Wide Awake: Managing Insomnia

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Speakers

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Supporter

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Disclosures

Julie A. Dopheide, PharmD, BCPP, FASHP, and Ericka L. Crouse, PharmD, BCPP, CGP, FASHP, received honoraria for participating as faculty for an APhA Insomnia webinar in November of 2015 and an Insomnia case study released in December 2015. Both activities were supported through educational grants provided to APhA by Merck pharmaceuticals. Ericka L. Crouse also reports honoraria from CPNP and ASCP for educational activities.

• Target Audience: Pharmacists
• ACPE#: 0202-0000-16-064-L01-P
• Activity Type: Application-based

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Learning Objectives
At the completion of this application-based activity, learners will be able to:

1. Describe conditions that result in inadequate sleep.
2. Discuss the impact of inadequate sleep on overall health and well-being.
3. Discuss the merit of educating patients to employ appropriate sleep hygiene practices.
4. Assess the role of the various pharmacologic approaches in treating insomnia, including their risks and benefits.
5. Discuss when pharmacotherapy is warranted to aid sleep and educate patients on appropriate use of available products.

Which of the following accurately describes an established health consequence of chronic insomnia?
A. Hyperthyroidism
B. Diabetes
C. Arthritis
D. Migraine

A 50 year old with chronic insomnia treated with CBT is counseled to get out of bed and read or stretch after 15 minutes of not sleeping. This recommendation is the main premise of:
A. Stimulus control
B. Relaxation training
C. Sleep restriction
D. Complementary therapeutics

According to the Agency for Healthcare Research and Quality’s executive summary on managing insomnia, a 35 year old patient with trouble falling asleep and staying asleep is most likely to benefit from:
A. Eszopiclone
B. Trazodone
C. Doxepin
D. Temazepam

Which of the following warnings were added to zolpidem’s product labeling in October 2014?
A. Allergy
B. Risk of falls
C. Next day sedation
D. Driving impairment

Which of the following is FDA approved for insomnia?
A. Doxepin
B. Trazodone
C. Mirtazapine
D. Amitriptyline
A thin 22 year old patient with asthma complains of 3 weeks of trouble falling asleep, excessive daytime sleepiness, and loss of muscle control to the point of falling after laughing. Which diagnosis is most likely?

A. Sleep deprivation  
B. Obstructive sleep apnea  
C. Narcolepsy  
D. Chronic insomnia

Organization of Presentation

Dopheide  
- Clinical Presentation and Diagnosis of Insomnia  
- Health Consequences of Insomnia and Excessive Hypnotic Use  
- Nonpharmacological Approaches for Treating Insomnia  
- Case Presentations: Child and Young Adult  

Crouse  
- Case Presentations: Medically Ill and Older Adult  
- Sleep-Wake Disorders  
- Selecting the right hypnotic for an individual patient  
- Counseling points

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What Is Insomnia?

Most common sleep complaint  
- Difficulty initiating or maintaining sleep  
- Waking up at night or too early in the morning  
- Non-restorative or poor quality sleep

Daytime symptoms  
- Fatigue or low energy  
- Inattention  
- Memory and concentration problems  
- Mood problems

Course:  
- Situational,  
- Episodic,  
- Recurrent,  
- Persistent


2014 Sleep in America Poll:  
Reasons for not getting a good night's sleep

Unintentionally Fell Asleep - Driving

http://www.cdc.gov/features/dssleep/
Short Sleepers ≤6 Hours Are at Greater Risk for Disease and Early Death

- Increased risk of ischemic stroke
- Increased risk of heart attack
- Increased obesity
- Impaired glucose tolerance and increased risk of type 2 diabetes
- Increased cancer risk: breast, prostate, endometrial, colorectal


10% to 15% of Americans Have at Least One Chronic Sleep Disorder

- Sleep deprivation
- Insomnia
- Circadian rhythm disorder
- Restless legs
- Sleep disordered breathing
- Narcolepsy


Patient Assessment

- Determine if medical and/or neuropsychiatric comorbidities need to be investigated before sleep hygiene, cognitive behavioral treatment or medication
- Type of insomnia and resulting impairment
  - Difficulty falling asleep, maintaining sleep
- What has the patient tried?
  - Consider drug and alcohol use
- Engage patient to set goals of treatment

Buysse DJ. Insomnia. JAMA 2013

Sleep Diary

- National Sleep Foundation Sleep Diary
- COMPLETE IN MORNING
  - How many minutes did it take to fall asleep?
  - I woke during the night ___ times
  - How did I feel upon awakening?
- COMPLETE AT END OF DAY
  - Medications?
  - Caffeinated drinks?
  - What did I eat 2 to 3 hours before bedtime?
  - How much exercise?

https://sleepfoundation.org/content/nsf-official-sleep-diary

DSM-5 Changes in Categorization of Insomnia by Duration

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient: &lt;1 week</td>
<td>Acute: 1-3 weeks</td>
</tr>
<tr>
<td>Short-term: 1-3 weeks</td>
<td>Subacute: 1-3 months</td>
</tr>
<tr>
<td>Chronic: ≥1 month</td>
<td>Chronic: ≥3 months</td>
</tr>
</tbody>
</table>

Comorbidity Specifier: Psychiatric/Medical/Sleep Disorder
Diagnostic and Statistical Manual of Mental Disorders 2013


NIH: Bidirectional Connection Between Medical/Psychiatric Conditions and Insomnia

1. No more primary vs. secondary insomnia
2. Comorbid insomnia depression, anxiety, pain
3. Need to treat all conditions concurrently

Executive Summary on Management of Insomnia

- Data evaluated: 3,572 citations; 169 randomized controlled trials and 12 observational studies met inclusion criteria (study design, duration, low bias)
- Evaluated existing scientific evidence for effectiveness and comparative adverse event risk for:
  - Cognitive Behavioral Interventions
  - FDA-approved hypnotic medications
  - Complementary and alternative treatments
- Limitations: meds not FDA-approved for insomnia (i.e. trazodone, lorazepam) not evaluated, youth not included, many comorbidities left out

Key Points from Insomnia Executive Summary

Evidence for Therapeutic Benefit
- Strongest evidence for multimodal cognitive behavioral therapy (CBT), eszopiclone (Lunesta), zolpidem (Ambien), and suvorexant (Belsomra) in managing insomnia in the adult population
- Decreased time to fall asleep (10 - 45 min)
- Decreased wakefulness after sleep onset (10- 45 min)
- Increased total sleep time (20 – 90 min)

Evidence for adverse effects
- Chronic hypnotic use (months) is correlated with dementia, fractures, major injuries and possibly cancer and death

Evidence for complementary approaches
- Insufficient evidence to recommend complementary or alternative treatments but adverse effects low

Executive Summary on Management of Insomnia

<table>
<thead>
<tr>
<th>Psychological or Behavioral Interventions</th>
<th>Definition of Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation training</td>
<td>Reduces somatic tension and control thought patterns, progressive muscle relaxation</td>
</tr>
<tr>
<td>Stimulus Control</td>
<td>Establish consistent sleep patterns. Go to bed only when sleepy, avoid TV, computer in bed</td>
</tr>
<tr>
<td>Sleep Restriction</td>
<td>Limits time in bed to sleep time; e.g. need to get out of bed if not asleep in 15 minutes</td>
</tr>
<tr>
<td>Brief Behavioral Intervention</td>
<td>Combines stimulus control and sleep restriction</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Replace dysfunctional beliefs about sleep</td>
</tr>
<tr>
<td>Cognitive Behavioral Therapy</td>
<td>A multi-modal approach that combines education, sleep restriction, stimulus control &amp; sleep hygiene</td>
</tr>
<tr>
<td>Sleep Hygiene Education</td>
<td>Establishes lifestyle choices that improve sleep</td>
</tr>
</tbody>
</table>

Key Points from Insomnia Executive Summary

- Cognitive Behavioral Therapy (CBT) Approaches Including Sleep Hygiene
- Medications
- Combination CBT and Medications

Zolpidem – Psychiatric Medication With the Most Patient Visits to ED for an Adverse Drug Event

Number of Cases and National Estimates of Annual ED Visits for Psychiatric Medication ADEs Among Adults 19 years and Older by Most Commonly Implicated Medications in the United States between 2009-2011

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of Cases</th>
<th>Estimated annual number of visits</th>
<th>Hospitalization Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem</td>
<td>445</td>
<td>10212</td>
<td>23.1</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>320</td>
<td>6900</td>
<td>24.9</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>241</td>
<td>5616</td>
<td>27.9</td>
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<tr>
<td>Lorazepam</td>
<td>233</td>
<td>5517</td>
<td>21.9</td>
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<tr>
<td>Haloperidol</td>
<td>250</td>
<td>4879</td>
<td>11.6</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>215</td>
<td>4571</td>
<td>24.2</td>
</tr>
<tr>
<td>Trazodone</td>
<td>182</td>
<td>4249</td>
<td>22.2</td>
</tr>
<tr>
<td>Citalopram</td>
<td>175</td>
<td>4143</td>
<td>9.8</td>
</tr>
<tr>
<td>Lithium</td>
<td>217</td>
<td>4034</td>
<td>50.6</td>
</tr>
</tbody>
</table>


Sleep Hygiene Recommendations

• Regular schedule – wake at the same time each day
• Regular moderate exercise early in the day
• Avoid heavy, spicy food; avoid eating late in the day
• Make the bedroom comfortable (e.g. cool, dark, quiet)
• Use the bedroom only for activities associated with sleep. Do not watch TV, eat, or pay bills in bed.
• If not asleep in 20 minutes, move to another room and engage in a boring or relaxing activity
• Sleep only as much as needed to feel refreshed/alert
• Avoid alcohol to 1 or 2 drinks and to early evening hours
• Cover the clock to prevent focusing on it at night

Cognitive Behavioral Therapy (CBT)

Can take 3 to 6 weeks for significant improvement
40-45% of patients achieve remission with CBT

<table>
<thead>
<tr>
<th>CBT Approach</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep hygiene training</td>
<td>Teaches healthy lifestyles for sleep. Not effective as sole treatment for chronic insomnia</td>
</tr>
<tr>
<td>Stimulus control</td>
<td>Reduces negative association between the bed and insomnia</td>
</tr>
<tr>
<td>Sleep restriction</td>
<td>Limits time in bed to sleeping</td>
</tr>
<tr>
<td>Cognitive behavioral therapy for insomnia (CBT-I)</td>
<td>Cognitive therapy (to change the patient’s unrealistic expectations of sleep) with stimulus control/ sleep restriction with or without relaxation</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>Lowers somatic and cognitive arousal states (e.g., progressive muscle relaxation, guided imagery)</td>
</tr>
</tbody>
</table>

Tai Chi Associated With Improvement in Insomnia, Overall Health


Yoga Over 4 to 6 Weeks Is More Effective than Ayurvedic Herbal Treatment


Acupuncture and Acupressure

• Better evidence for acupressure


Massage

• Lacking evidence for management of insomnia compared with other physical treatments
• Has been shown to assist in getting elderly individuals off benzodiazepine hypnotic when combined with warm milk and cognitive therapy

Assessment and Treatment of Insomnia: Case Studies

Emily Morris, 16 years old

Pediatric Insomnia

ID: 6-year-old boy brought in by parents
CC: “Our son only gets 4 to 5 hours of sleep”
PMH: Autistic spectrum disorder diagnosed at age 4 years. No other health problems.

Is medication appropriate?
What do you recommend?

 Starter Medications
- 6-15 Omega-3 fatty acid 1,000 mg daily
- 2-15 Acetyl-Cysteine 500 mg/day
- 2-15 Multivitamin daily

Strategies to Improve Sleep in Children with Autistic Spectrum Disorder (ASD)

Malow B A et al. Pediatrics 2012;130:S10S124
http://www.autismspeaks.org/docs/sciencedocs/aut/sleep-tool-kit.pdf

Steps for Managing Insomnia in ASD
1. Assess for medical contributing factors
2. Implement autism treatment network sleep tool-kit.
3. Establish bedtime routine and visual schedule
4. Melatonin 1 to 3 mg given 1 hour before bedtime

Erin, a 23 yr old student can’t sleep, (+) racing thoughts, tearful, dysphoric, anxious, diphenhydramine, melatonin ineffective…

- What additional questions will you ask to aid assessment?
  How long? worsening over 3-4 months, etoh? no, drugs? denies Diagnosis? MDD, GAD Medications? Citalopram 20mg
- What type of insomnia does Erin have?
  Chronic insomnia co-occurring with psychiatric illness
- What will you recommend to help Erin’s symptoms?
  Optimization of SSRI dose and consider Z-hypnotic such as zolpidem at night for sleep, consider CBT as well

Improved Outcomes when Depression, Anxiety & Insomnia Treated Concomitantly

- Benzodiazepine (alprazolam or clonazepam) given along with SSRI (sertraline, escitalopram) to manage insomnia and anxiety until SSRI has time to exert benefit
- RCT in depressed patients with insomnia taking fluoxetine and placebo or eszopiclone showed improved outcomes in those taking eszopiclone
- Advantage of benzodiazepine is anxiolytic effect
- Advantage of Z-hypnotic, less hangover
- Patient engagement and education essential

www.effectivehealthcare.ahrq.gov/reports/final.cfm
Zolpidem Peak Blood Levels Higher in Women and Elderly Adults

Who Is Likely to Abuse Hypnotics?

- Substance abuse history
- Chronic, untreated anxiety disorder
- Insomnia not relieved by prescribed dose of hypnotic; need to investigate other causes
- Supply of hypnotic given should take into account risk of abuse
- Intravenous misuse in drug abusers reported, even with Z-hypnotics

Jan 10 2013: FDA recommends Lower maximum dosages

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Virginia Commonwealth University Health System

Case Vignette – Insomnia with Co-morbidities

- A 55 year old obese (BMI 39) male comes to clinic requesting mixed amphetamine salts to help him stay awake at work and he is inquiring about trying suvorexant to help sleep on his days off. He feels tired “all the time”
- Upon further inquiry you find that he is a long-distance commercial truck driver. He prefers to do his driving overnight because there are less cars on the road. On the nights that he is off he has a hard time going to bed at the “normal” time with his family.
- Besides caffeine use, he denies any substance use

Case Vignette continued…

- PMH includes history of an MI, dyslipidemia, diabetes and high blood pressure.
- For insomnia he has tried
  - OTC diphenhydramine which helped only the first few nights, but made him so thirsty that he had to stop to urinate too often
  - Zolpidem 10 mg– at times “doubled his dose” taking up to 20 mg but felt it affected his driving the next morning
  - Eszopiclone 3 mg – gave him a horrible taste in his mouth
  - Trazodone 50 mg– did not help

Audience Poll

How many of you would

A. Recommend a stimulant like mixed amphetamine salts
B. Consider a trial of suvorexant
C. Further work up his complaint
### Warnings/Precautions on ALL Sedative/hypnotics
- If insomnia does not remit after 7 to 10 days, “Need to evaluate for co-morbid diagnoses.”
  - Changes in sleep can be a presenting symptom of a physical or psychiatric disorder, symptomatic treatment of insomnia should only be considered after further evaluation. If insomnia does not remit after 7 to 10 days a primary psychiatric or medical illness should be ruled out.


### Audience Poll
In this patient which of the following should you screen for?
A. Insomnia  
B. Narcolepsy  
C. Sleep Apnea  
D. Shift-work Disorder

### Prevalence of Sleep Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>Up to 1/3 of the population have complaints of insomnia</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>0.02-0.04% of the general population</td>
</tr>
</tbody>
</table>
| OSA          | 1-2% of children  
> 20% of elderly  
70% of people with OSA are overweight or obese |
| Shift Work   | 5-10% of night work population (15-20% of workforce)  
25-30% c/o daytime sedation or insomnia |

DSM-5, 2013; [www.cdc.gov](http://www.cdc.gov)  
[www.sleepfoundation.org](http://www.sleepfoundation.org)

### Narcolepsy
- **Symptoms:**
  - Excessive Daytime Sleepiness (EDS) – 100% of cases
  - “Sleep attacks”  
  - Cataplexy – 60-70% of cases  
  - Sleep Paralysis  
  - Hallucinations
    - Hypnagogic – during sleep onset  
    - Hypnopompic – during awakening

EDS occurs despite adequate sleep
Diagnosis:
- The “need to sleep” or lapsing into sleep at least 3 times/week over 3 months
- One of the following:
  - Cataplexy  
  - Hypocretin Deficiency  
  - Nocturnal polysomnography (PSG) – enter REM ≤ 15 minutes or Multiple Sleep Latency Test (MSLT) ≤ 8 mins

Sleep Apnea [a.k.a. Sleep Apnea Hypopnea]

• Signs and Symptoms
  – Snoring
  – Pauses in breathing
  – Choking/gasping
  – Excessive daytime sleepiness
    • Falling asleep in meetings
    • Falling asleep while stopped at a red light...
  – Snoring
  – Pauses in breathing
  – Choking/gasping
  – Excessive daytime sleepiness

http://www.nhlbi.nih.gov/health/health-topics/topics/sleepapnea/signs

Screening Tool: STOP-Bang for OSA

| S | Snoring | Snore loudly? | 1 |
| T | Tired | Daytime sleepiness? Fatigue? | 1 |
| O | Observed | Stopping breathing during your sleep? | |
| P | Pressure | History of or being treated for HTN? | Yes 1 |
| B | Body Mass Index | > 35 kg/m² | |
| A | Age | > 50 | Yes 1 |
| N | Neck circumference | > 40 cm | |
| G | Gender | Male? | Yes 1 |


Obstructive Sleep Apnea

• Diagnosis – Sleep study with polysomnography
  – Exhibit ≥ 5 apneas or hypopneas/hour accompanied by either
    • Snoring, gasping, pauses in breathing
    • EDS, fatigue or unrefreshing sleep
  – OR
  – Exhibit ≥ 15 apneas or hypopneas/hour with/without symptoms
• Goal of treatment:
  – Decrease apneic episodes
  – Improve quality of sleep
  – Reduce daytime sleepiness


Shift Work Disorder

• A circadian rhythm disorder characterized by
  – EDS at work
  – Sleep impairment at home
• Affects persons who work outside the “normal” work day
  – Your internal clock is telling you it is time to sleep
• Goals of treatment
  1. Re-regulate sleep cycle – consider off-label use of melatonin or ramelteon
  2. Improve falling asleep – off-label use of sedatives
  3. Help stay awake when on duty – modafinil and armodafinil are both FDA approved to treat shift work disorder

www.sleepfoundation.org DSM5, 2013

Occupational Errors

• 2012 Survey of ~ 5000 participants
  – 20% suffered insomnia 12 months
• Suggested insomnia is responsible for 274,000 workplace accidents and errors each year, adding up to $31 billion in extra costs.
  – Errors >> accidents
  – Insomnia was linked to ~ 7% of costly workplace accidents


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Key Points
• If primary complaint is difficulty staying awake
  – Evaluate for OSA or Narcolepsy
  – Evaluate for sedating medications taken in the morning
• If primary complaint is difficulty falling asleep
  – Evaluate for primary insomnia
  – Evaluate for psychiatric, medical causes of insomnia
  – Evaluate for medications that increase insomnia

Case continued...
• The patient goes for a sleep study
  – Is diagnosed with OSA
  – And meets criteria for shift-work disorder
• Considerations....
  – Remember his primary complaints were
    – Difficulty falling sleeping at home
    – Staying awake when driving his late-night shifts
    – Feeling fatigued most days

Choosing a Medication By Sleep Complaint [FDA approval]
Sleep Onset
- Estazolam, Flurazepam, Quazepam, Temazepam, Triazolam
- Eszopiclone, Zaleplon, Zolpidem
- Ramelteon
- Suvorexant

Sleep Maintenance
- Eszopiclone, Zolpidem CR
- Doxepin
- Suvorexant
- Frequent nocturnal awakenings or early morning awakening: Estazolam, Flurazepam, Quazepam

Middle of the Night Awakening
- Zolpidem SL (low-dose)

Treatment Approach
• OSA: Improvement in CPAP adherence is primary goal
• Shift Work: Encourage daytime driving
• Stimulants should only be considered after adherence to CPAP is confirmed and day time sleepiness continues to be a concern
• If a sleep medication is indicated in OSA
  – Avoid benzodiazepines especially those with longer t1/2 as they can reduce respiratory drive
  – Controversy regarding non-benzodiazepines
    • Zolpidem can be considered
    • Eszopiclone may even improve CPAP adherence

Comparing PK of Benzodiazepines To Non-benzodiazepines

Case Vignette continued....
• For insomnia he has tried
  • OTC diphenhydramine
    – “helped only the first few nights”: generally consider effective for short-term use; tolerance may develop
    – “made him so thirsty that he had to stop to urinate too often” — adverse effects include anticholinergic adverse effects; risk of next-day sedation
  • Zolpidem 10 mg – at times “doubled his dose” taking up to 20 mg but felt it affected his driving the next morning
  • Eszopiclone 3 mg– gave him a horrible taste in his mouth
  • Trazodone 50 mg – did not help
Case Vignette continued…

- For insomnia he has tried
  - OTC diphenhydramine
  - Zolpidem 10 mg – at times “doubled his dose” taking up to 20 mg but felt it affected his driving the next morning
    - Sex effects – lowered female dosing because of next day driving impairment; in studies similar effect was seen in males who took 20 mg
  - Eszopiclone 3 mg – gave him a horrible taste in his mouth
  - Trazodone 50 mg – did not help


FDA Alert May 2014

- Eszopiclone can cause next-day impairment of driving and other activities that require alertness.
  - Initial dose: eszopiclone to 1 mg at bedtime.
  - Previously recommended doses of 3 mg can cause impairment to driving skills, memory, and coordination lasting ≥11 hours after receiving an evening dose. Patients were often unaware they were impaired. A lower recommended initial dose of 1 mg should result in less drug in the blood the next day.
  - Women and men are equally susceptible to eszopiclone impairment, so both sexes should start at 1 mg.
  - Patients taking a 3 mg dose should be cautioned against driving or engaging in other activities that require complete mental alertness the day after use.

http://www.fda.gov/Drugs/DrugSafety/ucm397260.htm

Case Vignette continued…

- For insomnia he has tried
  - OTC diphenhydramine
  - Zolpidem – at times “doubled his dose” taking up to 20 mg but felt it affected his driving the next morning
  - Eszopiclone – gave him a horrible taste in his mouth
  - Trazodone – did not help

Off-label use: Most evidence supports its use in patients with co-morbid depression or those who experience insomnia as an adverse effect of their antidepressant (SSRIs, SNRIs)
- Less next day sedation than the “z” hypnotics
- Adverse effects include dizziness upon standing and orthostasis
- Rare risk of priapism


Case Vignette continued…

- For insomnia he has tried
  - OTC diphenhydramine
  - Zolpidem 10 mg – at times “doubled his dose” taking up to 20 mg but felt it affected his driving the next morning
  - Eszopiclone 3 mg – gave him a horrible taste in his mouth
    - Reported in up to 34% of patients taking eszopiclone
  - Note previously 2 mg was indicated for sleep onset; 3 mg for sleep maintenance. New recommendation all patients should start at 1 mg
  - Trazodone 50 mg – did not help

Eszopiclone prescribing information. Available at: www.dailymed.nlm.nih.gov

Comparing PK of Benzodiazepines To Non-benzodiazepines

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Peak</th>
<th>T1/2</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>Peak: 1 hr</td>
<td>T1/2: 2-3 hrs</td>
<td>Duration: 8-10 hrs</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Peak: 2 hrs</td>
<td>T1/2: ~1.5-5 hrs</td>
<td>Duration: &lt;4 hrs</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Peak: 1 hr</td>
<td>T1/2: 4 hrs</td>
<td>Duration: 4-6 hrs</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Peak: 1-2.6 hrs</td>
<td>T1/2: ~11.5-5 hrs</td>
<td>Duration: &lt;4 hrs</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Peak: 1-1.5 hrs</td>
<td>T1/2: ~6 hrs</td>
<td>Duration: &gt;6 hrs</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Peak: 2 hrs</td>
<td>T1/2: 28-43 hrs; metabolite 39-73 hrs</td>
<td>Duration: 8+ hrs</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Peak: 1.5 hrs</td>
<td>T1/2: 6-16 hrs</td>
<td>Duration: ~6 hrs</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Peak: 2 hrs</td>
<td>T1/2: ~1.5-5 hrs</td>
<td>Duration: &lt;4 hrs</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Peak: 0.5-1.6 hrs</td>
<td>T1/2: 10-24 hrs</td>
<td>Duration: 6-8 hrs</td>
</tr>
</tbody>
</table>

What the patient has not tried

- Other Sedating Antidepressants
  - Benzodiazepines
  - Melatonin Receptor Agonists
  - Suvorexant

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Sedating Antidepressants and Antihistamines

<table>
<thead>
<tr>
<th>Medication (mg)</th>
<th>H1 Antagonist</th>
<th>H2 Antagonist</th>
<th>α1 Antagonist</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine (25-50)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>4-8</td>
</tr>
<tr>
<td>Amitriptyline (25-50)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>15</td>
</tr>
<tr>
<td>Trazodone (25-100)</td>
<td>+++</td>
<td>NA</td>
<td>+++</td>
<td>7</td>
</tr>
<tr>
<td>Mirtazapine (7.5-45)</td>
<td>+++</td>
<td>NA</td>
<td>NA</td>
<td>20-40</td>
</tr>
<tr>
<td>Doxepin (1-6)</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>15</td>
</tr>
</tbody>
</table>


Antidepressants Used to Treat Insomnia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pros</th>
<th>Cons</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>FDA approved; Not a controlled substance; has been studied in the elderly population; beneficial for maintaining sleep; low-dose doxepin not on Beers List</td>
<td>Cost 6 mg at bedtime</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>Not a controlled substance; less next-day sedation than benzodiazepine receptor agonists; cost</td>
<td>“Off-label”; most evidence supports its use in depression or antidepressant induced insomnia 25-50 mg at bedtime</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Not a controlled substance; helps with comorbid depression and anxiety</td>
<td>“Off-label”; adverse effect of weight gain; cost 7.5-15 mg at bedtime</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Not a controlled substance; may help with comorbidities such as depression and pain; cost</td>
<td>“Off-label”; on Beers List, adverse effects (e.g., anticholinergic) 25 mg at bedtime</td>
<td></td>
</tr>
</tbody>
</table>


When to Consider Antidepressants

- Patients with comorbid anxiety/depression
- Patients with comorbid substance abuse
- Caution with trazodone in African American men with a history of sickle cell disease


Melatonin Receptor Agonists

- Ramelteon 8 mg at bedtime-FDA approved for sleep onset
- Consideration “off-label” in circadian rhythm disorders like shift work disorder
- Unique adverse effects: hyperprolactinemia or reduced testosterone (↓ libido)
- Counseling Points:
  - Take 30 minutes prior to bedtime
  - Do not take after high-fat meal
- For this patient
  - May be a consideration (or herbal melatonin) to regulate his sleep/wake cycle on days he is not working/driving
  - Not noted to be risk in OSA

What About Suvorexant?

- This patient was originally requesting suvorexant
- Novel mechanism of action
  - Orexin antagonist
- Approved for both help falling asleep (sleep onset) and maintaining sleep.
- What is orexin?
  - Orexin, also known as hypocretin is a WAKE promoting substance

Audience Poll

What is the recommended starting dose for suvorexant?

A. 5 mg at bedtime
B. 10 mg at bedtime
C. 20 mg at bedtime
D. 40 mg at bedtime

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Suvorexant

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Latency to Persistent Sleep (Night 1)</th>
<th>Latency to Persistent Sleep (Week 4)</th>
<th>Total Sleep Time Change (Night 1)</th>
<th>Total Sleep Time Change (Week 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>-3.4 min</td>
<td>-2.3 min</td>
<td>25.1 min</td>
<td>22.8 min</td>
</tr>
<tr>
<td>20</td>
<td>-8.4 min</td>
<td>-2.3 min</td>
<td>36.2 min</td>
<td>49.9 min</td>
</tr>
<tr>
<td>40</td>
<td>-23.1 min</td>
<td>-3.8 min</td>
<td>52.4 min</td>
<td>36.8 min</td>
</tr>
<tr>
<td>80</td>
<td>-25.4 min</td>
<td>-9.5 min</td>
<td>61.9 min</td>
<td>36.6 min</td>
</tr>
</tbody>
</table>

FDA approved dosing: suvorexant 10 mg at bedtime (maximum 20 mg)


FDA Approved Dosing for Suvorexant

- Dosing: 10 mg within 30 minutes of going to bed; with at least 7 hours remaining before awaking
  - Max dose: 20 mg
- Exposure to drug is higher in
  - Obese patients > non-obese patients
  - Females > Males
- Drug Interactions: CYP3A4 substrate

Suvorexant Major Safety Concerns

1. Daytime somnolence
   - Can be severe and occur suddenly; concern for patients driving while impaired
     - Somnolence 7% low dose; 11% high dose
     - Excessive daytime sleepiness 0.8% (low dose) and 1.1% (high dose); 0.5% while driving

2. Unconscious nighttime activity
   - Acting out dreams
   - Sleep walking
   - One case of an elderly patient on 30 mg lunging out of bed and hit head and face on wall

Suvorexant Major Safety Concerns

3. Suicidal Ideations
   - 5 patients (0.7%) in high-dose suvorexant; 4/5 did not have a history of SI
   - 1 patient (0.2%) low-dose; had a h/o SI
   - 1 patient (0.1%) placebo; had a h/o SI

4. Narcolepsy-like events
   - Sleep paralysis and hypnagogic hallucinations ~0.3%
   - Occurred at 20 and 30 mg doses
   - Cataplexy (mild) ~ 0.1%; concern that events of “weakness” may have been cataplexy-like

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Return to Patient Case – Insomnia with OSA and Shift Work Disorder

- Non-pharmacologic very important
  - Treat his OSA with CPAP
  - Avoid excessive caffeine
- If pharmacologic is indicated
  - The night he is coming off of a shift could consider diphenhydramine OR melatonin OR ramelteon
  - Would not recommend a stimulant at this time
  - Would not recommend any medication that causes next day sedation prior to him going to work.
  - Would not recommend suvorexant at this time
  - Although a study in OSA patients did not suggest a respiratory depressant effect


Insomnia in the Elderly

• Elderly are more likely to have sleep complaints ~10-20%
• The 2003 Sleep in America poll 44% of older persons reported experiencing ≥ 1 or more of the nighttime symptoms of insomnia a few nights per week or more.
• Common Complaints
  – Difficulty maintaining sleep
  – Early morning awakening
• Potential Consequences of Decreased Sleep
  – Memory impairment
  – Impaired concentration
  – Driving impairment
  – Increased risk of falls

https://sleepfoundation.org/sleep-topics/aging-and-sleep

Sleep Changes in the Older Adult

• Increase in nocturnal awakenings
• Remaining awake longer during interruptions
• Reduced total sleep time
• Reduced sleep efficiency
• Early morning awakening
• Reduced REM sleep
• Increase in daytime napping

Geriatric Case Vignette

• A 72 year old male with a history of dementia, COPD, GERD, and HTN was recently discharged from a 7-day hospital stay for pneumonia. His daughter brings in his discharge prescriptions

• Previous Medications
  – Donepezil 10 mg PO at bedtime
  – Lisinopril/HCTZ 20 mg/12.5 mg – 1 tablet PO daily
  – Salmeterol/fluticasone 1 inhalation BID

• Discharge scripts:
  – Amoxicillin/Clavulanate 500 mg PO every 12 hours
  – Prednisone 10 mg PO TID
  – Albuterol Inhalate 2 puffs every 4 hours PRN SOB
  – Zolpidem 10 mg PO at bedtime

Discharge Script

VCUHS Hospital  Dr. R. Blue DEA AB...

Name: Ms. SLP EE  Date 2/29/16
zolpidem 10 mg
Sig: Take 1 tab PO QHS
Quant: 30 tab
Refill: 5

J. Blue, MD

Zolpidem Peak Blood Levels Higher in Women and Elderly Adults


Audience Assessment Question

• Which of the following risks would you be MOST concerned about in this patient with new zolpidem Rx?
  – Driving impairment
  – Next day sedation
  – Risk of falls
  – Allergy

Zolpidem Labeling Change

• In October 2014 the Warnings/Precautions section updated to include
  – Risk for severe injuries – Zolpidem has been associated with sedation and reduced consciousness which may lead to falls and potentially severe injuries such as hip fractures and intracranial hemorrhage

Zolpidem and Falls
Mayo Clinic in non-ICU patients

• Zolpidem \( n=4962 \) vs non-receipt \( n=11,358 \)
  • Risk of falls was 3.04% vs 0.71%; \( p<0.001 \)
  • ↑ risk of falling even after accounting for insomnia, delirium & other factors
  • Did not differ in
    – Age
    – Other medications associated with falls


If not zolpidem….what would you recommend?

A. Doxepin
B. Melatonin
C. Diphenhydramine
D. No medication
**Beers Updates - Insomnia**

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>2002</th>
<th>2012</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>AVOID</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>TCAs (e.g. doxepin, amitriptyline)</td>
<td>AVOID tertiary amines</td>
<td>AVOID all tertiary amines except doxepin doses ≤ 6 mg (OK)</td>
<td>Same</td>
</tr>
<tr>
<td>Benzodiazepines (BZD)</td>
<td>AVOID long-acting Use lower doses of short acting (temazepam ≤ 15 mg; triazolam ≤ 0.25 mg)</td>
<td>AVOID all BZDs for insomnia</td>
<td>AVOID</td>
</tr>
<tr>
<td>Non-BZD -- &quot;Z&quot; hypnotics</td>
<td>Not mentioned</td>
<td>Avoid chronic use ≥ 90 days</td>
<td>AVOID, risk similar to BZDs</td>
</tr>
</tbody>
</table>

Long-acting benzodiazepines: flurazepam, quazepam, estazolam "Z" hypnotics include eszopiclone, zaleplon and zolpidem

**Other Pharmacologic Approaches in the Elderly**

- Benzodiazepines risk equivalent to "Z"-hypnotics
- Antidepressants
  - Doxepin – FDA approved was actually studied in the elderly and was not noted to increase anticholinergic effects at low doses
  - Off-label trazodone – Monitor for additive orthostatic hypotension
- Melatonin receptor agonists
  - Question if less balance impairment than GABA-ergic agents
- Orexin Antagonists
  - Studied in elderly, however at doses of 15-30 mg

**How Should We Approach?**

Non-pharmacologic treatment

- Reinforce good sleep hygiene
  - No napping!
- Light therapy
- Snozelen rooms
- Warm milk
- Lavender therapy
- Many of the options Julie previously discussed!

**Discharge Script**

VCUHS Hospital  
Dr. R. Blue DEA AB...

Name: Ms. SLP EE  
Date 2/29/16

Zolpidem 10 mg  
Sig: Take 1 tab PO QHS  
Quant: 30 tab  
Refill: 5

J. Blue, MD

**Beers Alternatives**

NONE

**Counseling for All Sedative/Hypnotics**
Counseling for Sedative Hypnotics
• Take medication immediately before bedtime
• Take on an empty stomach to improve effectiveness
• Should not be combined with alcohol or other CNS depressants
• May cause drowsiness; do not drive or operate machinery until you feel fully awake
• If insomnia does not improve in 7 to 10 days, you should consult a physician since insomnia may be a symptom of another underlying illness (i.e., medical or psychiatric)
• Hypnotics can worsen depression, suicidal thoughts, memory loss, confusion, and anxiety
• Use with caution if you have depression, asthma, COPD, or OSA
• Call MD if you experience symptoms of an allergic reaction (e.g., tongue swelling, trouble breathing, nausea and vomiting)

Medication Guide
After taking ________, you may get up out of bed not fully awake and do an activity that you may not remember the next morning. Activities include:
- Driving a car (“sleep-driving”)
- Preparing/eating food
- Talking on the phone
- Having sex
- Sleep-walking

Complex Sleep-Related Behaviors
Medication Guide:
• After taking ________, you may get up out of bed not fully awake and do an activity that you may not remember the next morning. Activities may include:
  - Driving a car (“sleep-driving”)
  - Preparing/eating food
  - Talking on the phone
  - Having sex
  - Sleep-walking

2007 – Press regarding zolpidem and sleep-eating and sleep-driving
These behaviors with sleep medications were described well before 2007 with benzodiazepine hypnotics.
- Note in 2006, brand name products for zolpidem were ranked 13th in drugs by sales
- Today, all sedatives/hypnotics including those that do not work on GABA (doxepin, ramelteon, and suvorexant) include this warning and should be dispensed with Medication Guide

Duration of Use
• Benzodiazepines: For short-term use (7-10 days); approval trials were 2 weeks in duration
• Longest was estazolam up to 12 weeks
• Zolpidem, zaleplon: Originally approved for <14 days
• Longest study of zolpidem was with intermittent weekly dosing
• Eszopiclone and zolpidem CR: Have trials up to 6 months in duration without development of tolerance
• Doxepin: Efficacy maintained up to 12 weeks in trials
• Ramelteon: Efficacy supported up to 6 months
• Suvorexant: Studied up to 1 year, but not approved for chronic use

Key Points
• 50% of patients with insomnia have a co-occurring psychiatric disorder that requires treatment along with insomnia.
• Recommend sleep studies in at risk patients
• Multimodal Cognitive Behavioral Treatment (CBT) is the most effective non-pharmacological treatment in adults.
• Zolpidem, eszopiclone, and suvorexant are the most effective hypnotic agents for insomnia in adults.
Key Points

- Hypnotic use increases risk of adverse events in all ages and lowest effective dose for shortest duration of time optimal.
  - Reduce initial dose of zolpidem in women and eszopiclone for both men and women
- Elderly are more susceptible adverse events, particularly falls, dementia, respiratory depression.
- Sleep-related behaviors are a class effect
- Melatonin is considered safe and effective for youth with insomnia associated with Autism spectrum or ADHD.
- Stress the importance of proper administration

Which of the following accurately describes an established health consequence of chronic insomnia?

A. Hyperthyroidism  
B. Diabetes  
C. Arthritis  
D. Migraine

A 50 year old with chronic insomnia treated with CBT is counseled to get out of bed and read or stretch after 15 minutes of not sleeping. This recommendation is the main premise of:

A. Stimulus control  
B. Relaxation training  
C. Sleep restriction  
D. Complementary therapeutics

According to the Agency for Healthcare Research and Quality’s executive summary on managing insomnia, a 35 year old patient with trouble falling asleep and staying asleep is most likely to benefit from:

A. Eszopiclone  
B. Trazodone  
C. Doxepin  
D. Temazepam

Which of the following warnings were added to zolpidem’s product labeling in October 2014?

A. Allergy  
B. Risk of falls  
C. Next day sedation  
D. Driving impairment

Which of the following is FDA approved for insomnia?

A. Doxepin  
B. Trazodone  
C. Mirtazapine  
D. Amitriptyline
A thin 22 year old patient with asthma complains of 3 weeks of trouble falling asleep, excessive daytime sleepiness, and loss of muscle control to the point of falling after laughing. Which diagnosis is most likely?

A. Sleep deprivation
B. Obstructive sleep apnea
C. Narcolepsy
D. Chronic insomnia