Mr. Sandman, Is Sleep with Fewer Side Effects Too Much to Ask? A Closer Look at Existing and Emerging Therapies

Julie Dopheide, PharmD, BCPP
MR. SANDMAN, IS SLEEP WITH FEWER SIDE EFFECTS TOO MUCH TO ASK? A CLOSER LOOK AT EXISTING AND EMERGING THERAPIES

ACTIVITY DESCRIPTION
In a fast paced, highly stimulatory society Americans continue to be plagued with sleep disorders. Every year prescription sleep aid use continues to rise. Current prescription sleep aids, although effective, have a high rate of adverse events and discontinuation due to broad effects on the central nervous system. This program will identify the most commonly prescribed therapies for the treatment of insomnia, provide an overview of problems associated with treatment of insomnia among current hypnotics, and describe emerging therapies for the treatment of insomnia.

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

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

- Given a case of insomnia, recommend appropriate evaluation and explain the available cognitive-behavioral and pharmacologic treatment options
- Compare the advantages and disadvantages of available over-the-counter and prescription medications for the treatment of insomnia
- Discuss emerging treatments for insomnia, including those that modulate the orexin system and explain how they compare to currently available treatments

After completing this activity, the pharmacy technician will be able to:

- List prescription medications that are used to treat insomnia
- List over-the-counter medications that are used to treat insomnia

ACCREDITATION

PHARMACY
PharmCon, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

NURSING
PharmCon, Inc. is approved by the California Board of Registered Nursing (Provider Number CEP 13649) and the Florida Board of Nursing (Provider Number 50-3515). Activities approved by the CA BRN and the FL BN are accepted by most State Boards of Nursing.

CE hours provided by PharmCon, Inc. meet the ANCC criteria for formally approved continuing education hours. The ACPE is listed by the AANP as an acceptable, accredited continuing education organization for applicants seeking renewal through continuing education credit. For additional information, please visit http://www.nursecredentialing.org/RenewalRequirements.aspx

Universal Activity No.: 0798-0000-14-008-H01-P&T
Credits: 1 contact hour (0.1 CEU)

Release Date: December 19, 2014
Expiration Date: June 19, 2015

ACTIVITY TYPE
Knowledge-Based Home Study Webcast

FINANCIAL SUPPORT BY:
Merck
ABOUT THE AUTHOR

Dr Dopheide is a Professor of Clinical Pharmacy, Psychiatry and the Behavioral Sciences, at the University of Southern California in Los Angeles. She received her PharmD from the University of Nebraska and completed a residency in psychiatric pharmacy practice at the University of Southern California. Dr. Dopheide is a board certified psychiatric pharmacist and provides clinical service for adults and children with psychiatric illness at Los Angeles County + USC Medical Center. She supervises the psychiatric pharmacy resident in the provision of comprehensive medication management at the Center for Community Health (CCH) located in downtown Los Angeles. She is actively involved in teaching pharmacy students, medical students allied health and and psychiatry residents in both the classroom and clinical settings.

Dr. Dopheide has over 40 publications in peer-reviewed journals, textbooks and educational publications. She is a nationally recognized expert in psychiatric pharmacy, particularly child/adolescent psychopharmacology, sleep medicine and depression. Dr. Dopheide is the current president of the College of Psychiatric and Neurologic Pharmacists (CPNP) and is active in the American Society of Hospital Pharmacists (ASHP), American Pharmacists Association and the National Alliance for the Mentally Ill (NAMI).

FACULTY DISCLOSURE

It is the policy of PharmCon, Inc. to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a sponsor has with the manufacturer of any commercial product(s) and/or service(s) discussed in an educational activity. Julie Dopheide reports no actual or potential conflict of interest in relation to this activity.

Peer review of the material in this CE activity was conducted to assess and resolve potential conflict of interest. Reviewers unanimously found that the activity is fair balanced and lacks commercial bias.

Please Note: PharmCon, Inc. does not view the existence of relationships as an implication of bias or that the value of the material is decreased. The content of the activity was planned to be balanced and objective. Occasionally, authors may express opinions that represent their own viewpoint. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient or pharmacy management. Conclusions drawn by participants should be derived from objective analysis of scientific data presented from this monograph and other unrelated sources.
Mr. Sandman,
Is Sleep with Fewer Side Effects Too Much To Ask?
A Closer Look at Existing and Emerging Therapies for Insomnia

Julie A. Dopbeide, PharmD, BCPP

Learning Objectives

1. Given a case of insomnia, recommend appropriate evaluation and explain the available cognitive-behavioral and pharmacologic treatment options.
2. Compare the advantages and disadvantages of available over-the-counter and prescription medications for the treatment of insomnia.
3. Discuss emerging treatments for insomnia, including those that modulate the orexin system and explain how they compare to currently available treatments.

Empowering People to Improve Health by Improving Sleep

- Overview of Sleep in America and Insomnia
- Cognitive Behavioral Therapy and Self Care Options
  - Sleep Hygiene
  - Stimulus Control and Sleep Restriction
  - Exercise, Yoga, Meditation
- Pharmacologic Treatments
  - Nonprescription medications and herbal remedies
  - Benzodiazepine receptor active agents
  - Antidepressants: Doxepin, Trazodone
  - Melatonin receptor agonists: Ramelteon, Tasimelteon
  - Orexin-receptor antagonists: Suvorexant
2014 Sleep in America Poll: Reasons for not getting a good night's sleep

<table>
<thead>
<tr>
<th>Activity</th>
<th>Kids (%)</th>
<th>Parents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening activities</td>
<td>38%</td>
<td>41%</td>
</tr>
<tr>
<td>Homework</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Temperature</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Inside noise</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Outside noise</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Light</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td>Pets</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>


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

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

N = 10,986 adults


Poor Sleep Increasing Each Decade: Percentage reporting < 6h sleep

- Men 1985
- Men 2004
- Women 1985
- Women 2004

Short-sleepers ≤ 6 hrs 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


What is Insomnia?

- The Most Common Sleep Complaint
  - Difficulty initiating or maintaining sleep,
  - Waking up at night or too early in the morning, or
  - Non-restorative or poor quality of sleep
- Daytime Symptoms
  - Fatigue or low energy
  - Inattention
  - Memory and concentration problems
  - Mood problems – irritability, dysphoria
- Course: situational/episodic, recurrent, persistent

DSM-5 Changes in Insomnia Categorization 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>Short-term: 1-3 months</td>
</tr>
<tr>
<td>Chronic: &gt; 1 month</td>
<td>Chronic: &gt; 3 months</td>
</tr>
</tbody>
</table>

Comorbidity Specifier: mental, medical or sleep disorder

(From – Diagnostic and Statistical Manual of Mental Disorders)

NIH – Bidirectional Connection Between Medical/Psych Conditions & Chronic Insomnia

- Insomnia
  - No more primary vs. secondary insomnia
  - "Comorbid or Co-occurring insomnia"
  - MDD 10x > insomnia
  - HTN, Gl, Cancer, Pain: 2-3 x > chronic insomnia
- Medical/Psych Condition
  - Need to treat all conditions concurrently

Improved Outcomes when Major Depression, Anxiety & Insomnia Co-treated

- Benzodiazepine (alprazolam or clonazepam) given along with SSRI 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 Assessment

- Determine if medical and/or neuropsychiatric comorbidities need to be investigated before treatment is initiated
- Screen for obstructive sleep apnea and refer to sleep lab if needed
- Type of insomnia and resulting impairment
  - Difficulty falling asleep (DFA), maintaining sleep (DMS)
- What has the patient tried?
  - Consider drug and alcohol use
- Engage patient to set goals of treatment

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?

www.sleepfoundation.org

Cognitive Behavioral Approaches

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

Increased Mortality and Cancer Risk Associated with Hypnotic Use

- US study N=10,529 matched controls: 23,678
- Mean age 54, men and women
- Followed over average of 2.5 years (2002-2007)
- Individuals who took > 132 doses of hypnotics/year had highest mortality rates (4 – 6 x greater)
- Overall cancer risk 35% with high-dose hypnotic
- Hypnotics: zolpidem, temazepam, eszopiclone, zaleplon, other benzodiazepines, barbiturates
- Risk of adverse outcome dose-related
Increased Mortality Associated with Heavy Hypnotic Use

Balance Risks of Hypnotic Use with Benefits of a Good Night Sleep

Neurochemistry of the Sleep/Wake Cycle
- Wakefulness & sleep: antagonistic states competing for control of brain activity
- Wakefulness promoting: NE, DA, histamine, acetylcholine, hypocretin/orexin
- Sleep promoting: GABA, opioids, enkephalins, endorphins, 5HT
- Environment, stress, genetics, medications, medical/psychiatric illnesses all influence the sleep/wake cycle

Polysomnography Graph
increased deep sleep in 1st half of night; lighter sleep With more REM episodes closer to morning
Sleep Stage Significance

- NREM - 75% of total sleep time
  - stage 1 - relaxed wakefulness
  - stage 2 - rest for brain and muscles
  - stage 3 - feeling of rejuvenation
  - stage 4 - immune enhancement, growth hormone release
- REM - 25% of total sleep time
  - higher cortical areas and neurotransmitters active while body resting
  - autonomic instability, temperature drops
  - Information from the day stored as memories

Non-Prescription Options

- Diphenhydramine, doxylamine excessive daytime hangover, tolerance develops, anticholinergic effects; discourage use; hydroxyzine less problems
- Melatonin best for circadian rhythm sleep disorder, short-term use, well-tolerated in most
- Valerian smelly root, widespread use in Europe, has activity at Bz receptor, withdrawal symptoms reported after chronic use, liver toxicity reported
- Kava-kava Fijian powder, risk of hepatotoxicity

Melatonin 1 – 6 mg Effective for Insomnia in Children with ASD/ADHD

- Several chart reviews and smaller controlled trials show melatonin effective for insomnia in Autism Spectrum Disorder & Attention Deficit Hyperactivity Disorder
- Prospective controlled trial n=24 children with ASD showed decrease in sleep latency, increased sleep time
  - 1 to 3mg effective for most children, 2 needed 6mg
- Prospective controlled trial n=105 children with ADHD
  - 3 to 6mg effective in decreasing sleep latency, ↑ total sleep time
- Natrol brand liquid melatonin used in trials, well tolerated

Comparing Traditional Benzodiazepine (Bz) Hypnotics C-IV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Onset (minutes)</th>
<th>T1/2 (hours)</th>
<th>Metabolite</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam</td>
<td>0.125-0.5</td>
<td>20-30</td>
<td>2-3</td>
<td>2-3</td>
<td>2-3</td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5-30</td>
<td>60-120</td>
<td>8-20</td>
<td>6-10</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>15-30</td>
<td>30-60</td>
<td>3-8</td>
<td>40-120</td>
<td>10+ &quot;hangover&quot;</td>
</tr>
</tbody>
</table>

Duration of effect based on active metabolites, fat solubility, and single vs. multiple dosing
MOA: Activation of GABA-A Receptor Through Stimulation of BZ-receptor

- Chloride channels open
- Hyper-polarization of postsynaptic membrane
- Facilitates GABA; inhibitory neurotransmitter
- Sleep consolidation
- BZRA-α1 subunit selective
Z hypnotics have minimal muscle relaxant, anticonvulsant, or anxiolytic properties

Comparing “Z” Hypnotics: C-IV

<table>
<thead>
<tr>
<th>Z-Hypnotic</th>
<th>Usual Dose</th>
<th>Onset (minutes)</th>
<th>Half-life (hours)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon</td>
<td>5-10 mg</td>
<td>30</td>
<td>1.1</td>
<td>2-4</td>
</tr>
<tr>
<td>Sonata®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5-10 mg</td>
<td>30</td>
<td>2.5</td>
<td>4-6</td>
</tr>
<tr>
<td>Ambien® and generics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem CR</td>
<td>6.25 mg</td>
<td>30</td>
<td>2.8</td>
<td>4-7</td>
</tr>
<tr>
<td>Ambien CR®</td>
<td>12.5 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1-3 mg</td>
<td>45</td>
<td>6</td>
<td>5-8</td>
</tr>
<tr>
<td>Lunesta®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most prescribed in blue based on 2012 Top 200 drug list www.drugtopics.com
Adapted from each drug’s package insert and post-marketing clinical trial comparing PK effects

Clinical Comparison of Benzodiazepine Receptor Active Agents

**Benzodiazepine**
- non-selective
- anxiolytic
- muscle relaxant
- anticonvulsant
- suppresses REM
- slow wave sleep
- abuse potential
- CNS side effects

**Z-hypnotic**
- α-1 selectivity
- not anxiolytic
- not muscle relaxant
- not anticonvulsant
- no significant impact on REM or slow wave sleep
- less abuse potential
- CNS side effects

Adverse Effects of BZ-receptor Active Hypnotics

- Sedation
- Dizziness
- Memory problems, confusion
- Loss of coordination
- Gastrointestinal Upset (Z-hypnotics)
- Complex Sleep Behaviors – eating, driving, walking while “asleep”
Zolpidem Peak Blood Level and AUC Higher in Females and Elderly

Jan 10, 2013 – Zolpidem Warning

- Driving Simulations and Alertness studies showed significant impairment in 15% women and 3% men who took zolpidem the night before
- Women - maximum starting doses lower
  - 5 mg IR, 6.25 mg CR
- Men - should take the lowest effective dose that improves sleep

Doxepin 6 mg Found Safe and Effective for Chronic Insomnia in Healthy Elderly

Trazodone

- Comparable to zolpidem short-term in young adults
- More effective and better tolerated than quetiapine in psychiatric inpatients
- Long-term tolerance reports mixed
- Usual dosing: 50-150 mg (25-300 mg)
- Half-life 6-12 hours, hangover possible
- m-CPP metabolite can cause anxiety, insomnia, dysphoria, HA in some; tolerance can develop
- Significant AE profile: orthostatic hypotension, dry mouth, constipation, priapism, arrhythmia
Suprachiasmatic Nucleus (SCN)

- Melatonin stimulates MT1 receptors non-selectively.
- Ramelteon stimulates MT1 and MT2 receptors in SCN.

AMT 1 receptor - regulates sleepiness
MT 2 receptor – regulates phase shifts day to night

Ramelteon (Rozerem®)

- MT1 and MT2 receptor agonist
- FDA approved for "sleep onset" insomnia
- No comparative data vs. other hypnotics
- No abuse potential, safe in mild to moderate sleep disordered breathing (apnea)
- Dosing: 8 mg in young adults and elderly
- Food delays T_max (45 min) ↑ AUC 31%
- t1/2: 1.1–2.6 hrs; active metabolite 2–5 hrs
- CYP 1A2 (major), CYP 3A4 (minor)
- ADRs: dizziness, nausea, fatigue, HA, endocrine effects (↓ testosterone, ↑ prolactin, ↑ cortisol)

Melatonin Modulating Agents

- Controlled release melatonin – (Circadin®)
  - 2 mg prescription formulation for insomnia in ≥ 55 years old
  - Take 1-2 hours before bedtime; effective vs plbo x 3 mo.
- Tasimelteon (Hetlioz®) – granted orphan drug status for non-24 hr sleep-wake disorder in the blind
  - MT1 and MT2 receptor agonist; 20mg dose
  - Hepatotoxicity possible
  - Clinical trials underway for jet lag and insomnia
- Agomelatine (Valdoxan) – melatonin receptor agonist
  - MT1 and MT2 receptor agonist
  - 5HT2c antagonist, therefore increase in slow-wave sleep
  - Hepatotoxicity; US market stopped in 2011


Campaign to Decrease Bz/Z Hypnotic Use More Effective when PR melatonin prescribed

The Netherlands - Delta 2006 to SUx10³

UK - Delta 2006 to SUx10³

Netherlands: Decreased Bz hypnotic use when no longer covered by insurance
UK - Insurance coverage resulted in NO use of PR melatonin / not in guidelines

Orexin (hypocretin) – A wakefulness promoting center in the brain

Dual-Acting Orexin Receptor Antagonist

DORA - Suvorexant

- Currently under FDA review / most studied DORA
- Orexin: neuropeptide that regulates wakefulness in hypocretin area of the brain; active during wakefulness
- Narcolepsy correlated with damage to hypocretin or “wakefulness” center of the brain
- Unique Effects on Sleep Architecture
  - Increased REM sleep
  - Increased Stage 2 sleep
  - No change in Stage 3, 4 or slow wave sleep
  - Abuse potential and impact on appetite and weight is unknown

FDA – Efficacy and Safety Review of Suvorexant for Insomnia

- Phase III Clinical trials completed in ~ 2,000 patients
  Effective for inducing and maintaining sleep at all doses studied (15, 20, 30, 40mg)
- Not safe at these doses according to driving tests
  - Next day impairment in alertness and reaction time
  - 20% adults above alcohol impairment cut-off at 20mg dose
- Phase 2 data shows 10mg may have similar efficacy and better safety, lower doses may still be effective
- Safety concerns: daytime somnolence, headaches, complex sleep behaviors, sleep paralysis, cataplexy, suicidal ideation, hallucinations
**Suvorexant’s Pharmacokinetic Profile Promotes Sleep Onset and Maintenance**

- Tmax - 1-2 hours fasting, 3 hours fed state
- Food increases Cmax by 1.5 times
  - Higher AUC (bioavailability in obese subjects)
- Half-life - 9 to 13 hours
- Hepatically metabolized – CYP 3A4
  - Studies show increased levels of simvastatin when co-administered with suvorexant
- No studies in impaired organ function or co-occurring medical/psychiatric illness

**Insomnia Treatment Algorithm**

- Assess Co-occurring Conditions
- Substance Abuse Mx
- Psychiatric and/or Medical Diagnosis

- Sleep Apnea suspected
- Sleep Lab Referral
- Referral to Rehab
- Sleep Apnea Confirmed

- Avoid sedating medication until sleep study completed (CPAP / surgery or other treatment)
- Avoid R2 receptor antagonist effect sedating antidepressant

- DFA, DMS, EMA: Difficulty falling asleep, difficulty maintaining sleep, early morning awakening.

**Clinician’s Role - Insomnia**

- Recommend optimal assessment for patients with sleep complaints
- Educate providers and patients on appropriate non-drug and drug treatment
- Given a medication regimen, screen for causes of insomnia and drug interactions
- Counsel patients with hypnotic prescriptions on how to safely and effectively use their medication

**Is Sleep with Fewer Side Effects Too Much to Ask?**

Weigh the Benefits and Risks
ACTIVITY TEST

1. Melatonin has the most evidence for therapeutic benefit and safety in:
   A. Adults with chronic insomnia associated with sleep apnea.
   B. Children with insomnia and autism spectrum disorder.
   C. Elderly with chronic insomnia.
   D. Adults with major depression.

2. Which of the following conditions puts a patient at greatest risk for an adverse health outcome such as early death, stroke, or heart attack?
   A. Sleeping more than 8 hours per night
   B. Taking a prescription hypnotic consecutively for 4 weeks
   C. Getting less than 6 hours of sleep per night
   D. Using doxylamine or diphenhydramine once per week

3. Benzodiazepine-receptor active hypnotics increase time in which sleep stage?
   A. REM sleep
   B. Stage 1
   C. Stage 2
   D. Stage 3

4. Worsening anxiety, insomnia, dysphoria and headache can occur in some patients who take trazodone 50mg for insomnia due to:
   A. A bad reaction to the m-CPP metabolite
   B. Undiagnosed bipolar disorder
   C. An impurity in the generic formulation
   D. A drug interaction with a CYP 2D6 inhibitor

5. Tasimelteon entered the prescription sleep-aid market in January of 2014 and is FDA approved to manage:
   A. Circadian-rhythm sleep disorders.
   B. Advanced sleep-phase syndrome.
   C. Non-24 sleep/wake disorder in the blind.
   D. Persistent or chronic insomnia in adults.
6. Which of the following duration of time accurately describes the categorization of chronic or persistent insomnia in the DSM-5?
   A. One month
   B. Greater than one month
   C. Three months
   D. Greater than three months

7. Which hypnotic is most associated with rebound insomnia upon abrupt discontinuation?
   A. Triazolam
   B. Zolpidem
   C. Temazepam
   D. Eszopiclone

8. Which of the following sleep complaints would prompt you to refer the patient to a sleep laboratory for evaluation?
   A. Early morning awakening and daytime fatigue
   B. Heavy snoring and frequent awakenings
   C. Getting less than 6 hours of sleep per night
   D. Difficulty falling asleep nightly for > 3 weeks

9. Cognitive behavioral therapy for insomnia includes which of the following?
   A. Regular aerobic exercise
   B. Recording dreams upon awakening
   C. Counseling to change unrealistic expectations about sleep
   D. Utilizing sleep aids such as melatonin, valerian or kava-kava

10. Available research on the investigational hypnotic, suvorexant show it:
    A. Has a short half-life of less than 3 hours with little risk of next-day hangover.
    B. Will have increased bioavailability (AUC) when taken with food
    C. Will have significant abuse potential.
    D. Has the ability to suppress REM sleep.

Please submit your final responses on freeCE.com. Thank you.