Insomnia from A to ZZzzs

October 2, 2013
Tina Waters, MD
Objectives

- Summarize the basic principals of sleep and describe normal sleep patterns versus insomnia
- Review the clinical and diagnostic evaluation of insomnia as well as negative health and social consequences of sleep loss
- Achieve a basic understanding of the neurophysiology underlying sleep/wake cycles and the benzodiazepine receptor site
- Differentiate among sedative hypnotics with respect to their relative risks, benefits, and indications
Sleep architecture

Source: National Sleep Foundation (2008)
Two Process Model of Sleep

**Process S**: Homeostatic sleep drive or sleep pressure - sleep occurs naturally in response to how long we are awake; longer awake, the stronger sleep drive

**Process C**: Circadian process - this process controls the timing of sleep and wakefulness during the day-night cycle. Timing is regulated by the circadian biological clock that is located in the brain in the SCN (suprachiasmatic nucleus)
Circadian and Homeostatic Regulation of Sleep

Sleep inertia/pressure builds over the course of the day.

Circadian factors keep us awake—drive for wakefulness:
- Afternoon low-normal
- “second wind” then down again

Helps us go to sleep at night.

Normal Sleep

Napping

Less pressure to sleep at night;
More difficult to fall asleep at night.
How Much Sleep Do You Really Need?

<table>
<thead>
<tr>
<th>Age</th>
<th>Sleep Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns (0-2 months)</td>
<td>12-18 hours</td>
</tr>
<tr>
<td>Infants (3 to 11 months)</td>
<td>14 to 15 hours</td>
</tr>
<tr>
<td>Toddlers (1-3 years)</td>
<td>12 to 14 hours</td>
</tr>
<tr>
<td>Preschoolers (3-5 years)</td>
<td>11 to 13 hours</td>
</tr>
<tr>
<td>School-age children (5-10 years)</td>
<td>10 to 11 hours</td>
</tr>
<tr>
<td>Teens (10-17)</td>
<td>8.5-9.25 hours</td>
</tr>
<tr>
<td>Adults</td>
<td>7-9 hours</td>
</tr>
</tbody>
</table>

Source: National Sleep Foundation

This table identifies the "rule-of-thumb" amounts most sleep experts have agreed upon; however there is no “magic number”
• 75% of adult Americans experience sleep disorder symptoms at least a few nights per week
• Sleep loss impacts on all facets of life and virtually all organ systems
  - Untreated apnea doubles the risk of recurrent atrial fibrillation
  - Sleep disorders cause academic and behavior problems in kids
  - Sleep loss increases the risk of obesity and diabetes
  - Drowsy driving is responsible for over $12 billion in reduced productivity/property loss
Sleep Disorder Symptoms on the Rise

Average adults sleep 6.9 hr (weekdays), 7.5 hr (weekends)
68% sleep less than 8 hr on weeknights
39% sleep less than 7 hr on weeknights

National Sleep Foundation 2008 Sleep In America Poll.
Habitual Sleep Duration < 6 hours is associated with a variety of adverse consequences:

- **↑** risk of diabetes and heart problems
- **↑** inflammatory markers
- **↑** risk for psychiatric conditions including depression and substance abuse
- **↑** health care utilization
- **↑** risk of motor vehicle accidents
- **↓** ability to pay attention, react to signals or remember new information
- **↓** leptin and **↑** ghrelin levels → greater likelihood of obesity due to increased appetite caused by sleep deprivation

More Sleep ≠ Better Health?

- Long sleep durations (> 9 hours) have been found to be associated with increased morbidity (illness, accidents) and mortality.
- Some research has found "U-shaped" curve where both sleeping too little and sleeping too much may put you at risk.
Insomnia defined

- Repeated difficulty with:
  - Sleep initiation
  - Sleep duration
  - Sleep maintenance
  - Sleep quality – nonrestorative sleep
- ...despite an adequate time and opportunity for sleep
- ...and results in some form of daytime impairment
- Insomnia is not sleep deprivation

Daytime impairment

Must complain of at least one of these below:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue or malaise</td>
<td>Tension, HAs or GI symptoms</td>
</tr>
<tr>
<td>Mood disturbance or irritability</td>
<td>Proneness for errors or accidents at work or while driving</td>
</tr>
<tr>
<td>Memory, attention or concentration impairment</td>
<td>Motivation, energy or initiative reduction</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>Concerns or worries about sleep</td>
</tr>
<tr>
<td>Social or vocational dysfunction or poor school performance</td>
<td></td>
</tr>
</tbody>
</table>
Insomnia’s Evolution

**NIH-1983**

Insomnia as a symptom, not a disorder

Insomnia as SECONDARY to a primary disorder

Important to treat primary disorder; insomnia may receive attention, may not

**NIH-1995**

Insomnia as a disorder

Insomnia as CO-MORBID with other disorders

Important to treat medical and psychiatric disorders as well as co-morbid insomnia

Epidemiology of Insomnia

- General population: 10-15%
- Elderly: 10-20% - Older adults, particularly women, and those residing in nursing facilities are much more likely to use hypnotics

- Comorbid insomnia accounts for ≥80% of cases
  - Impacts quality of life and worsens clinical outcomes
  - Predisposes patients to recurrence
  - May continue despite treatment of the primary condition

Mellinger et al. 1986; Ohayon, 2002
Prevalence Estimates by Definition

Ohayon (2002) Sleep Medicine Reviews
The Economic Burden of Insomnia

About 5.3 billion in US dollars

Populations at Risk for Insomnia

- Female sex
- Increasing age
- Comorbid medical illness (respiratory, chronic pain, neurological disorders)
- Comorbid psychiatric illness (depression, depressive symptoms)
- Lower socioeconomic status
- Widowed, divorced
- Non-traditional work schedules
Prevalence of insomnia by age group

Large-scale community survey of non-institutionalized American adults, aged 18 to 79 years

Comorbid Insomnia

- **Cardiovascular diseases**
  - Ischemic heart disease
  - Nocturnal angina
- **Respiratory diseases**
  - Chronic obstructive pulmonary disease
  - Bronchial asthma
- **Gastrointestinal diseases**
  - Peptic ulcer disease
  - Gastroesophageal reflux
- **Neurological diseases**
  - Parkinson’s/Alzheimer’s
- **Rheumatic disorders**
  - Fibromyalgia
  - Osteoarthritis
- **Psychiatric disorders**
- **Dyspnea**

- **Endocrine syndromes**
  - Diabetes
  - Menopause
  - Hyperthyroidism
- **Pain**
- **Associated sleep disorders**
  - Sleep apnea
  - Restless legs syndrome
  - Periodic limb movement disorder
- **Miscellaneous conditions**
  - Dermatologic
  - Chronic fatigue syndrome
  - HIV/AIDS
  - Lyme disease
  - Systemic cancer
  - Pregnancy
  - Medical treatment induced
Increased prevalence of medical disorders in those with insomnia

- Heart Disease
- Cancer
- HTN
- Neuro
- Resp
- Urinary
- Diabetes
- Chronic Pain
- GI
- Any medical problem

$p$ values are for Odds Ratios adjusted for depression, anxiety, and sleep disorder symptoms. From a community-based population of 772 men and women, aged 20 to 98 years old.

Insomnia prevalence increases with medical comorbidity

Self-reported questionnaire data from 1506 community-dwelling subjects aged 55 to 84 years

ICSD2 Subtypes of Insomnia

- Adjustment Insomnia (Acute Insomnia)
- Psychophysiological Insomnia
- Paradoxical Insomnia
- Idiopathic Insomnia
- Insomnia due to Mental Disorder
- Inadequate Sleep Hygiene
- Behavioral Insomnia of Childhood
- Insomnia due to Drug or Substance
- Insomnia due to Medical Condition
- Insomnia not due to Substance or known Physiological Condition, unspecified
- Physiological Insomnia, unspecified

Adjustment Insomnia

- Associated with identifiable stressor
  - Psychological, psychosocial, interpersonal, environmental, or physical
- Short duration: few days to weeks
- Must last < 3 months
- Insomnia resolves when stressor resolves or when adapted to the stressor
- Features may include:
  - Prolonged sleep latency
  - Increased number or duration of awakenings from sleep
  - Short sleep duration
  - Poor quality
Adjustment Insomnia

• Estimated 1 year prevalence: 15-20% among adults (especially women, older adults)
• Predisposing factors: h/o insomnia and adjustment insomnia
• Can have recurrent episodes to either the same or different stressor
• Contributes to development of a sequence of maladaptive sleep behaviors and associations which may lead to more persistent insomnia
Psychophysiological Insomnia

- Essential feature: heightened arousal and learned sleep-preventing associations that result in complaint of insomnia & associated decreased functioning during wake
Psychophysiological Insomnia: Diagnostic Criteria

- Symptoms meet insomnia criteria
- Present for > 1 month
- One or more of the following:
  - Excess focus on and heightened anxiety about sleep
  - Difficulty falling asleep in bed at desired time or during planned naps, but not during other monotonous activities
  - Ability to sleep better away from home
  - Mental arousal in bed: intrusive thoughts or perceived inability to volitionally stop mind racing
  - Heightened somatic tension in bed - perceived inability to relax the body to allow sleep
Psychophysiological Insomnia

- Individuals have physiological arousal and learned sleep preventing associations
- Physiological arousal may be associated with emotional reactions that do not meet criteria for separate disorders
- Mental arousal in the form of “mind racing” is characteristic
- Associations can be learned in response to internal thoughts or external stimuli
  - Over-concern with inability to sleep
The vicious cycle...

- Increased drive to sleep
- Reduced ability to fall asleep
- Increased agitation
• **Demographics:**
  - 1-2% of general population
  - 12-15% of patients seen at sleep centers
  - Women > men

• **Predisposing factors:**
  - H/o light sleepers or episodic poor sleepers
  - Stress, environmental factors, life change
  - Anxious over-concern about health, well-being or daytime functioning

• **Familial patterns are unknown**
• **Onset:**
  - Insidious onset
    • Insomnia present in early life or young adulthood
  - Acute onset:
    • Adjustment insomnia failed to resolve

• **May persist for decades if untreated**

• **Complications:**
  - Higher risk for first episode or recurrence of major depression
  - Excessive use of prescription or OTC sleep aids

• **Further directions**
  - Individuals may have innate vulnerability for insomnia – altered sleep-inducing or arousal system
The AASM guidelines do NOT recommend use of PSG for routine evaluation of insomnia unless there is a suspected additional sleep disorder or patient has failed previous behavioral and/or pharmacological treatment of insomnia.
# Neurotransmitters in Wake

<table>
<thead>
<tr>
<th>Neurotransmitter (Activating/Arousal Promoting)</th>
<th>Location</th>
</tr>
</thead>
</table>
| Acetylcholine                                 | - Basal forebrain  
- Pedunculopontine tegmentum (PPT)/laterodorsal tegmentum (LDT) |
| Dopamine                                      | - Ventral periaqueductal gray matter  
- Substantia nigra |
| Glutamate                                     | - Ascending reticular activating system  
- Thalamocortical system |
| Histamine                                     | - Tuberomammillary nucleus (TMN)/posterior hypothalamus |
| Hypocretin/Orexin                             | - Lateral hypothalamus |
| Norepinephrine                               | - Locus coeruleus (LC) |
| Serotonin                                     | - Raphe nuclei, thalamus |

The Wake “Switch”
# Neurotransmitters in Sleep

<table>
<thead>
<tr>
<th>Neurotransmitter (Sleep Promoting)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>- Basal forebrain</td>
</tr>
<tr>
<td>Melatonin</td>
<td>- Pineal gland</td>
</tr>
<tr>
<td>GABA (located in 30% of all brain synapses)</td>
<td>- Ventrolateral preoptic nucleus (VLPO)</td>
</tr>
<tr>
<td>Galanin</td>
<td>- Ventrolateral preoptic nucleus (VLPO)</td>
</tr>
</tbody>
</table>

The Sleep “Switch”

Management of Insomnia

- Treat any underlying cause(s)/comorbid conditions
- Promote good sleep habits (improve sleep hygiene)
- Most individuals with insomnia rely on passive strategies: ‘do nothing, read, try to relax’
- The first line of treatment often involves alcohol, OTC drugs, dietary/natural products
- When professional help is sought by a physician, treatment is usually limited to a sleep medication
Epidemiology of hypnotic use

- General adult population: 4% (3-10%)
- Elderly: 10-20%
- Older adults, particularly women, and those residing in nursing facilities are much more likely to use hypnotics

(Mellinger et al. 1986; Ohayon, 2002)
Commonly Used Classes of Insomnia Medications

- Benzodiazepines (BZ)
- Benzodiazepine Receptor Agonists (BzRAs)
- Antidepressants
- Antipsychotics
- Melatonin Receptor Agonists
- Antihistamines
- Anticonvulsants
- “Natural” supplements/OTC Agents
### Relative Frequency of Insomnia Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Occurrences (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>2.730</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>2.074</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>0.774</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.662</td>
</tr>
<tr>
<td>Temazepam</td>
<td>0.558</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.459</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>0.405</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.394</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>0.293</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.287</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.277</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.216</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>0.205</td>
</tr>
<tr>
<td>Doxepin</td>
<td>0.199</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>0.195</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>0.192</td>
</tr>
</tbody>
</table>

FDA-Indicated Sedative Hypnotics

- Benzodiazepines (BZs)
  - Estazolam (ProSom)
  - Flurazepam (Dalmane)
  - Quazepam (Doral)
  - Temazepam (Restoril)
  - Triazolam (Halcion)
- Melatonin Receptor Agonist: Rozerem (Ramelteon)
- Tricyclic Antidepressant: Doxepin (Silenor)

- Benzodiazepine Receptor Agonists (BzRAs)
  - Eszopiclone (Lunesta)
  - Zaleplon (Sonata)
  - Zolpidem (Ambien)
  - Zolpidem Extended Release (Ambien CR)
  - Zolpidem Sublingual (Intermezzo)
### FDA-Indicated Sedative Hypnotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (mg)</th>
<th>Onset (min)</th>
<th>Half-life (hr)</th>
<th>Active metabolite</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam</td>
<td>0.5 – 2.0</td>
<td>15 – 30</td>
<td>8- 24</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15 – 30</td>
<td>30 – 60</td>
<td>2- 5</td>
<td>Yes</td>
<td>SMI</td>
</tr>
<tr>
<td>Quazepam</td>
<td>7.5 – 30</td>
<td>20 – 45</td>
<td>15 – 30</td>
<td>Yes</td>
<td>SMI</td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5 – 30</td>
<td>45 – 60</td>
<td>8 – 20</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125 – 0.25</td>
<td>15 – 30</td>
<td>1.5 – 5</td>
<td>No</td>
<td>SOI</td>
</tr>
<tr>
<td><strong>Benzodiazepine Receptor Agonists (BzRAs):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1 – 3</td>
<td>60</td>
<td>6.0</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>5 – 10</td>
<td>15</td>
<td>1.0</td>
<td>No</td>
<td>SOI, SMI</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5 – 10</td>
<td>30</td>
<td>1.5 – 4.5</td>
<td>No</td>
<td>SOI, SMI</td>
</tr>
<tr>
<td>Zolpidem ER</td>
<td>6.25 – 12.5</td>
<td>90</td>
<td>1.6 – 4.0</td>
<td>No</td>
<td>SOI, SMI</td>
</tr>
<tr>
<td>Zolpidem SL</td>
<td>1.75 – 3.5</td>
<td>35</td>
<td>1.4 – 3.6</td>
<td>No</td>
<td>SMI</td>
</tr>
<tr>
<td><strong>Melatonin Receptor Agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td>8</td>
<td>30 – 90</td>
<td>1 – 2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>SOI</td>
</tr>
<tr>
<td><strong>Tricyclic Antidepressant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td>3-6</td>
<td>210</td>
<td>15.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>SMI</td>
</tr>
</tbody>
</table>

<sup>a</sup> = parent compound; <sup>b</sup> = active metabolite; SMI = sleep maintenance insomnia; SOI = sleep onset insomnia
Question

Which of the following medications have been recommended by the NIH to treat insomnia?

• 1: Benzodiazepines (BZ)
• 2: Benzodiazepine Receptor Agonists (BzRAs)
• 3: Antidepressants
The 2005 NIH State-of-the-Science report on the management of chronic insomnia concluded: benzodiazepine receptor agonists are the only medications with an established scientific basis (clearly defined risk benefit by dose) for treating insomnia.

GABA<sub>A</sub> Receptor Complex
## GABA<sub>A</sub> Receptor Alpha Subunits

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Action</th>
<th>Proportion of GABA Receptors</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Sedative, amnestic, anticonvulsant</td>
<td>60%</td>
<td>All brain regions cortex, hippocampus</td>
</tr>
<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Anxiolytic, myorelaxant</td>
<td>15–20%</td>
<td>Cortex, hippocampus, amygdala, forebrain, hypothalamus</td>
</tr>
<tr>
<td>α&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Anxiolytic, myorelaxant</td>
<td>10–15%</td>
<td>Cerebral cortex, thalamus (reticular nucleus)</td>
</tr>
<tr>
<td>α&lt;sub&gt;4&lt;/sub&gt;, α&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Insensitive to BZ</td>
<td></td>
<td>Dentate gyrus</td>
</tr>
<tr>
<td>α&lt;sub&gt;5&lt;/sub&gt;</td>
<td>High affinity for BZ, low zolpidem affinity, BZ tolerance</td>
<td></td>
<td>Cerebral cortex, hippocampus</td>
</tr>
</tbody>
</table>

Receptor Affinities

- Benzodiazepines (BZ) have a high affinity for all the subtypes.
- On the other hand, the Benzodiazepine Receptor Agonists (BzRAs) demonstrate selectivity:

<table>
<thead>
<tr>
<th></th>
<th>ALPHA 1</th>
<th>ALPHA 2</th>
<th>ALPHA 3</th>
<th>ALPHA 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon</td>
<td>17×</td>
<td>2×</td>
<td>2×</td>
<td>1×</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>21×</td>
<td>1×</td>
<td>1×</td>
<td>Negligible</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>8×</td>
<td>5×</td>
<td>1×</td>
<td>8×</td>
</tr>
</tbody>
</table>

1× = the lowest affinity of a given drug for any receptor.

BZ & BzRAs: Effects on Sleep

- Improved sleep continuity
  - Decreased sleep latency
  - Increased total sleep time
  - Decreased wake after sleep onset
- PSG changes
  - Decreased NREM 3 (less with BzRAs)
  - Reduced amplitude of slow waves
  - Increased sleep spindles (BZ)
- Decrease in REM sleep (less with BzRAs)
- Decreased periodic limb movements (BzRAs)
BZ & BzRAs: Side Effects

- Residual daytime sedation
- Dose-related anterograde amnesia
- Discontinuation phenomenon:
  - Rebound insomnia (worsening symptoms - less with BzRAs)
  - Withdrawal (new symptoms)
  - Insomnia recurrence
- Falls/hip fractures in the elderly (long-acting BZ)
- Respiratory suppression (minor effect, more with long-acting BZ)
BzRAs: Warnings

- Risk factors for complex sleep-related behaviors while using BzRAs include:
  - Higher doses (2-3 times the indicated clinical dose)
  - Prior history of parasomnias
  - Prior history of brain injury
  - Concurrent use with alcohol
BzRAs: General Considerations

- Use lowest dose for shortest time possible
- Take on an empty stomach
- Not recommended in pregnant or nursing women
- Not recommended in advanced liver disease
- Rapid reduction in dose or withdrawal can cause withdrawal symptoms including rebound insomnia
- Use long-acting BZ with caution in patients with OSA or lung disease (COPD)
- Potential for abuse or dependence thought to be low for BzRAs

Berry, *Fundamentals of Sleep Medicine*, 2012, Ch 25
Tolerance?

- Eszopiclone (Lunesta) showed continued effect on sleep latency over 12-months
- Led to discontinuation of duration limits on BzRAs (prior had been 35 days)

Roth, et al., *Sleep Medicine*, Nov 2005
On January 10, 2013, the FDA informed the manufacturers of zolpidem (Ambien) that the recommended dose be lowered for women from 10 to 5 mg for immediate-release products and from 12.5 to 6.25 mg for extended-release products.
Antidepressants

- Hypnotic properties most strongly related to antagonism of serotonin 5-HT$_2$, histamine H$_1$, and α1 adrenergic receptors
- Commonly used medications include trazodone, mirtazapine, amitriptyline, and doxepin
- Doses used for insomnia are much lower than those used for depression
- Doxepin was approved in 2010 for maintenance insomnia (3 and 6 mg), because it has histamine selective properties at low doses
Antidepressants

- Few studies—strongest evidence for efficacy is for tricyclics (doxepin, amitriptyline, trimipramine)

- Specific adverse effects need to be considered:
  - **Tricyclics**: anticholinergic side effects
  - **Trazodone**: hypotension, rare priapism
  - **Mirtazapine**: weight gain
  - **SSRIs**: insomnia, exacerbate RLS
Antipsychotics

- Atypical antipsychotics such as quetiapine and olanzapine have indications for psychotic disorders and mania
- Antagonize dopamine, histamine ($H_1$), serotonin ($5HT_{2A}$), muscarinic, cholinergic, and $\alpha_1$ receptors
- Similar to antidepressants, used at lower doses for treating insomnia: quetiapine 25-200 mg, olanzapine 2.5-20 mg
- Olanzapine has longer half-life than quetiapine: 21-54 hours versus 6-7 hours, respectively
Antipsychotics

- Studies in patient populations other than primary insomnia:
  - Decreased sleep latency
  - Olanzapine may increase deeper NREM sleep
  - Quetiapine may reduce REM sleep
- Significant potential risks:
  - Akathesia
  - Weight gain
  - Orthostatic hypotension
  - Contribution to metabolic syndrome
Melatonin Receptor Agonist

- Ramelteon became first melatonin receptor agonist approved for treating insomnia (2005)
- \(17\times\) more potent at melatonin type I (decreased waking signal) than type II (circadian rhythms) receptors
- Primary benefit on sleep latency
- Non-scheduled medication — lacks potential for abuse or dependence
- Adverse effects: nausea, headache, fatigue
Antihistamines

- Diphenhydramine, doxylamine, and hydroxyzine are the most commonly used for insomnia
- Tolerance to daytime sedation and similar decrease in effectiveness as a hypnotic can develop in 4 days\(^1\)
- Anticholinergic activity needs to be considered, especially in the elderly

Anticonvulsants

- Pregabalin and gabapentin bind to voltage-gated calcium channels → diminish release of glutamate and norepinephrine
- FDA indications: partial seizures, pain, fibromyalgia
- Gabapentin used at doses of 100-900 mg for insomnia
- Common adverse effects include sedation, dizziness, ataxia
Melatonin

- Produced by pineal gland; "turned on" by the SCN at night by darkness
- Melatonin on its own will not induce sleep, it is more like a “darkness” signaler
- If taken in the evening or when it's dark, melatonin can speed up sleep preparation, and it can tell the body clock to shift its sleep cycle to an earlier time
- For some people, melatonin seems to help improve sleep. Of the few studies involving people with insomnia, results are inconclusive
Melatonin

- Dosage is very important.
- Most drug stores and health stores carry tablet sizes 3-10mg.
- New evidence shows that adult males only need 150 micrograms, and the average female needs only 100 micrograms, so 20 - 50 times more than what is needed.
- Large studies are needed to demonstrate if melatonin is effective and safe for some forms of insomnia, particularly for long-term use.
Hypnotic Selection

Hypnotic indicated
- Consider cost, prior treatment failures, side effects, co-morbidities, interactions

Short to intermediate BZRA or Ramelteon
- SOI: Zaleplon, Ramelteon
- SOI, SMI: zolpidem, eszopiclone, temazepam

Improved
- Duration too long, AM grogginess
- Use shorter active BZRA

Duration not long enough
- Use longer acting BZRA

Ineffective
- Increase dose or switch

Intolerable side effects
- Switch

Improved?

Y
- Continue

N or
- BZRA + sedating antidepressant
- Sedating antidepressant

Adapted from Berry, Fundamentals of Sleep Medicine, 2012, Ch 25
Sedative Hypnotics: General Considerations

- Ensure patients dedicated an adequate amount of time to sleep
- Consider pharmacokinetic and pharmacodynamic properties, cost, side effects, and duration of use
- Do not combine with alcohol!
- Use caution with other sedatives
- Consider patient preference for treatment modality
- Evaluate contributions to insomnia from other medications and medical conditions
- Consider drug interactions when choosing an agent
Selecting a Sedative Hypnotic

- If patient has a history of alcohol or recreational drug dependence: consider non-controlled medications:
  - Ramelteon, doxepin, antidepressants, antipsychotics, or anticonvulsants
  - Antipsychotics should be reserved for cases with primary psychiatric disorders.
- If patient has co-morbid pain, seizures, RLS, PLMD, or fibromyalgia
  - Gabapentin or pregabalin
- Consider CBT-I (cognitive behavioral therapy for insomnia) for chronic insomnia
When to discontinue hypnotics...

• ...desire to stop
• ...is no longer effective
• ...is contraindicated
  - Alcohol abuse/dependence
  - Pregnancy
• ...escalating dosage and demonstrating signs of tolerance and/or abuse
• ...adverse effects such as cognitive impairment or psychomotor performance issues
• ...has been using the medication longer than recommended?
“Am I an addict?”

- **Tolerance** – Reduction of pharmacological effect after repeated administration of drug
- **Dependence** – Neuroadaptation phenomenon resulting from chronic administration, characterized by withdrawal syndrome
- **Abuse** – Loss of control over drug taking, preoccupation with drug, continued use despite adverse consequences, use for “high”

Brady et al., Current Psychiatric Treatment II, 1997
Withdrawal Symptoms

- Rebound Insomnia
- Anxiety
- Restlessness
- Increased perceptual acuity
- Impaired concentration
- Tend to be more severe with higher dosages and with shorter half lives
Rebound Insomnia

- Worsening of sleep upon discontinuation of medication
- Level of sleep disturbance can be more severe than before starting medication
- This transient symptom is misinterpreted as a chronic problem, therefore prompts patients to resume or increase medication use
- Need to provide education on rebound insomnia phenomenon as well as implementing tapering plan to minimize withdrawal
Cycle of Hypnotic Dependent Insomnia

Dependence
Resume use of Medication

Withdrawal: Rebound Insomnia

Attempt to Stop Medication

Tolerance: Decreased effectiveness
Increase Sleep Medication

Tolerance
Insomnia
Sleep Medication
Strategies for discontinuing hypnotic medications

- Abrupt discontinuation
- Tapering from short-acting hypnotics
- Substitute and taper long-acting hypnotic
- Use of other drug to facilitate
- CBTi as an adjunct
Spielman Model: Three P’s

<table>
<thead>
<tr>
<th>Predisposing Factors</th>
<th>Precipitating Factors</th>
<th>Perpetuating Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic traits</td>
<td>Medical illness</td>
<td>Excessive time in bed</td>
</tr>
<tr>
<td>Psychological traits</td>
<td>Psychiatric illness</td>
<td>Napping</td>
</tr>
<tr>
<td>Social factors</td>
<td>Stressful life events</td>
<td>Conditioning</td>
</tr>
</tbody>
</table>

**Figure**: A Model of Chronic Insomnia

<table>
<thead>
<tr>
<th>Stage</th>
<th>Insomnia Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td></td>
</tr>
<tr>
<td>Short-term</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
</tr>
</tbody>
</table>

Cognitive-Behavioral Treatment of Insomnia

- Multi-component treatment
  - Sleep hygiene education
  - Stimulus control
  - Sleep restriction
  - Relaxation therapy
  - Cognitive restructuring

- Most behavioral sleep medicine clinicians use a multi-modal approach - combining the techniques above
Psychophysiological Insomnia
Circadian Disruption
Improper Sleep Scheduling
Cognitive Factors Dysfunctional Beliefs
Inhibitory Factors Poor sleep hygiene Conditioned arousal Pre-bed & In-bed habits
Sleep Hygiene
Stimulus Control
Sleep Restriction
Psychophysiological Insomnia
Homeostatic Dysregulation Excessive TIB Napping
Relaxation
Edinger & Means, 2005
Cleveland Clinic

Every life deserves world class care.