Sleep Disorders with New Perspectives:

Overcoming challenges in Treating Insomnia and OSA

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Disclosures

• My presentation is not representative of any position of the US government or Department of Veteran Affairs

• I don’t have any conflict of interest pertaining to the material presented in this talk
LEARNING OBJECTIVES

• Update on Insomnia
  • Define and describe Insomnia disorder
  • Summarize recent changes in the nomenclature of insomnia
  • Identify neurotransmitter systems involved in sleep
  • Identify newer medications and their mechanism of action
  • Summarize American College of Medicine guidelines

• Update on OSA Treatments
  • Identify 2 newer treatment options for OSA
Sleep Disorders are very common and often go unrecognized and untreated.
Sleep Apnea and Insomnia are the most common
As physicians you see these patients every day
Treating sleep disorders help with other co-morbid medical and psychiatric disorders
Insomnia Disorder DSM-5

- Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening
- The sleep disturbance causes significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
- The sleep difficulty occurs at least 3 nights/week, for at least 3 months, and despite adequate opportunity for sleep
- The insomnia does not co-occur with another sleep disorder
- The insomnia is not explained by coexisting mental disorders or medical conditions
INSOMNIA

• Marked Departure from the ICSD-2 and DSM IV
• No distinction of Acute vs Chronic
• No distinction of Primary Vs. Secondary
NIH State-of-the-Science Conference and Co-Morbid Insomnia

• As much as 85% of insomnia may be co-morbid with other conditions
• “Co-morbid insomnia” is an appropriate term
  • Mechanistic and causal pathways not known

• WHY CHANGE
  • The term secondary insomnia may promote under-treatment
  • Share many characteristics between primary and secondary

• NIH National Institute of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults. Sleep 2005
INSOMNIA (ICSD-3)

• Chronic Insomnia Disorder
• Short-Term Insomnia Disorder
• Other Insomnia Disorder
Insomnia as a disorder rather than a symptom

Figure 1. Overlap of Symptoms Between Psychiatric and Sleep Disorders

- Psychiatric Disorders
  - Depression
  - Bipolar disorder
  - Anxiety disorders
  - Schizophrenia
  - Substance use disorders

- Sleep Disorders
  - Irritability
  - Depression
  - Inattention
  - Cognitive impairment
  - Fatigue
  - Insomnia
  - Apnea
  - Restless legs
  - Parasomnias
  - Hypersomnias
  - Circadian sleep-wake disorders

\(^a\text{Based on American Psychiatric Association}^1 \text{ and Palmer and Alfano}^2\)
Overview of Neurotransmitter System Relevant to Sleep
Sleep Promoting and Wake Promoting Neurotransmitters

- Adenosine
- Gamma-aminobutyric acid (GABA)-A
- Galanin
- Melatonin

Neurotransmitters That Block the Activity of Wake-Promoting Systems:
- Norepinephrine
- Serotonin
- Acetylcholine
- Histamine
- Orexin/hypocretin

(Saper et al., 2005)
Sleep and Wake Neurotransmitters
Brains’ Flip Flop Switch

## Prescription Drugs used for Insomnia: Main Characteristics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Action</th>
<th>T1/2 h</th>
<th>Recommended Use</th>
<th>Dose (mg)</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NBBzRA</strong></td>
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<tr>
<td>Zopiclone</td>
<td>GABA(A) alpha 1,2,3</td>
<td>5</td>
<td>Sleep onset/maintenance</td>
<td>3.75-7.5</td>
<td>+</td>
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<tr>
<td>Eszopiclone</td>
<td>GABA(A) alpha 1,2,3</td>
<td>6</td>
<td>Sleep onset/maintenance</td>
<td>1-3</td>
<td>+</td>
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<tr>
<td>Zolpidem</td>
<td>GABA(A) alpha 1,2,3</td>
<td>2.6</td>
<td>Sleep onset/maintenance</td>
<td>1.75-10 6.25-12.5 ER</td>
<td>+</td>
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<tr>
<td>Zaleplon</td>
<td>GABA(A) alpha 1,2,3</td>
<td>0.7-1.4</td>
<td>Sleep onset</td>
<td>5-20</td>
<td>+</td>
</tr>
<tr>
<td>Drug (Class)</td>
<td>Mode of Action</td>
<td>T1/2(h)</td>
<td>Recommended Use</td>
<td>Dose (mg)</td>
<td>FDA</td>
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<tr>
<td>Orexin receptor antagonists</td>
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<tr>
<td>Suvorexant</td>
<td>OXR1 and OXR2</td>
<td>12</td>
<td>Sleep onset / Maintenance</td>
<td>5-20</td>
<td>+</td>
</tr>
<tr>
<td>Melatonin and Melatonin receptor agonists</td>
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<td></td>
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<tr>
<td>Ramelteon</td>
<td>Receptor agonism</td>
<td>1-2.5</td>
<td>Sleep onset</td>
<td>8</td>
<td>+</td>
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<tr>
<td>Melatonin</td>
<td>Receptor agonism</td>
<td>~0.75</td>
<td>Not recommended</td>
<td>N/A</td>
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<tr>
<td>Circadin</td>
<td>Receptor agonism</td>
<td>3.5-4</td>
<td>Sleep onset/Maintenance age &gt;55 Y</td>
<td>2</td>
<td>-</td>
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</table>
### Prescription Drugs used for Insomnia: Main Characteristics-Cont.

<table>
<thead>
<tr>
<th>Drug (Class)</th>
<th>Mode of Action</th>
<th>T1/2(h)</th>
<th>Recommended Use</th>
<th>Dose (mg)</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>Doxepin</td>
<td>H1 antagonism</td>
<td>20</td>
<td>Sleep maintenance</td>
<td>3-6</td>
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<tr>
<td>Amitriptyline</td>
<td>H1, alpha1, M1 antagonism</td>
<td>30</td>
<td>Not recommended</td>
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<tr>
<td>Trazodone</td>
<td>5HT2A, alpha1 antagonism</td>
<td>9</td>
<td>Not recommended</td>
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<tr>
<td>Mirtazapine</td>
<td>H1,5HT2A/2C</td>
<td>25</td>
<td>Not recommended</td>
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<td><strong>Antipsychotics</strong></td>
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<tr>
<td>Quetiapine</td>
<td>H1, alpha1,M1,5HT, D2 antagonism</td>
<td>6</td>
<td>Not recommended</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>H1, alpha1,M1,5HT, D2 antagonism</td>
<td>20-54</td>
<td>Not recommended</td>
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<td>-</td>
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</table>
Studies on Treatments of Insomnia Disorder

The k values refer to number of studies. CBT = cognitive behavioral therapy.
Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Mary Ann Forciea, MD; Molly Cooke, MD; and Thomas D. Denberg, MD, PhD; for the Clinical Guideline Panel of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the management of chronic insomnia disorder in adults.

Methods: This guideline is based on a systematic review of randomized, controlled trials published in English from 2004 through September 2015. Evaluated outcomes included global outcomes assessed by questionnaires, patient-reported sleep outcomes, and harms. The target audience for this guideline includes all clinicians, and the target patient population includes adults with chronic insomnia disorder. This guideline grades the evidence and recommendations by using the ACP grading system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Recommendation 1: ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence.)

Recommendation 2: ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence.)

Update on Obstructive Sleep Apnea Treatments
Some Newer Treatments
Hypoglossal Nerve Stimulation for OSA
Primary and Secondary Improvements with Hypoglossal Nerve Stimulation in the STAR Trial

Conclusion

- Insomnia is a chronic condition which is co-morbid with many psychiatric and medical disorders
- Insomnia should be considered as a separate disorder and treated simultaneously with co-morbid conditions
- Some newer hypnotic medications are safer, but the first line of treatment is CBT-I
- CPAP and dental appliances are the main treatment options for OSA
- Upper airway stimulation is a novel treatment option for patients in which CPAP does not work