Challenges in Optimally Managing Insomnia in the Elderly
Thomas Roth, Ph.D. - Dana Saffel, PharmD, CPh, BCGP, FASCP

Home Study Webcast
2 Slides Per Page
Challenges in Optimally Managing Insomnia in the Elderly

ACTIVITY DESCRIPTION
Insomnia is common among the elderly and is known to have a negative effect on quality of life in this population. Due to many safety concerns with medications in the elderly, even geriatric specialized providers tend underdiagnose and undertreat this condition. Targeted to consultant and community pharmacists, this 90-minute webinar will feature a sleep specialist and board-certified geriatric pharmacist teaming up to provide insights into sleep science and conditions commonly associated with insomnia in the elderly while diving deep into the safety concerns and recommendations surrounding medications that treat insomnia. Dr. Roth and Dr. Saffel are ready to take your questions following the webinar!

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

• Review the basic science of sleep knowledge necessary to care for elderly patients with insomnia
• Recognize the impact of insomnia in the elderly to include comorbidities commonly encountered as well as the consequences of untreated or inadequately treated insomnia
• Review properties of medications used to treat insomnia to include efficacy, safety, and mechanism of action
• Describe safety concerns of insomnia medications frequently used in the elderly to include BEERS list status
• Identify key counseling and follow up points for elderly patients receiving drug therapy to treat insomnia

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ACTIVITY TYPE
Knowledge-Based Home Study Webcast

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ABOUT THE AUTHOR
Thomas Roth, Ph.D., founded the Sleep Disorders and Research Center at the Henry Ford Hospital in Detroit, Michigan in 1978 and has since served as Director of the Center. Dr. Roth is also a Professor in the Department of Psychiatry at Wayne State University School of Medicine in Detroit, Michigan, and serves as a Clinical Professor in the Department of Psychiatry at the University of Michigan’s College of Medicine in Ann Arbor.

Dr. Roth primarily publishes on the epidemiology, pathophysiology, diagnosis, comorbidity with other disorders, and treatment of insomnia. His research focuses on sleep loss, sleep fragmentation, and deviation from sleep processes, including pharmacological effects and sleep pathologies.

After serving as President of the Sleep Research Society and the Founding President of the National Sleep Foundation (NSF), Dr. Roth became Chairman of the National Center on Sleep Disorders Research Advisory Board at the National Institute of Health. He has also served on the Board of Directors of the Associated Professional Sleep Societies (APSS). In 2002, Dr. Roth received the NSF’s Lifetime Achievement Award for his accomplishments and contributions to sleep science, sleep medicine, and public health. He also received a Distinguished Research Award from the Sleep Research Society as well as the Nathaniel Kleitman Award from the Academy of Sleep Medicine.

Dr. Roth is the past Editor-in-Chief of the journal Sleep. He currently sits on the editorial boards of Sleep Reviews, Stress Medicine, Advances in Therapy, and Human Psychopharmacology. Dr. Roth has published over 500 manuscripts, 13 edited volumes, 250 chapters, and 621 abstracts.

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ABOUT THE AUTHOR

Dana Saffel, PharmD, CPh, BCGP, FASCP, is President and CEO of PharmaCare Strategies, a market development firm that specializes in assisting pharmaceutical manufacturers and health care providers in the appropriate utilization of key products in specialty channels such as long-term care, managed care, Medicaid/Medicare and hospital markets.

Prior to starting PharmaCare Strategies, Dr. Saffel was Vice President of United Pharmacy Services, a long-term care pharmacy serving over 12,000 nursing facility, assisted living facility, correctional and developmentally disabled residents throughout Georgia, North Carolina, and South Carolina.

Dr. Saffel is active in many areas of senior-focused professional organizations such as ASCP, AMDA, AGS, AMCP, AADNS and AHCA and is a frequent lecturer at national and regional meetings on disease management, Medicare and Medicaid health care policy and regulatory and reimbursement issues affecting the long-term care industry. Dr. Saffel currently serves on the Board of Directors of ASCP and is past chairman of the FL chapter of ASCP.

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Learning Objectives:

• Review the basic science of sleep knowledge necessary to care for elderly patients with insomnia

• Recognize the impact of insomnia in the elderly to include comorbidities commonly encountered as well as the consequences of untreated or inadequately treated insomnia.

• Review properties of medications used to treat insomnia to include efficacy, safety and mechanism of action.

• Describe safety concerns of insomnia medications frequently used in the elderly to include BEERS list status.

• Identify key counseling and follow up points for elderly patients receiving drug therapy to treat insomnia.
Age related changes to sleep

Based on a meta-analysis of quantitative sleep parameters

<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>Adult lifespan†</th>
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<tbody>
<tr>
<td>Total sleep time</td>
<td></td>
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<tr>
<td>Time to fall asleep</td>
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<tr>
<td>Time awake after sleep onset</td>
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<td>Sleep efficiency</td>
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<tr>
<td>Stage 1 nonREM</td>
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<td>Stage 2 nonREM</td>
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<tr>
<td>Slow-wave sleep</td>
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<tr>
<td>REM sleep</td>
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</table>

†These changes are most notable across the ages of 18–40 and 40–60, with persons aged ≥60 and older demonstrating only continued reductions in sleep efficiency.
REM: rapid-eye movement.

Other biological changes in sleep with aging

- Age-related changes in growth-hormone secretion appears to correlate with less time spent in deep nonREM or slow-wave sleep, particularly in men.

24-hour plasma growth hormone profile men matched for body-mass index

Consequences of Disturbed Sleep

- Difficulty sustaining attention
- Slowed response time
- Difficulty with memory
- Decreased performance
- May all be misinterpreted as dementias
Insomnia by Age Group

Persistence of Insomnia in Older Adults at 2 Years

*Persistence of daytime somnolence was significantly associated with mortality; $P = 0.049; n = 1,050$.

DFA = difficulty falling asleep  
EMA = early morning awakening  
SCD = sleep continuity disturbance  
DaSom = uncontrollable daytime somnolence
Possible Underlying Causes of Insomnia in Older Adults

Conditions More Prevalent in Older Adults Impact Insomnia\(^1,2\)

- Altered Sleep Regulation and Circadian Rhythms\(^1\)
- Medical, Neurologic, and Psychiatric Conditions\(^1\)
- Psychosocial Factors\(^2\)
- Difficulty Initiating and Maintaining Sleep
- Chronic Pain Pulmonary Disease
- Depression
- SDB (Sleep Apnea) Nocturnal Myoclonus
- Late-life Stressors

Prevalence of Insomnia Increased in Common Comorbid Medical Conditions


MI = myocardial infarction; CHF = congestive heart failure; mean age = 54 ± 16 (n = 3,445)
Sleep Problems and Multiple Medical Conditions

![Chart showing self-reported questionnaire data from 1,506 community-dwelling subjects aged 55 to 84. The x-axis represents the number of medical conditions (0, 1, 2 or 3, 4), and the y-axis represents the percent of respondents reporting any insomnia.]


Older persons go to sleep and wake earlier

- Additionally, the phase of awakening relative to circadian phase markers is earlier in older persons

Older Adults Exhibit Advanced Sleep-Phase Syndrome (ASPS)

Effect of Aging on the Suprachiasmatic Nucleus (SCN)

- SCN is the “circadian pacemaker”
OSA Increases With Age

Habitual Snorers (19.0%)

Men 24.1%

Women 13.8%

Event Index (Per Hour of Sleep)

- AH1 ≥ 10
- OAHI > 10
- AH1 ≥ 10 Plus Clinical Symptoms of OSA

Age Groups

- 20 – 44
- 45 – 64
- ≥ 65

Acute Complications of Arousals

Sleep → Apnea

Ventilation → Arousal

Abnormal Sleep Structure

- Sleep disruption
- Decreased SWS
- Decreased REM

Prevalence of Sleep Disturbance in Obstructive Respiratory Diseases

Klink M, Quan SF. Chest. 1987;91:540-546.

Nocturia and Poor Sleep

Attributed Causes of Disturbed Sleep Maintenance
1485 Dutch Men and Women, Ages 50-93

<table>
<thead>
<tr>
<th>Cause</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>Nocturia</td>
<td>72.1</td>
<td>63.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>15.2</td>
<td>15.7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Worries</td>
<td>1.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Other</td>
<td>10.2</td>
<td>13.2</td>
</tr>
</tbody>
</table>

Nocturia and Poor Sleep:
Prevalence of Poor Sleep in 3669 Swedish Women Ages 40-64

Consequences of Poor Sleep

- Difficulty Sustaining Attention and Slowed Response Time
- Decreased Ability to Accomplish Daily Tasks
- Impairments In Memory & Concentration
- Increased Consumption of Healthcare Resources
- Increased Risk of Falls
- Shorter Survival
- Inability to Enjoy Social Relationships
- Increased Incidence of Pain

Consequences of poor sleep in older adults

- N=1026 community dwelling representative French sample
  - aged 60-101 years
- Mean sleep duration 7:08h (range 7:04-7:10)
- Poor health status associated with insomnia symptoms
  - Short sleep duration
  - Long sleep latency (>80 min)
  - Late bedtime
  - Early wake-up time
- Cognitive impairment associated with
  - Short sleep duration of <6h and daytime nap of >1h
- Obesity associated with
  - Short sleep duration (<4.5h)

Chayon and Vecchierini, Sleep 2005. 28:981-989

Chronic Insomnia Independently Predicts Cognitive Decline in Elderly Men

Risks for Nursing Home Placement (Males)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>RR</th>
<th>CI</th>
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</thead>
<tbody>
<tr>
<td>Disturbed Sleep</td>
<td>5.3</td>
<td>1.7-16.1</td>
</tr>
<tr>
<td>Age &gt; 74</td>
<td>1.3</td>
<td>0.0-4.3</td>
</tr>
<tr>
<td>ADL Problems</td>
<td>2.8</td>
<td>0.9-8.6</td>
</tr>
<tr>
<td>Fair-Poor Health</td>
<td>0.8</td>
<td>0.2-2.8</td>
</tr>
<tr>
<td>Low Income</td>
<td>1.4</td>
<td>0.4-4.6</td>
</tr>
<tr>
<td>Mental Impairment</td>
<td>4.6</td>
<td>1.4-15.2</td>
</tr>
<tr>
<td>Depression</td>
<td>1.0</td>
<td>0.2-4.7</td>
</tr>
<tr>
<td>Living Alone</td>
<td>2.0</td>
<td>0.6-6.2</td>
</tr>
</tbody>
</table>


Sleep Disturbance and Institutionalization

Nursing Home Placement by Insomnia

Nursing home placements represent percent of the sample permanently assigned to a nursing home over a 3.5 year follow-up period.

Disturbed Sleep and Falls

<table>
<thead>
<tr>
<th>Sleep Problem</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falling asleep at night</td>
<td>1.53</td>
<td>1.04-2.24</td>
</tr>
<tr>
<td>Waking up during the night</td>
<td>1.91</td>
<td>1.44-2.54</td>
</tr>
<tr>
<td>Waking up too early and unable to fall back to sleep</td>
<td>1.64</td>
<td>1.10-2.42</td>
</tr>
</tbody>
</table>

At Least 1 Fall in the Last 12 Months in a Community Population (n=1526)


Sleep disturbance, falls and mortality

- In older women, a 30–40% increased risk of subsequent falls was associated with
  - TST <7h/night
  - SE ≤65%
- There was an increased mortality risk in older women with
  - TST <5h/night
  - SE ≤65%
  - >2h naps

After adjusting for race, age, BMI, medical conditions, depression, cognitive function, exercise, instrumental activities of daily living, use of anti-depressant or benzodiazepine. n=3022

Sleep Disturbance and Mortality

Electroencephalographic sleep assessments are controlled for age, gender, and baseline medical burden.

Sleep latencies > 30 minutes: 2.14x
Greater mortality risk ($P = 0.005$)

Sleep efficiency < 80%: 1.93x
Greater mortality risk ($P = 0.014$)

Survival as a Function of Sleep Latency

Survival as a Function of Sleep Efficiency

SLEEP DURATION AND FALLS

Fig. 3. Effect of objectively-measured sleep duration on risk of falls [25]. Sleep duration was measured by actigraphy. Vertical error bars denote 95% confidence intervals; ** denotes statistically significant difference from reference (P < 0.05).
Falls in the Elderly

- 34,163 nursing home residents (76% women), aged 65 and older and with 150-210 days of follow-up
- The relationship between insomnia, hypnotic use, falls, and hip fractures was examined in older people
- Results
  - Insomnia did predict future falls
  - Hypnotic use did not predict falls
- Conclusion
  - In elderly nursing home residents, insomnia, but not hypnotic use, is associated with a greater risk of subsequent falls


INSOMNIA AND BLOOD PRESSURE


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31
INSOMNIA AND BLOOD PRESSURE

Orexin A and AGE

Fig. 1. Relationship between plasma orexin-A concentrations and age. Closed and open circles indicate values of men and women, respectively.

OREXIN A AND AGE


CSF OREXIN INSOMNIAIA and Mild Cognitive Impairment

Fig. 2. CSF concentrations of orexin in MCI–SC, MCI–wSC, ctrl–SC, and ctrl–wSC. Data points represent MCI patients and controls, whiskers show means. Abbreviations: MCI, mild cognitive impairment; CSF, cerebrospinal fluid; SC, with sleep complaints; wSC, without sleep complaints; ctrl, controls.

C. Liguori et al. / Neurobiology of Aging 40 (2016)
Rest-Activity Rhythm and Cognitive Performance

More fragmentation is associated with more cognitive decline

**Figure 1.** Cognitive performance in relation to fragmentation of the rest-activity rhythm. Four equal groups were created according to increasing rest-activity fragmentation scores (IV, 0.27–0.42, 0.42–0.53, 0.53–0.67, 0.67–1.39). Cognitive performance reflects average z-score (+ SEM) for each domain.


Chronic insomnia independently predicted incident cognitive decline

- 3-year longitudinal, community-based study of 6444 men and women aged >65 years,
- OR for cognitive decline for men with chronic insomnia (adjusted for multiple variables, including baseline cognitive function, age, race, education level, household income, and marital status)
  - Not depressed = 1.49
  - Depressed = 2.18
- For women, chronic insomnia was associated with an increased risk of cognitive impairment, but only in those who had high levels of depressive symptoms.
  - However, the investigators noted that more sensitive measures of cognitive performance could potentially confirm whether insomnia is associated with cognitive decline in women.

Case – AB

- Patient Information - 74 year old male
- BMI 26
- Chief complaint - Has difficulty falling back to sleep after nocturnal awakenings and early morning awakenings
- Past history hypertension, arthritis, nocturia
- Family history - no significant sleep history

Case – AB, continued

- Social history, retired, stopped smoking 25 years ago, 1-3 glasses of wine per week
- Sleep history snoring, excessive wake during night early morning awakenings ESS=11
- Current Medications beta blocker, ace inhibitor
- Physical exam and clinical laboratory tests: unremarkable
Therapeutics

• Now that have reviewed the prevalence and morbidity associated with insomnia in the elderly Dr. Saffel will review the safety and efficacy of various therapeutic options for treating insomnia in an elderly patient.

Medication Management of Insomnia

Goals of Therapy

- SOL – sleep onset latency
- WASO – wakefulness after sleep onset
- TST – total sleep time

Case Study

• JG is a 78yo widowed female who presents at her PCP office with complaints of difficulty falling asleep and frequent nighttime awakenings over the past 4 months. She reports that she gets less than 4 hours of restful sleep each night.

Comorbidities:
• Diabetes x 10 years
• Hypertension x 15 years
• Osteoarthritis x 5 years
• OCD (checking home multiple times that door is locked and stove is off)

Medications:
• Insulin glargine/lixisenatide
• Olmesartan/HCT
• Celecoxib
• Fluvoxamine

• She has attempted cognitive behavioral therapy for insomnia (CBTI) for the past 2 months but is still experiencing sleep onset latency and multiple nighttime awakenings. When she awakes, she has to circulate through the house checking the locks and stove multiple times. She asks for a pill to help her sleep through the night.

• Her PCP reaches out to you asking for a recommendation for the most appropriate medication for treating insomnia in an older patient.

Medications that Are Used to Treat Insomnia

Antidepressants
- Doxepin
- Mirtzapine
- Trazodone

Benzodiazepines
- Estazolam
- Flurazepam
- Lorazepam
- Oxazepam
- Quazepam
- Temazepam
- Triazolam

“Z” Drugs
- Eszopiclone
- Zaleplon
- Zolpidem

Melatonin Receptor Agonists
- Ramelteon

Orexin Antagonists
- Suvorexant

Miscellaneous Agents
- Olanzapine
- Quetiapine
- Gabapentin
- Pramipexole
- Tiagabine
- Diphenhydramine
- Doxylamine
- Melatonin
- Valerian
Antidepressants

- Sedating low-dose antidepressants can be used to treat insomnia when comorbid depression is present
- Antidepressants commonly used for insomnia include:
  - Doxepin
  - Mirtazapine
  - Trazodone
- Little data exists to support use of sedating antidepressants to treat primary insomnia
  - Exception is low-dose doxepin (3 mg and 6 mg) – which is FDA approved for insomnia but not for depression

Antidepressant MOA and Therapeutic Effect

- Pharmacology
  - Doxepin (low dose) – blocks histamine
  - Mirtazapine – blocks histamine, and 5-HT₂ receptors, enhances noradrenergic transmission to increase melatonin synthesis
  - Trazodone – blocks α-adrenergic and histaminergic receptors
- Metabolism
  - Doxepin – CYP2D6, CYP2C29
  - Mirtazapine – CYP3A4, CYP2D6 and CYP1A2
  - Trazodone – CYP2D6 and CYP3A4
- Effect
  - Improved sleep latency
  - Improved total sleep time
  - Improved sleep maintenance
  - Reduce dose when coadministered with moderate CYP inhibitors
  - Avoid use with potent CYP inhibitors
  - Mirtazapine
  - Trazodone
  - Doxepin

# Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Doxepin    | Not specified (perhaps 10) | 30              | 15 – 20 (80 active metabolite) | Off-label           | • Avoid use in the elderly  
• Dose-dependent risk of CV risk  
• Anticholinergic side effects  
• Narrow therapeutic window     |
| Doxepin (Silenor) | 3 | 30 | 15 (31 active metabolite) | Insomnia: sleep maintenance (increases total sleep time approx 30 min) | • Less anticholinergic side effects than higher doses  
• Little evidence of rebound insomnia  
• Do not take within 3 hours of meal due to delayed absorption & next-day sedation  
• Take 30 minutes before bedtime |
| Mirtazapine | 7.5 - 15                  | N/A             | 20 - 40           | Off-label for sleep latency | • Increased risk of restless legs syndrome & periodic limb movements in sleep  
• Some evidence of reducing insomnia in depression early in treatment  
• Lower anticholinergic side effects (compared to doxepin)  
• Residual daytime sedation  
• Weight gain |
| Trazodone  | 25                        | 30 - 60         | 11.6 (elderly)    | Off-label for sleep maintenance | • Limited efficacy in primary insomnia  
• Can cause priapism, even at low doses  
• Lower anticholinergic side effects (compared to doxepin)  
• Daytime sedation  
• Orthostasis |
Benzodiazepines

- Originally approved in the mid-1950s
  - Most commonly prescribed drugs worldwide by late 1970s
- Class uses:
  - Anticonvulsant
  - Anxiolytic
  - Muscle relaxant
  - Sedative/hypnotic
- Tolerance and withdrawal symptoms became apparent during this period
  - However, dose escalation was rare among elderly taking hypnotic doses
- Controlled substance
  - Schedule C-IV

Class Adverse Effects
- Anterograde memory disturbance
- Ataxia
- Daytime sedation
- Delirium
- Falls
- Fractures
- Motor vehicle accidents
- Rebound insomnia

Benzodiazepine MOA and Therapeutic Effect

- Pharmacology
  - Non-selective binding to all Y-aminobutyric acid (GABA) α receptors in ventral lateral preoptic area that controls sleep
    - Inhibits neuronal excitation
    - GABA_A is the primary inhibitory receptor in the CNS
      - α1 - receptors selectively mediate sedation and hypnotic effects
      - α2-, α3-, and α5-receptors mediate anxiolytic pathways
  - Metabolism
    - CYP450 oxidation followed by glucuronidation
      - Except temazepam which undergoes glucuronidation only
  - Effect
    - Improvement in sleep quality
    - Improvement in total sleep time (mean 34 minutes)
    - Decreased nighttime awakenings

Physiologic Effects
- Reduced time to REM sleep
- Shortened sleep onset latency
- Decreased nocturnal awakenings

## Benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Duration (hours)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estazolam</td>
<td>0.5</td>
<td>60 – 120</td>
<td>10 – 24</td>
<td>Insomnia: Sleep onset latency &amp; maintenance</td>
<td>6 – 10</td>
<td>• Avoid use in the elderly</td>
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<td>• Short-term use only</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Contraindicated with strong Cyp450 3A4 inhibitors</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15</td>
<td>60 – 120</td>
<td>100 * (including active metabolites)</td>
<td>Insomnia: Sleep onset latency &amp; maintenance</td>
<td>10 – 20</td>
<td>• Avoid use in the elderly due to active metabolite long t&lt;sub&gt;1/2&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(15 – 45 with chronic dosing)</td>
<td></td>
<td></td>
<td></td>
<td>• Short-term use only</td>
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<td></td>
<td></td>
<td></td>
<td>• Potential for daytime sedation</td>
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<td></td>
<td></td>
<td></td>
<td>• Caution in seizure disorder, respiratory depression, several hepatic disease, renal impairment</td>
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<td></td>
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<td>• C-IV controlled substance</td>
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## Benzodiazepines (con’t)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Duration (hours)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Lorazepam</td>
<td>0.25 – 1</td>
<td>≈ 30</td>
<td>≈ 18 hr</td>
<td>Off-label for sleep maintenance</td>
<td>---</td>
<td>• Avoid use in the elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Short-term use only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Generally used for insomnia secondary to anxiety</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>10 – 15</td>
<td>30 – 60</td>
<td>6 – 11 hr</td>
<td>Off-label for sleep onset latency</td>
<td>---</td>
<td>• Avoid use in the elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Limited data on efficacy</td>
</tr>
<tr>
<td>Quazepam</td>
<td>7.5 – 15</td>
<td>60 – 120</td>
<td>47 – 100 (including active metabolites)</td>
<td>Insomnia: Sleep onset latency &amp; maintenance</td>
<td>10 – 20</td>
<td>• Avoid use in elderly due to active metabolite long t&lt;sub&gt;1/2&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Short-term use only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Potential for daytime sedation</td>
</tr>
</tbody>
</table>

Benzodiazepines (con’t)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Duration (hours)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>7.5</td>
<td>60 – 120</td>
<td>3.5 – 18.4</td>
<td>Insomnia: Sleep onset latency &amp; maintenance</td>
<td>6 - 10</td>
<td>• Avoid use in the elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Short-term use only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Not eliminated by Cyp450</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125 – 0.25</td>
<td>15 – 30</td>
<td>1.5 – 5.5</td>
<td>Insomnia: Sleep onset latency</td>
<td>2 - 5</td>
<td>• Avoid in the elderly due to risk of cognitive and behavioral side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Short term use only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Caution in seizure dx, respiratory depression, several hepatic disease, renal impairment</td>
</tr>
</tbody>
</table>

Selective Benzodiazepines ("Z-Drugs")

- Originally approved in the mid-1980s
  - Most commonly prescribed hypnotic agents worldwide today
  - Frequently referred to as "Z drugs"
  - Developed to be effective with less adverse effects than benzodiazepines
- Tolerance and withdrawal symptoms became apparent during this period
  - However, dose escalation was rare among elderly taking hypnotic doses
- Controlled Substance
  - Schedule C-IV

Class Adverse Effects
- Dementia
- Delirium
- Fractures
- Increase in hospitalizations
- Motor vehicle accidents
- Serious injury
- Sleepwalking

“Z drugs” MOA and Therapeutic Effect

- **Pharmacology**
  - Binds more selectively to the GABA<sub>A</sub> receptor α1 subunits*
  - GABA<sub>A</sub> is the primary inhibitory receptor in the CNS
    - α1 receptors selectively mediate sedation and hypnotic effects
    - α2-, α3-, and α5-receptors mediate anxiolytic pathways
  - Results in more therapeutic sedative and hypnotic effects with less risk of negative consequences

- **Metabolism**
  - CYP4503A4 oxidation
    - Zaleplon primarily aldehyde oxidase and less CYP3A4
    - Eszopiclone also through CYP2E1 to active metabolites

- **Effect**
  - Improvement in sleep quality
  - Improvement in total sleep time (mean 34 minutes),
  - Decreased nighttime awakenings

  *Eszopiclone demonstrates little to no selectivity for GABA<sub>A</sub> receptors similar to benzodiazepines.

**Physiologic Effects**
- Shortened sleep onset latency
- Decreased nocturnal awakenings

**Selective Benzodiazepines (“Z-Drugs”)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset Latency (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Duration (hours)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Eszopiclone | 1 (onset latency) 2 (maintenance) | 30 | 6 | Insomnia: Sleep onset latency and maintenance | 8 | - Not limited to short-term use
|          |                             |                         |                  |                     |                 | - Avoid use in elderly
|          |                             |                         |                  |                     |                 | - Taking with or after meal delays onset
|          |                             |                         |                  |                     |                 | - Metallic aftertaste
| Zaleplon | 5                           | 30                      | 1                | Insomnia: Sleep onset latency | 2 - 4 | - Avoid use in elderly
|          |                             |                         |                  |                     |                 | - Short-term use only
|          |                             |                         |                  |                     |                 | - Taking with or after meal delays onset
|          |                             |                         |                  |                     |                 | - Less likely to have CYP450 interactions
|          |                             |                         |                  |                     |                 | - No apparent withdrawal symptoms
| Zolpidem | 5 6.25 (CR) 1.75 (SL)       | 30                      | 1 – 4.5          | Insomnia: sleep onset latency (CR: latency & maintenance) (SL: nighttime awakening) | 8 (SL: 4) | - Avoid use in elderly
|          |                             |                         |                  |                     |                 | - Short-term use only
|          |                             |                         |                  |                     |                 | - Taking with or after meal delays onset
|          |                             |                         |                  |                     |                 | - Anterograde amnesia, hallucinations, delirium, unusual nighttime behaviors


Melatonin Receptor Agonists MOA and Therapeutic Effect

**Ramelteon**
- **Pharmacology**
  - Innervates the suprachiasmatic nucleus (SCN) via G protein-coupled receptors (MT₁/MT₂) 6-fold and 4-fold higher than melatonin
  - Regulates mammalian circadian rhythm
- **Metabolism**
  - CYP1A2 is primary metabolic biotransformation to an active metabolite
    - Do not use in combination with fluvoxamine
  - Primarily renally eliminated
- **Effect**
  - Does not cause CNS sedation
  - Reduces sleep latency
  - Is not effective for sleep maintenance or total sleep time


### Melatonin Receptor Agonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Duration (hours)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramelteon</td>
<td>8</td>
<td>30</td>
<td>1 – 2.6 (2 – 5 active metabolite)</td>
<td>Insomnia: Sleep onset latency</td>
<td>8</td>
<td>• Not limited to short-term use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Not a CNS depressant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Not a controlled substance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Taking with or after a meal delays onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Minimal abuse potential</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Minimal withdrawal effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Metabolized by CYP1A2 – use with fluvoxamine contraindicated</td>
</tr>
</tbody>
</table>

Orexin Antagonist MOA and Therapeutic Effect

**Suvorexant**

- **Pharmacology**
  - Blocks endogenous neuropeptides (Orexin A and B) secreted by the hypothalamus involved in promotion and maintenance of wakefulness. Blockage results in:
    - Inhibition of the arousal system

- **Metabolism**
  - Primarily CYP3A4
    - Reduce dose when coadministered with moderate CYP3A4 inhibitors
    - Avoid use with potent CYP3A4 inhibitors

- **Effect**
  - Improved sleep induction
  - Improved sleep maintenance

- **Controlled substance**
  - Schedule C-IV

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**Orexin Antagonist**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Duration (hours)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Suvorexant** | 5 – 15                      | 30              | 12                | Insomnia: Sleep onset latency and maintenance | 7               | • Taking with or after a meal delays onset  
  • **No rebound insomnia**  
  • **No withdrawal symptoms**  
  • Take within 30 minutes of going to bed  
  • Take only if patient can guarantee minimum 7 hrs of sleep  
  • Long term (up to 1 year) efficacy                                                                 |

---

3. Yan CP. *Drugs*. 2014; 74(17-182.)
Miscellaneous Drugs

- Quetiapine, olanzapine, gabapentin, pramipexole and tiagabine are used off-label for insomnia but have not been studied for the treatment of insomnia in the elderly.
  - These agents may only be appropriate in patients with comorbid psychiatric or neuropathic diagnoses
  - **Avoid use in elderly** due to lack of data to support efficacy for primary insomnia and adverse effects

### Antipsychotic Agents
- Blockade of H₁ and 5-HT₂ receptors thought responsible for sedation
- Lack of robust data for efficacy in insomnia
- Boxed warning – increased risk of death in elderly patients with dementia
- High adverse event risk
- Risk outweighs benefit

### Gabapentin
- Interacts with α₂-δ₁ subunits of voltage-gated calcium channels
- Release of excitatory neurotransmitters causes sedation
- **Off-label** for sleep maintenance

### Pramipexole
- Dopamine agonist at D₂ and D₃ receptors
- Used as 2nd line treatment for REM Behavioral Sleep (RBS) disorder
- **Off-label** for RBS

### Tiagabine
- Anti-seizure med
- Inhibits the uptake of GABA

---

### Miscellaneous

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Gabapentin | 100                        | N/A             | N/A               | **Off-label** for sleep maintenance                                  | • Possibly beneficial in patients with comorbid restless leg syndrome or chronic neuropathic pain  
  • Dose adjustment in renal impairment (renally cleared) |
| Pramipexole | 0.125                       | N/A             | N/A               | **Off-label** for RBS                                                | • Administer 2 – 3 hrs before bedtime  
  • Insomnia reported in up to 27% of patients  
  • Hallucinations (likely due to dopamine agonism)  
  • Dose adjustment in renal impairment (renally cleared) |
| Tiagabine  | 2                           | N/A             | N/A               | **Off-label** to increase Stage I and slow-wave sleep                |                                                                                   |
### OTC Agents & Supplements

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose in Elderly (mg)</th>
<th>Onset (minutes)</th>
<th>Half-Life (hours)</th>
<th>Insomnia Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>25 - 50</td>
<td>30 - 60</td>
<td>2.4 – 9.3</td>
<td>OTC claim for sleep onset latency and maintenance</td>
<td>• Avoid use in the elderly&lt;br&gt;• Anticholinergic side effects&lt;br&gt;• Impaired memory&lt;br&gt;• Poor evidence of efficacy&lt;br&gt;• Tolerance&lt;br&gt;• Residual daytime sedation&lt;br&gt;• Give 30 min before bedtime</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>25</td>
<td>30</td>
<td>10</td>
<td>OTC claim for sleep onset latency</td>
<td>• Avoid use in the elderly&lt;br&gt;• Anticholinergic side effects&lt;br&gt;• Poor evidence of efficacy&lt;br&gt;• Residual daytime sedation&lt;br&gt;• Give 30 min before bedtime</td>
</tr>
<tr>
<td>Melatonin</td>
<td>1</td>
<td></td>
<td></td>
<td>OTC claim for sleep onset latency</td>
<td>• Inconsistent results&lt;br&gt;• Residual daytime sedation&lt;br&gt;• Give 1 hr before bedtime</td>
</tr>
<tr>
<td>Valerian</td>
<td>300</td>
<td></td>
<td></td>
<td>OTC claim label for sleep onset latency</td>
<td>• Inconsistent results&lt;br&gt;• Depression&lt;br&gt;• Give up to 2 hrs before bedtime</td>
</tr>
</tbody>
</table>


### Safety Concerns of Insomnia Medication
Physiological Changes with Aging Can Impact Drug Elimination

- Increase in drug elimination time ($t^{1/2}$) due to:
  - Increase in body fat
  - Decrease in total body water
  - Reduction in plasma proteins
- Alteration in phase I metabolism can reduce activity in the cytochrome P450 (CYP) system (oxidation)
- Glucuronidation (hydrolysis) is not impacted
- Absorption of drugs by passive absorption is not affected

Benzodiazepine Safety Concerns

- Age related changes in the GABA system resulting in:
  - Increased sensitivity to benzodiazepines
  - Predisposition to:
    - Ataxia
    - Sedation
    - Cognitive impairment
- Age related changes in oxidative capacity
  - Reduced metabolism and increased drug exposure
  - Increased drug-drug interactions with CYP inhibitors, inducers and substrates
- Physical dependence with withdrawal syndrome
  - Gradual dose reduction is recommended
    - 5% to 10% every 1 to 2 weeks till discontinuation
- In patients $> 60$ yo, benefits of benzodiazepines may not justify the increased risk of adverse events.
“Z drug” Safety Concerns

- Anterograde amnesia
- Balance impairment
- Delirium
- Driving impairment / motor vehicle crashes
- Hallucinations
- Higher risk of major injury requiring hospitalization
- Increased risk of fracture
- Memory impairment
- Complex sleep-related behaviors
- Abnormal thinking and behavioral changes
- CNS depression

Additional Safety Concerns

- **Ramelteon** lacks withdrawal effects, rebound insomnia, CNS sedation and abuse potential.
  - Worsening of Depression/Suicidal ideation (in depressed patients)
  - Abnormal thinking and behavioral changes
  - Exacerbation of insomnia
  - *May be an attractive option due to favorable side effect profile*
- **Suvorexant** has few serious adverse effects. Lacks withdrawal effects or rebound insomnia. Adverse effects were rare and include:
  - Excessive daytime sleepiness
  - Driving impairment (at 20mg dose)
  - Worsening of Depression/Suicidal ideation (in depressed patients)
  - Sleep paralysis
  - Complex sleep-related behaviors
  - Abnormal thinking and behavioral changes
  - CNS depression
  - *May be an attractive option due to proven efficacy and tolerability in the elderly*
Beers Criteria Guidance for Insomnia Medications

- **Benzodiazepines**: Strongly recommends *avoid use in elderly* patients due to:
  - Increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents
  - Increased risk of:
    - Cognitive impairment
    - Delirium
    - Falls
    - Fractures
    - Motor vehicle crashes

- **Z drug BzRAs**: Strongly recommends *avoid use in elderly* patients without consideration for duration of use due to:
  - Adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures);
  - Increased emergency department visits and hospitalizations;
  - Motor vehicle crashes;
  - Minimal improvement in sleep latency and duration

Beers Criteria Guidance for Insomnia Medications (con’t)

- **Antipsychotic Agents**: Strongly recommends *avoid use in elderly* except for schizophrenia, bipolar disorder, or short-term use as antiemetic during chemotherapy

- **Diphenhydramine/Doxylamine**: Strongly recommends *avoid use in elderly* patients
  - Highly anticholinergic: risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity
  - Clearance reduced with advanced age
  - Tolerance develops when used as hypnotic;
  - Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate

- **Doxepin > 6mg**: Strongly recommends *avoid use in elderly* patients
  - Highly anticholinergic
  - Sedation
  - Orthostatic hypotension;
  - (Safety profile of low-dose doxepin (≤6mg/d) comparable with that of placebo)
Key Points for Managing Elderly Adults on Insomnia Medications

General Consensus

• The future direction of insomnia treatment should focus on:
  • Nonpharmacologic interventions
  • Treating comorbid conditions
  • Using benzodiazepines and Z drugs as last resorts
• Cognitive behavioral therapy for insomnia should always be first line treatment
• An ideal medication treatment for insomnia should:
  • Improve sleep latency and sleep duration with limited awakenings, and
  • Avoid significant adverse effects such as daytime somnolence or decreased alertness

Additional Guidance

• Sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder
  • Symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient.

• The failure of insomnia to remit after a reasonable period of treatment at an appropriate dose of medication may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

• Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient.

Medication Key Take-Aways

• Sedating low-dose antidepressants
  • Should only be used for insomnia when the patient has comorbid depression
  • Trazodone is a favorable option compared with hypnotics, benzodiazepines, Z drug BzRAs, and tricyclic antidepressants

• Antipsychotic agents
  • Have not been extensively studied in an older population
  • All have considerable adverse effects

• Gabapentin
  • May be useful in patients with restless leg syndrome or chronic neuropathic pain and insomnia

• Pramipexole
  • May be useful in patients with REM Behavioral Sleep disorder

• Valerian and melatonin
  • Unregulated products with small impact on sleep onset latency
  • Can produce residual sedation

Medication Key Take-Aways (con’t)

- **Diphenhydramine & Doxylamine**
  - Avoid in the elderly

- **Benzodiazepine receptor agonists**
  - Avoid in the elderly

- **Z drug benzodiazepine receptor agonists**
  - Avoid in the elderly
  - Have improved safety profiles compared with benzodiazepines.
  - Side effects including dementia, serious injury, and fractures, which should limit their use

Medication Key Take-Aways (con’t)

- **Ramelteon**
  - Effective for sleep onset latency
  - Mild adverse effects include: somnolence, dizziness, nausea, fatigue, headache, and insomnia exacerbated
    - Discontinuation < 1%
  - No overall differences in safety or efficacy were observed between elderly and younger adult subjects
  - Valuable early pharmaceutical option in the elderly who have trouble falling asleep after sleep hygiene has failed

- **Suvorexant**
  - Improves sleep onset and maintenance
  - Mild adverse effects include: somnolence and residual daytime sedation
    - Discontinuation < 1%
  - The adverse reaction profile in elderly patients was generally consistent with non-elderly patients
  - Valuable early pharmaceutical option in the elderly who have difficulty falling and staying asleep after sleep hygiene has failed

Summary

• Most commonly used insomnia treatments should be avoided in the elderly patient
  • If benzodiazepines or “Z drugs” are used routinely, consider a gradual dose reduction and re-
    evaluation of underlying conditions to resolve associated sleep disturbances
• If medication is required to manage insomnia, consider:
  • Ramelteon – for sleep onset latency
  • Suvorexant – for sleep onset latency and frequent nighttime awakenings
• Counsel elderly patients to avoid taking a sedative / hypnotic every night and improve
  sleep hygiene by:
  • Avoid caffeine and other stimulants after 6pm
  • Avoid eating a large meal within 4 hours before sleep
  • Avoid watching television or using computer, tablet or phone in bed
  • Keep the bedroom dark, cool and quiet
  • If sleep onset is delayed, get up and perform a relaxing activity before returning to bed.
Exam Questions:

1. The most profound age related change in sleep is
   a. less slow wave sleep
   b. takes much longer to fall asleep
   c. decrease need for sleep
   d. increased need for sleep

2. Elderly people fall during the night more mostly because
   a. they have insomnia
   b. sleep medications
   c. nocturia
   d. b and c
   e. a, b, and c

3. The Beers Criteria of Drugs that are Potentially Inappropriate in Older Adults recommends which of the following drugs be avoided in the elderly:
   a. Benzodiazepines
   b. Z drugs
   c. Suvorexant
   d. Ramelteon
   e. a and b
   f. a, b, and c

4. Common over-the-counter medications used for the treatment of insomnia that should be avoided in the elderly include:
   a. Diphenhydramine
   b. Melatonin
   c. Doxylamine
   d. a and c
   e. a, b, and c

5. Which of the following medications would be a reasonable choice when treating an older adult with insomnia not responsive to cognitive behavioral therapy?
   a. Ramelteon 8mg
   b. Doxepin 3mg
   c. Suvorexant 5mg
   d. a and b
   e. a, b, and c
6. Elderly with insomnia have which of the following circadian rhythm disorders?
   a. phase delay syndrome
   b. irregular sleep wake disorder
   c. phase advance syndrome
   d. phase reversal

7. What system appears to be involved with mild cognitive impairment (MCI)?
   a. GABA
   b. Orexin
   c. histamine
   d. serotonin

8. Which of the following attributes are similar between benzodiazepines and Z drugs:
   a. Generally recommended for short-term use only
   b. Tolerance and withdrawal symptoms occur
   c. Schedule C-IV controlled substance
   d. b and c
   e. a, b, and c

9. The primary mechanism of action of suvorexant is:
   a. Non-selective binding to all γ-aminobutyric acid (GABA) α receptors
   b. Blocks endogenous neuropeptides secreted by the hypothalamus
   c. Selective binding to α1 subunits of γ-aminobutyric acid (GABA) α receptors
   d. Innervates the suprachiasmatic nucleus via G protein-coupled receptors (MT1/MT2)

10. The primary mechanism of action of ramelteon is:
    a. Non-selective binding to all Y-aminobutyric acid (GABA) α receptors
    b. Blocks endogenous neuropeptides secreted by the hypothalamus
    c. Selective binding to α1 subunits of Y-aminobutyric acid (GABA) α receptors
    d. Innervates the suprachiasmatic nucleus via G protein-coupled receptors (MT1/MT2)
11. Of the following medication which does not bind to the benzodiazepine receptor
   a. Zolpidem
   b. Eszopiclone
   c. Zaleplon
   d. Suvorexant

12. In addition to medications, what has been documented to effectively treat insomnia
   a. Sleep hygiene
   b. Cognitive behavioral therapy
   c. Relaxation training
   d. A and C
   e. A, B, and C

13. All of the following medication classes used to treat insomnia are C-IV controlled substances except:
   a. Melatonin receptor agonists
   b. Non-benzodiazepine receptor agonists
   c. Orexin antagonists
   d. Benzodiazepine receptor agonists

14. Which one of the following medication classes does not cause CNS sedation:
   a. Benzodiazepine receptor agonists
   b. Non-benzodiazepine receptor agonists
   c. Melatonin receptor agonist
   d. Antidepressants

15. Which of the following medications does not target sleep transmitter systems.
   a. Suvorexant
   b. Low dose doxepin
   c. Ramelteon
   d. A and B
   e. A, B, and C