What Keeps You Up at Night? Understanding Insomnia and the Clinical Utilization of Pharmacotherapy

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Home Study Webcast
4 Slides Per Page
What Keeps You Up at Night? Understanding Insomnia and the Clinical Utilization of Pharmacotherapy

ACTIVITY DESCRIPTION
“I can’t sleep. What should I do?” Pharmacists are easily accessible healthcare providers and are frequently sought for guidance regarding the treatment of insomnia. This presentation will review the current evidence based recommendations for managing insomnia disorder with pharmacotherapy including efficacy, toxicity, and patient counseling points.

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

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:
• Explain the clinical presentation and associated signs and symptoms of insomnia
• Relate the pharmacology and mechanism of action of available pharmacotherapy for the management of insomnia
• Comprehensively evaluate efficacy, safety, and tolerability of treatment options for insomnia

After completing this activity, the pharmacy technician will be able to:
• Describe the signs and symptoms of insomnia
• Recognize the mechanism of action of the available pharmacotherapy approved to treat insomnia
• Review the safety profiles of medications used to treat insomnia

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ABOUT THE AUTHOR

Dr. DiPaula is a residency trained, board certified psychiatric pharmacist. She is an Associate Professor with the University of Maryland, School of Pharmacy and has served as Director of Pharmacy at state-funded psychiatric hospitals for 16 years. She has acted as a residency preceptor for 16 years and Director of the University of Maryland PGY2 Psychiatric Pharmacy Residency program for 8 years. She currently collaborates with 2 community clinics, providing medication management and direct patient care for individuals with a variety of psychiatric disorders. She also provides medication reviews and consultations at a residential adolescent facility.

Dr. DiPaula has presented at local and national programs and serves as Instructor and/or Coursemanager for several University didactic and experiential courses. She has published articles, continuing education programs, and a book chapter on psychiatric and substance use disorders. Her major area of research and practice interest is in patients with comorbid psychiatric and substance use disorders.

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**Objectives**

- Explain the clinical presentation and associated signs and symptoms of insomnia
- Relate the pharmacology and mechanism of action of available pharmacotherapy for the management of insomnia
- Comprehensively evaluate efficacy, safety, and tolerability of treatment options for insomnia

**How common is insomnia?**

- 33-50% of adults experience insomnia symptoms
- More common in women
- 80% of elderly complain of insomnia
- 10-20% of primary care patients complain of significant insomnia
- 40-50% with insomnia have a comorbid psychiatric disorder
- 6-10% meet criteria for insomnia disorder
- Many sleep disorders go untreated

**Benefits of Sleep**

- Important for neural development, learning, memory, emotional regulation, CV function, metabolic function
- Sleep essential for optimal health and quality of life
- Rat studies demonstrate mortality after 3 weeks of total sleep deprivation
- Sleep deprivation contributes to the development of chronic diseases such as obesity, hypertension, diabetes, depression, anxiety
  - Elderly particularly susceptible
  - Associated with absenteeism, work/driving accidents
Sleep Architecture

- Cycle between NREM and REM sleep
  - NREM Sleep (75%)
    - Stage 1 transition from wakefulness. Initiation of sleep occurs over 25-30 minutes
    - Stage 2 lighter alpha wave sleep that makes up half of total sleep time
    - Stage 3 and 4 (delta sleep) deep or restorative sleep where there appears to be wound healing, protein synthesis, and immune restoration
  - REM Sleep (25%)
    - Associated with dreaming
    - Occurs every 90 minutes (4-5x/night)

Neurotransmitters

- Sleep-wake cycle produced by balance of arousing and sleep-inducing physiologic systems
- Sleep promoting
  - Gamma-aminobutyric acid (GABA)—main inhibitory NT
  - Adenosine—may inhibit wake promoting neurons
  - Melatonin—regulates circadian rhythm
- Wake promoting
  - Norepinephrine
  - Acetylcholine
  - Histamine
  - Serotonin
  - Dopamine
  - Orexin

Sleep Needs

- Varies based on individual and age
- Young Adults:
  - Sleep architecture similar to adults
  - Teens often have sleep deficits during the week. Extra weekend sleep does not correct deficit
  - American Thoracic Society (ATS) recommends school start times allow for adequate sleep
- Adult:
  - Optimal 7-9 hrs
  - <6hr/24hr is associated adverse outcomes including mortality
  - >9-10hr/24hr associated with adverse outcomes
- Elderly:
  - Age related changes in sleep
  - Difficulty initiating sleep, ↑ in awakenings and time awake
  - ↓ in delta sleep, may not occur at all in some

Common Symptoms of Insomnia

• Difficulty falling asleep (DFA)
• Frequent awakenings (FA)
• Waking up too early/not sleeping long enough
• Excessive daytime sleepiness
• Fatigue
• Difficulty concentrating
• Memory impairment

DSM-5 Criteria for Insomnia Disorder

• Unsatisfying sleep quantity or quality with ≥1:
  • Sleep initiation (difficulty falling asleep)
  • Sleep maintenance (frequent awakenings or difficulty returning to sleep)
  • Early-morning awakening
• Symptoms associated with distress or impairment (social, occupational, academic, behavioral)
• Not associated with another sleep-wake, psychiatric disorder, medical disorder, substance abuse, prescribed medication

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric Disorders</td>
<td>mood, anxiety, delirium, dementia, eating disorders, personality disorders</td>
</tr>
<tr>
<td>Medical Disorders</td>
<td>angina, arrhythmias, congestive heart failure, arthritis, chronic pain, asthma, bronchitis, COPD, hepatic or renal failure, congestive heart failure, cystic fibrosis, diabetes, epilepsy, GERD, peptic ulcer disease, head injury, hyperthyroidism, hypoglycemia, malignancy, Parkinson’s disease</td>
</tr>
<tr>
<td>Medications (RX/Herbal)</td>
<td>Antidepressants (SSRIs, SNRIs, MAOIs), stimulants (methylphenidate, amphetamines, ephedrine, caffeine), decongestants (pseudoephedrine, phenylephrine, phenylpropanolamine), narcotic analgesics, β-blocker, α-receptor agonist and antagonists, diuretics, lipid lowering agents, theophylline, albuterol, green tea, ginseng, guarana, ma huang</td>
</tr>
<tr>
<td>Substances of Abuse</td>
<td>alcohol (↑ sedation but ↓ quality of sleep), stimulants, nicotine, caffeine</td>
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Treatment Goals

• Improve sleep quality and quantity
• Alleviate distress or dysfunction

Insomnia Treatment Options

• Nonpharmacologic (Cognitive Behavior Therapy for Insomnia) 1st line
• Pharmacotherapy
  • BZD
  • Non-BZD receptor agonists-Zolpidem (Ambien®), Zaleplon (Sonata®), Eszopiclone (Lunesta®)
  • Melatonin receptor agonists-Ramelteon (Rozerem®)
  • Orexin-receptor antagonist-Suvorexant (Belsomra®)
  • Antidepressants (Doxepin, Amitriptyline, Mirtazapine, Trazodone)
  • Antihistamines (Diphehydramine, Hydroxyzine, Doxylamine)
  • Antipsychotics (Quetiapine)

Nonpharmacologic

• Initial treatment should include a nonpharmacologic intervention (behavioral therapy)
• Types
  • Stimulus control therapy
  • Relaxation therapy
  • Sleep hygiene
  • Cognitive behavioral therapy for insomnia (CBT-I)

Behavioral Therapy

• Stimulus Control Therapy
  • Avoid associating bed with inability to sleep
  • Lie down to sleep only when tired
  • Use bed only for sleep
  • Leave bed when unable to sleep
  • Set alarm to same time every day
  • Avoid napping during the day
• Relaxation Training
  • Progressively relax muscles from head to feet
Sleep Hygiene

- Sleep hygiene only in combination with other nonpharmacologic therapy
  - Data limited as monotherapy
- Go to bed and get up at the same time each day
- Keep the bedroom dark, comfortable, and quiet
- Get up after 20 minutes, if you have not fallen asleep, and return to bed when tired
- Only use bed for sleeping (not work)
- Turn the clock face aside to ↓ anxiety about falling asleep

Sleep Hygiene

- Avoid napping. Limit to <30 min/d
- ↓ or d/c alcohol, caffeine containing beverages. Stop smoking
- Exercise regularly (3-4x/wk): not in the evening if this interferes with sleep
- Do not eat heavy meals before bedtime
- Limit liquids before bed

Behavioral Therapy

- Cognitive Behavioral Therapy (CBT-I) effective
  - Guidelines recommend 1st line before pharmacologic
  - Incorporates sleep restriction, stimulus control, sleep hygiene, cognitive therapy such as relaxation techniques
  - General Population: improves remission, treatment response, sleep onset latency, wake after sleep onset, sleep efficiency, sleep quality
  - Elderly: some evidence that improves sleep onset and sleep efficiency
  - Harm associated is minimal and mild
  - Found to be as effective as Rx short term treatment and benefits may persist beyond termination of treatment
  - Few providers, limited insurance coverage
    - Telephone and web-based modules available

Pharmacotherapy

- ACP guidelines recommend pharmacotherapy for adults with chronic insomnia disorder in whom CBT-I alone has failed
- Discussion should include benefits, harm, costs of short term use to determine optimal therapy

Quencer, A. Ann Intern Med. 2016;165:125-133
Pharmacologic Treatment Summary

- 2nd line treatment. Should be in conjunction with nonpharmacologic therapy
- Limited evidence makes it difficult to compare relative safety and efficacy of pharmacologic alternatives
- Intended for short term use with many studies ≤4 weeks
- Analysis by American College of Physicians found
  - Eszopiclone, Zolpidem, Suvorexant improved global outcomes and sleep variables for selected adults with insomnia
  - Need more data for elderly, comparative data on efficacy and tolerability
  - Antipsychotics reserved for patient with history of psychotic symptoms

Benzodiazepines

- Mechanism
  - GABA is an inhibitory CNS NT which ↓ neuronal excitability
  - BZD work only in conjunction with GABA
  - BZD are positive allosteric modulators, which enhance the effects of GABA
  - BZD bound to a GABA<sub>A</sub> receptor in the presence of GABA causes the Cl<sub>channel</sub> to open more frequently than when GABA alone is present
- Efficacy:
  - ↓ sleep latency, ↑ stage 2 sleep, ↓ Stage 3, 4, REM (may feel less rested)
  - Insufficient evidence to determine benefits in general population or elderly
  - Pts who take long term report > fatigue than with good sleepers

Pharmacologic Options

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
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<tbody>
<tr>
<td>Benzodiazepines</td>
<td>triazolam, estazolam, temazepam, flurazepam, quazepam</td>
</tr>
<tr>
<td>Nonbenzodiazepine Hypnotics (z Drugs)</td>
<td>zaleplon, zolpidem, eszopiclone</td>
</tr>
<tr>
<td>Orexin Receptor Antagonist</td>
<td>suvorexant</td>
</tr>
<tr>
<td>Melatonin Receptor Agonist</td>
<td>ramelteon</td>
</tr>
<tr>
<td>Other</td>
<td>antidepressants, antipsychotics, antihistamines</td>
</tr>
</tbody>
</table>
### Benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comment</th>
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</table>
| Triazolam (Halcion®) | 0.25-0.5 mg hs 0.125 (elderly) | • Short t½  
• DFA, maintenance |
| Temazepam (Restoril®) | 15-30 mg hs 7.5mg mg (elderly) | • Intermediate t½  
• DFA, maintenance |
| Estazolam (Prosom®) | 1-2mg hs 0.5mg (elderly)       | • Intermediate t½  
• DFA, maintenance |
| Flurazepam (Dalmane®) | 15-30mg hs                  | • Long t½  
• Not recommended in the elderly |
| Quazepam (Doral®)   | 7.5-15mg hs                  | • Long t½  
• Not recommended in the elderly |

**Benzodiazepines (cont.)**

- **Side Effects**
  - Most common: drowsiness—lessened by taking shorter acting agent, dizziness, headache
  - Others: cognitive impairment, anterograde amnesia, paradoxical effects (Disinhbition), psychosis, nightmares
  - Relapse, rebound—usually lasts 1-2d, withdrawal (15%-40% report severe with LT use)
  - Severe effects
    - Dementia—associated with higher doses, BZD with t½ > 24hrs.
    - Serious injury, fractures
  - Drug Interactions: most substrates for CYP4503A/4

- **Selection Considerations:**
  - Marketing
  - Pharmacokinetics
    - Onset
    - t½ (duration, active metabolites)
- **Contraindications:**
  - Pregnancy cat (D or X)
  - Sleep apnea
  - COPD

**Patient Counseling**

- Do not combine with alcohol
- Can exacerbate depression or suicidal ideation
- Associated with abnormal thinking or behaviors such as sleep driving, sleepwalking, eating during sleep
- Caution driving and operating heavy machinery
- Generally for short-term use (7-14 days)
- Withdrawal symptoms can develop with discontinuation after sustained administration
Non-Benzodiazepine Receptor Agonists (NBRAs)

- **Agents:** Eszopiclone, Zaleplon, Zolpidem
- **“Z Drugs”**
- **Mechanism:**
  - Bind to the GABA\(\alpha\) receptor but to more selectively than BZD
  - Zaleplon, Zolpidem: BZD Omega 1 and 2 receptor subunit agonist
  - Eszopiclone: BZD Omega receptor subunit agonist. Not selective but binding different than BZD
- **Target sedative effect only not anxiolytic**
- **Efficacy:**
  - Commonly prescribed
  - ↓ sleep latency 42 min vs 20 min with placebo

**Adverse Effects:**
- Similar to BZD. More common at higher doses
- Lightheadedness, dizziness, headache, unpleasant taste (eszopiclone), parasomnias, withdrawal symptoms (>2 wks)
- May cause less tolerance and withdrawal. More likely for abuse at high doses
- Drug Interactions: substrate for CYP4503A/4

### Drug Dose Comment

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td><strong>Eszopiclone (Lunesta®)</strong></td>
<td>1-3 mg hs, 1 mg hs, max 2mg (elderly, severe hepatic impairment)</td>
<td>Used for DFA (1mg), maintenance (2-3mg) Improved total sleep time, wake after sleep onset in older adults</td>
</tr>
<tr>
<td><strong>Zolpidem (Ambien®, Zolpimist®, Intermezzo®, Edular®,)</strong></td>
<td>5-10mg hs, max 10mg 5mg (female, elderly, hepatic impairment) CR: 6.25-12.5mg SL: 3.5mg males, 1.75mg females</td>
<td>Comes in multiple dosage forms (CR, SL, spray, tab) Used for DFA (regular release), maintenance (CR), FA (SL) Improved sleep latency (by 15 min), total sleep time, wake after sleep onset variability by formulation ↓ sleep onset latency in older adults</td>
</tr>
<tr>
<td><strong>Zaleplon (Sonata®)</strong></td>
<td>5-10mg hs, 5mg (elderly, hepatic impairment)</td>
<td>Used for DFA Did not improve total sleep time in general population Short t1/2 not for sleep maintenance</td>
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**Ramelteon (Rozerem®)**

- **Mechanism:**
  - Melatonin regulates sleep wake cycle. Disruption of release or ↓ in release associated with insomnia. Pronounced with time zone change or shift work
  - Melatonin 1 and 2 receptor agonist. No effect on melatonin 3
- **Dose:** 8mg hs
- **Onset and duration:**
  - Onset within 30 minutes
  - May require regular administration for up to 3 weeks for full effect
  - Prior BZD use associated with less satisfaction
  - Duration of action unclear but > elimination half-life
  - Efficacy for up to 6 months of continuous treatment
**Ramelteon (Rozerem®)**

- **Efficacy:** primarily used for DFA. Some evidence sleep onset latency in older adults. Effect modest
- **Adverse effects:** morning sedation, dizziness, fatigue, GI upset, headache, unpleasant taste, exacerbation of depression in depressed patients
  - No abuse potential
- **Patient counseling**
  - High fat meal may reduce efficacy
  - Take 30 minutes before bedtime
  - No risk of dependence or withdrawal

**Suvorexant (Belsomra®)**

- **Mechanism:**
  - Endogenous orexin binds to orexin receptors which regulate arousal and wakefulness
  - Orexin receptor antagonist. Selective for OX1R, OX2R
- **Duration:** efficacy up to 1 year
- **Efficacy:**
  - General population - ↑ treatment response, improved sleep onset latency, total sleep time, wake after sleep onset compared with placebo
  - Older adults - ↑ treatment response, improved sleep onset latency (8-10 min vs placebo), total sleep time (22-23 min vs placebo), wake after sleep onset compared with placebo
  - Recommended for sleep maintenance insomnia. No comparator with other meds or shift work data

**Suvorexant (Belsomra®)**

- **Dosing:**
  - Start 10mg hs (within 30 minutes of bedtime)
  - Can ↑ up to 20mg hs. Higher doses associated with >SE including driving impairment
  - Administration with food can delay effect
  - ↑ exposure with females (17% > AUC)
- **Drug Interactions:**
  - Substrate for CYP450 3A/4
  - ↑ impairment ETOH, opioids, depressants

**Suvorexant (Belsomra®)**

- **Adverse effects**
  - Daytime somnolence, avoid driving
  - Dose dependent sleep paralysis, hypnagogic hallucinations, cataplexy-like symptoms
  - Worsening of depression in those with depression
  - Abuse potential similar to zolpidem in drug liking, no withdrawal sx
- **Patient counseling**
  - ↑ risk for suicidal ideation, depression
  - Notify MD if temporary weakness in legs (cataplexy)
  - Take 30 minutes before bed ≥ 7 hours to sleep
  - Caution driving with doses of 20mg/d
Sedating Antidepressants

- MOA: antihistaminic, anticholinergic (TCA)
- More likely to have hangover effects compared with hypnotics, associated with 1 road accidents
- TCA: Doxepin, amitriptyline. Doxepin primarily for sleep maintenance insomnia
- Trazodone: 5HT1a, 5HT2, α1 adrenergic receptor antagonist. May not be effective in those without depression. Limited data demonstrating benefit for 1 wk
  - 25-150mg hs
- Mirtazapine: more sedating at lower doses (7.5-15mg hs). Limited data

Antipsychotics

- American Psychiatric Association does not recommend for routine 1st line treatment of insomnia
- Quetiapine 25-150mg hs. Not recommended without comorbid psychiatric symptoms

Antihistamines

- Agents-diphenhydramine, hydroxyzine, doxylamine
- Generally not recommended
- Available OTC Studies for pregnancy-induced insomnia
- Tolerance after 1-2 wks of continuous administration
- Side effects-daytime hangover, anticholinergic effects (urinary retention, confusion, dry mouth)
- Contraindications: narrow angle glaucoma, acute asthma

Complementary Alternatives

- Insufficient data to determine safety and efficacy in general or older population. Not recommended for sleep onset or maintenance.
- Melatonin
  - Data in circadian rhythm disorders (jet lag), low endogenous melatonin levels.
  - ↓ sleep latency 7 min and ↑ total sleep time 8 min, favorable side effect profile
  - Dose: 0.5-5mg hs
  - Drug interaction: inhibits CYP1A2
- Valerian
  - Central GABA effects
  - Adverse effects: GI upset, headache, restless sleep, bitter taste, heart palpitations, depression, hepatotoxicity (rare), pancreatitis (rare), BZD-like withdrawal
  - Drug interactions: CYP2D6, 3A4, Pgp transporters
Case 1-Summary

• KR is 28 yo who comes into your community pharmacy and complains of difficulty falling asleep. Which pharmacologic agents do most recent guidelines recommend for this type of complaint?


Eszopiclone
Zaleplon
Zolpidem
Ramelteon
Temazepam
Triazolam

Case 2-Summary

• LR is 32 yo who comes into your community pharmacy and complains of difficulty staying asleep and not getting enough sleep. Which pharmacologic agents do most recent guidelines recommend for the management of this complaint?


Eszopiclone
Zolpidem
Suvorexant
Temazepam
Doxepin
Special Populations

- JL is 71 yo F with h/o depression and hypertension. She is currently taking sertraline 50mg hs, enalapril 5mg am. She c/o difficulty falling asleep (sleeps 4-6 hrs/nt). She is often tired during the day and frequently naps. What issues should be considered in managing insomnia in this patient?

- CBT-I effective and should be 1st line, when available
- Review nonpharmacologic strategies - ie napping
- Depression can be associated with sleep disturbance
- Consider antidepressant and schedule
- More sensitive to side effects. May require dose adjustments
- Melatonin or Ramelteon good option. No dose ↓
- BEERS criteria suggest avoiding
  - BZD: ↑ Falls, cognitive impairment, delirium, fractures, MVA
  - Anticholinergic (diphenhydramine)

Special Population

- JS is a 28 yo F who is 20 weeks pregnant and has developed insomnia. She would like a recommendation on treatment options which would be safe for her baby.

- Nonpharmacologic 1st
- Diphenhydramine and doxylamine studied
- Avoid BZD
Insomnia Treatment Pearls

- Assess for treatable causes such as pain or caffeine use
- Consider pharmacotherapy based on
  - Type of insomnia (sleep onset vs maintenance)
  - Patient variables (age, depression, psychosis, SUD, glaucoma)
- Tolerance to pharmacotherapy can develop within 1-2 weeks
- Dependence to BZD can occur after >1-4 week of administration

- Duration of treatment unclear
  - Short term studies initially supported treatment of only 2-3 weeks
  - Recent, longer studies suggest up to a year with some hypnotics (eszopiclone, zolpidem, ramelteon)
  - Clinical practice is often longer
- Consider alternating agents
- Avoid taking on consecutive nights

Conclusion

- CBT-I considered first line therapy
- Pharmacologic therapy second line and primarily studied for short term use
- Selection of pharmacotherapy generally based on patient related variables and risk of adverse effects
- Evidenced based comparator data needed to better determine hierarchy of selection

Questions
EXAM QUESTIONS:

1. TS, a 50 yo female with good sleep hygiene, complains of difficulty falling asleep. Based on recent guidelines, which one of the following medications would you recommend to manage insomnia.
   a. Quetiapine  
   b. Zaleplon  
   c. Suvorexant  
   d. Diphenhydramine

2. Which of the following neurotransmitters is a target for pharmaceutical therapy due to its effects of promoting “wake” in the sleep-wake cycle?
   a. Gamma-aminobutyric acid (GABA)  
   b. Melatonin  
   c. Orexin  
   d. Adenosine

3. JR, a 43 yo male with no relevant comorbidities, complains of frequent awakenings and not sleeping long enough. Based on recent guidelines, which one of the following medications would you recommend to manage insomnia.
   a. Ramelteon  
   b. Zaleplon  
   c. Suvorexant  
   d. Trazodone

4. Which one of the following is an example of a nonbenzodiazepine receptor agonist?
   a. Eszopiclone  
   b. Temazepam  
   c. Suvorexant  
   d. Valerian

5. KS is a 32 yo F with bipolar disorder and insomnia disorder. Which one of the following might be recommended specifically based on KS’s comorbidity?
   a. Trazodone  
   b. Mirtazapine  
   c. Quetiapine  
   d. Triazolam
6. Which one of the following is an appropriate patient counseling point with ramelteon?
   a. Take with a heavy meal before bed
   b. May cause seizures if suddenly discontinued
   c. Take as needed for best effect
   d. Take 30 minutes before bedtime

7. To meet DSM criteria for insomnia disorder, symptoms must have persisted for at least?
   a. 3 hours
   b. 3 days
   c. 3 weeks
   d. 3 months

8. Zolpidem may be associated with toxicity when combined with which one of the following agents?
   a. CYP450 3A4 inhibitor
   b. CYP450 2D6 inhibitor
   c. CYP450 1A2 inhibitor
   d. This agent is not associated with drug interactions

9. Which one of the following has no effect on benzodiazepine receptors?
   a. Zaleplon
   b. Zolpidem
   c. Triazolam
   d. Suvorexant

10. Which one of the following does not require a dose adjustment for a 78 yo F?
    a. Zolpidem
    b. Ramelteon
    c. Zaleplon
    d. Eszopiclone