Emerging Pharmacology

Sleep Promoting Agents – Dennis Auckley
Alertness Promoting Agents – Lynn Trotti
Delirium and Sleep After Surgery – Balachunder Subramaniam
Gabapentin: ERAS Darling to the Dark Side – Michael Pilla

Sleep Promoting Pharmacologics: New Agents and Challenges

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Financial Disclosures

• UpToDate – written 2 sections

• ABIM Sleep Medicine Exam Committee
  • No exam questions will be disclosed during this presentation

Objectives

• Define insomnia and prevalence
• Briefly review the anatomy and pathophysiology of insomnia
• Discuss pharmacologic therapies for insomnia
  • Emphasis on newer agents
  • Perioperative considerations
• Consider challenges in the development of new pharmacotherapies
What is Insomnia?

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

(Despite adequate opportunity and circumstance)
(Not better explained by another sleep disorder)

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

Next-day Consequences
(Fatigue, irritability, poor performance, inability to concentrate, decreased motivation, sleepy, etc.)


Insomnia Prevalence

US VA Facilities
N= 10 million
ICD dx

True increase?
Increased awareness?
Better methodology?

Alexander et al, Sleep 2016
Insomnia Pathophysiology: The 3 P’s of Insomnia

Spielman et al, Case Studies in Insomnia 1991

Natural History of Insomnia
- Perpetuating factors
- Precipitating factors
- Predisposing factors

Medications
Behavioral therapies > Medications

Premorbid Acute Insomnia Short-term Insomnia Chronic Insomnia

Insomnia Therapy

Bonnet et al, Sleep Med Rev 2014
Insomnia Pathophysiology

- Hyperaroused state
  - Increased heart rate and altered heart rate variability
  - Increased whole-body metabolic rate (cortisol, ACTH) (particularly near sleep onset)
  - Increased body temperature
  - Increased high-frequency EEG activity (NREM sleep)
  - Increased catecholamine levels
  - Increased daytime alertness and reactivity to stress

- No discrete structural brain pathology can be identified in most individuals with insomnia

Mechanisms of Sleep: Neurotransmitters

<table>
<thead>
<tr>
<th>Wake-promoting neurotransmitters</th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>GABA</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Galanin</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Adenosine</td>
<td>GABA</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Melatonin</td>
<td>Glycine (muscle atonia)</td>
</tr>
<tr>
<td>Serotonin</td>
<td></td>
<td>Glutamate</td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orexin/hypocretin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

= traditional therapies
= newer therapies

Owens et al, J Atten Dis 2012
Wake Control Centers

Sleep Promotion

Sleep is the suppression of wakefulness

- VLPO and MnPN neurons are both in the anterior hypothalamus
- Activation leads to GABA release, that inhibits wake promoting areas

Principles and Practice of Sleep Medicine, 6th Ed
Insomnia Therapy

What People Take for Insomnia

- Formal sleep indication?
  - No
  - Yes
- Prescription required?
  - No
  - Yes
- Assorted Sedating Medications “Off-label”
- Over-the-counter options (Antihistamines, melatonin and/or plant extracts)

**Insomnia Therapy:**

**“Traditional” FDA-Approved Medications**

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME</th>
<th>AVAILABLE DOSES (MG)</th>
<th>ELIMINATION HALF-LIFE (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepine Immediate Release</strong> (GABA agonists)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam</td>
<td>ProSom</td>
<td>1, 2</td>
<td>10 - 24</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>15, 30</td>
<td>2.9/48 - 160 active metabolites</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Donil</td>
<td>7.5, 15</td>
<td>39/75 active metabolite</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>7.5, 16, 22.5, 30</td>
<td>3.5 - 18.4</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>0.125, 0.25</td>
<td>1.5 - 5.5</td>
</tr>
<tr>
<td><strong>Nonbenzodiazepine Immediate Release</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Lunesta</td>
<td>1, 2, 3</td>
<td>6/9 in elderly</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Sonata</td>
<td>5, 10</td>
<td>1</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Ambien</td>
<td>5, 10</td>
<td>2.8 in males</td>
</tr>
<tr>
<td><strong>Nonbenzodiazepine Extended Release</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem ER</td>
<td>Ambien CR</td>
<td>6.25, 12.5</td>
<td>1.6 - 4.5</td>
</tr>
</tbody>
</table>

Neubauer et al, J CNS dz 2018
Insomnia Therapy: “Newer” FDA-Approved Medications

Neubauer et al, J CNS dz 2018

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<th>BRAND NAME</th>
<th>AVAILABLE DOSES (MG)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SELECTIVE MELATONIN RECEPTOR AGONIST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelton</td>
<td>Rozerem</td>
<td>8</td>
<td>1–2.6</td>
</tr>
<tr>
<td>SELECTIVE HISTAMINE RECEPTOR ANTAGONIST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin (low dose)</td>
<td>Silenor</td>
<td>3, 6</td>
<td>15.3</td>
</tr>
<tr>
<td>DUAL OREXIN RECEPTOR ANTAGONIST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suvorexant</td>
<td>Belsomra</td>
<td>5, 10, 15, 20</td>
<td>12</td>
</tr>
</tbody>
</table>

Neubauer et al, J CNS dz 2018

Insomnia Therapy

Neubauer et al, J CNS dz 2018
Insomnia Therapy:
“Traditional” FDA-Approved Medications

Benzodiazepines and NBRA
- Bind to several (B) / single (NBRA) GABA type A receptors
- Reduce sleep latency and awakenings, and increase TST
  - Approved for sleep-onset and sleep-maintenance insomnia (agent depd)
- All hepatically metabolized (CYP3A4)
- SE: daytime sleepiness, cognitive impairment, motor incoordination, worsen OSA (B), respiratory depression (B), and complex sleep-related behaviors (NBRA)
  - Inpatient: increased fall risk and increased delirium
  - Rebound insomnia can occur with withdrawal

*AASM 2017 Strength of Recommendation: all WEAK

Insomnia Therapy:
“Newer” FDA-Approved Medications

Melatonin receptor agonist (Ramelteon)
- Targets melatonin receptors (MT1 and MT2)
- Reduces sleep latency and increases TST (though marginally)
  - Approved for sleep-onset insomnia
- Hepatically metabolized (CYP1A2)
- SE: somnolence, dizziness, HA
  - No withdrawal or rebound insomnia

*AASM 2017 Strength of Recommendation: WEAK
Insomnia Therapy: “Newer” FDA-Approved Medications

Antidepressants (Doxepin)
- Antihistamine antidepressants have sedation as a SE
- Decrease wake time after sleep onset, increase TST
  - Approved for sleep-maintenance insomnia
- Hepatically metabolized (CYP2D6)
- SE: somnolence, nausea, HA
  - May see withdrawal syndrome or rebound insomnia

*AASM 2017 Strength of Recommendation: WEAK

Insomnia Therapy: “Newer” FDA-Approved Medications

Orexin receptor antagonist (Suvorexant)
- Orexin receptor antagonists are relatively new/novel therapies
- Reduce sleep latency and awakenings, and increase TST
  - Approved for sleep-onset and sleep-maintenance insomnia
- Hepatically metabolized (CYP3A4)
- SE: somnolence, HA, narcolepsy-like sx
  - May worsen OSA
  - Rebound insomnia can occur with withdrawal

*AASM 2017 Strength of Recommendation: WEAK
Insomnia Therapy:
NonFDA-Approved Medications

- **Trazodone**: antidepressant serotonin modulator, has sedation as a SE
  - Can reduce sleep latency, awakenings, and increase TST
  - Hepatically metabolized (CYP3A4)
  - SE: somnolence, *confusion*, dizzy, nausea, dry mouth, HA
    - Orthostatic hypotension, arrhythmias
    - May see severe withdrawal syndrome

- **Mirtazapine (Remeron)**: antidepressant serotonin agonist / alpha2 antagonist, has sedation as a SE
  - Can reduce sleep latency and increase TST
  - Hepatically metabolized (CYP3A4 + others)
  - SE: somnolence, appetite/weight gain, dry mouth

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Insomnia Therapy:
NonFDA-Approved Medications

**Over-the-counter medications**

- OTC preparations: antihistamine, melatonin or herbal
- Little evidence for their clinical effectiveness
- **Common drugs**
  - Diphenhydramine (“PM”) / Doxylamine (Unisom)
  - Melatonin
  - Valerian (Sleep Aid)
- Hepatically metabolized
- SE: mostly antihistamines – somnolence, *cognitive impairment, delirium, anticholinergic effects*
Insomnia Therapy: NonFDA-Approved Medications

• Propofol?
  • Controlled trial of patients with refractory chronic primary insomnia (n=103)
  • 2 hours of IV propofol per night x 5 nights (vs placebo)
  • Results: improved subjective and objective sleep at the end of the 5 days that held to 6 months f/u
    Xu et al, Cell Biochem Biophys 2011

Insomnia Therapy: ClinicalTrials.gov

• Orexin receptor antagonists – “me too” agents
• Esmirtazipine
• Quetiapine (Seroquel): antipsychotic with serotonin, dopaminergic, histamine and adrenergic effects
• Gamma Hydroxybutyrate (GHB/Xyrem): GABA B receptor agonist / GHB receptor agonist
• Lavender oil: aroma therapy

• No studies on THC or cannabinoids
Insomnia and Perioperative / Inpatient Considerations

• The perioperative / inpatient provider should be aware of insomnia therapies (prescribed or self-medicated)
  • Side effects relevant to the perioperative / inpatient environment can occur (CNS, cardiac and pulmonary effects)
    • Some may be enhanced in the inpatient environment
    • Liver failure can be a major problem
  • Drug-drug interactions exist
    • Watch for overlapping effects with opioids
  • However, abruptly stopping therapies may be deleterious
  • Beware of ETOH used as a sleep aid

Insomnia Therapy: Challenges for New Agents

• Desire a rapid onset of action
  • And “appropriate” duration of action
  • And OK for intermittent administration
• Consider gender-related and age-related factors
• Minimize side effect profile
• Limited to no abuse potential
• Impact on / by co-morbidities
• Need a better understanding of sleep neurophysiology
Sleep Promoting Pharmacologics: New Agents and Challenges

- New, more physiologically-appropriate, medical therapies are available for Insomnia
  - All have limitations in terms of efficacy and side effects
- Current work is mostly comparative, population specific or involves combinations of therapy
- Common therapies for insomnia have the potential to impact perioperative / inpatient care
- Further work based on a better understanding of sleep neurophysiology is needed

See you DC!
SASM2020

Thank You

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