td>Alternate delivery</td>
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<tr>
<td>Zolpidem oral spray</td>
<td>Zolpimist</td>
<td>5, 10</td>
<td>~2.5</td>
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<tr>
<td>Zolpidem sublingual</td>
<td>Edluar</td>
<td>5, 10</td>
<td>~2.5</td>
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<tr>
<td><strong>Selective melatonin receptor agonist</strong></td>
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<tr>
<td>Ramelteon</td>
<td>Rozerem</td>
<td>8</td>
<td>1 – 2.6</td>
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New Directions in Insomnia Pharmacotherapy

• Candidates in development
  – Alternate delivery BZRA formulations*
  – Doxepin – ultra-low dose
  – 5-HT$_{2A}$ antagonists
  – Orexin (Hypocretin) receptor antagonists
  – CRF antagonists
  – Neurosteroids, Substance P antagonists
  – H$_1$ receptor antagonists (selective)
  – H$_3$ receptor agonists
New Directions in Insomnia Pharmacotherapy

MEDA Pharmaceuticals: Edluar

NovaDel: Zolpimist
Summary

- Insomnia is a common clinical problem that is chronic for many individuals
- Effective treatment approaches include behavioral, cognitive, and pharmacologic interventions
- Insomnia treatment may involve the collaboration of a variety of health care providers
- There have been significant developments in both pharmacodynamic and pharmacokinetic approaches
- New approaches to delivering both cognitive-behavioral and pharmacologic insomnia therapies are being investigated.
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References:


