Insomnia Pharmacotherapy
A Practical Guide for Primary Care

Offices in Jacksonville, Florida

Fortis Spectrum is the educational partner for this session.
Session 3: Insomnia Pharmacotherapy: A Practical Guide for Primary Care

Learning Objectives
Upon completion of this activity, participants should be able to:
- Define 3 practice interventions that will enhance the diagnosis and treatment of insomnia.
- Describe the components of an effective risk-benefit analysis leading to an insomnia treatment plan.

Faculty
David N. Neubauer, MD
Associate Director
The Johns Hopkins Sleep Disorders Center
Assistant Professor, Department of Psychiatry
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Dr David N. Neubauer is associate director of The Johns Hopkins Sleep Disorders Center and assistant professor in the Department of Psychiatry at The Johns Hopkins University School of Medicine in Baltimore. He is also medical director of the Psychiatric Mobile Treatment Program at the Johns Hopkins Bayview Medical Center.

Dr Neubauer earned his bachelor’s and master’s degrees in anthropology, and a bachelor’s degree in biology at Florida Atlantic University in Boca Raton. He also pursued further graduate study in anthropology at the University of British Columbia in Vancouver. He went on to earn his medical degree at the University of Miami School of Medicine, and then completed his residency in psychiatry at the Henry Phipps Psychiatric Service at Johns Hopkins Hospital.

Dr Neubauer is a fellow of the American Psychiatric Association and a diplomate of the American Board of Sleep Medicine. He is a member of several professional organizations, including the American Academy of Sleep Medicine, the Sleep Research Society, and the Society for Light Treatment and Biological Rhythms. Dr Neubauer is a consultant to the US Food and Drug Administration Center for Drug Evaluation and Research and serves on the editorial board of the journal Sleep. He is a frequent guest lecturer and the author of journal articles, book chapters, and abstracts.

Paul Doghramji, MD
Family Physician
Collegeville Family Practice

Dr Paul P. Doghramji is cofounder of Brookside Family Practice and Pediatrics, a current affiliate of Pottstown Medical Specialists in Pottstown, Pennsylvania. He has also been attending physician in family practice, chair of the Utilization Management Committee, and physician advisor at Pottstown Memorial Medical Center. Most recently, he moved his practice location to Collegeville Family Practice in Collegeville, Pennsylvania, a subsidiary of Pottstown Medical Specialists, Inc.

Dr Doghramji received his medical degree from Jefferson Medical College and completed his residency in family practice at Chestnut Hill Hospital, both in Philadelphia. He is a fellow of the American Academy of Family Physicians and a member of the National Headache Foundation and the Chronic Fatigue and Immune Dysfunction Syndrome Association. He was certified by the American Board of Family Practice in 1985, and has been recertified every 6 years since then.

Faculty Financial Disclosure Statements
The presenting faculty report the following:
Dr Neubauer is a consultant for Neurocrine Biosciences, Inc.; Pfizer Inc.; sanofi-aventis U.S.; and Takeda Pharmaceuticals North America, Inc.
Dr Doghramji receives honoraria and speaker fees from Takeda Pharmaceuticals North America, Inc.; sanofi-aventis U.S.; and Sepracor Inc.

Session 3
Education Partner Financial Disclosure Statement
The content collaborators at Fortis Spectrum have nothing to disclose.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>agomelatine</td>
<td>Valdoxan</td>
<td>temazepam</td>
<td>Restoril</td>
</tr>
<tr>
<td>estazolam</td>
<td>ProSom</td>
<td>tiagabine hydrochloride</td>
<td>Gabitril</td>
</tr>
<tr>
<td>eszopiclone</td>
<td>Lunesta</td>
<td>triazolam</td>
<td>Halcion</td>
</tr>
<tr>
<td>flurazepam hydrochloride</td>
<td>Dalmate</td>
<td>zaleplon</td>
<td>Sonata</td>
</tr>
<tr>
<td>gabapentin</td>
<td>Neurontin</td>
<td>zolpidem tartrate</td>
<td>Ambien</td>
</tr>
<tr>
<td>pregabalin</td>
<td>Lyrica</td>
<td></td>
<td></td>
</tr>
<tr>
<td>quazepam</td>
<td>Doral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ramelteon</td>
<td>Rozerem</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Off-Label

doxyphen         | Sinequan|
mirtazapine      | Remeron |

Investigational

eplivanserin     |         |
gaboxadol        |         |
indiplon         | M100907 |
ritanserin       | NGD96-3 |

Suggested Reading List


Insomnia Pharmacotherapy:
A Practical Guide for Primary Care

Course Objectives:

- Define three practice interventions that will enhance the diagnosis and treatment of insomnia
- Describe the components of an effective risk-benefit analysis leading to an insomnia treatment plan

Part I: Insomnia Overview

Insomnia Defined

- Complaint of inadequate or insufficient sleep despite adequate opportunity
- Adversely affect waking function

Prevalence of Specific Insomnia Complaints

- “Sleep disruption” in general population ~30%
- Sustained insomnia with daytime functional impairment (= insomnia diagnosis) ~10%
- Symptoms in general practice ~50%

Primary vs. Comorbid Insomnia

- Psychiatric Disorders 44%
- Medical disorders 11%
- Other Sleep Disorders 9%
- No DSM-IV Diagnosis 24%
Impact of Comorbid Disease on Insomnia Prevalence

Insomnia prevalence is increased in:
- Major psychiatric disorders, e.g., depression, anxiety, schizophrenia
- Neurological disorders, e.g., Parkinson’s disease, dementia
- Medical disorders, e.g., COPD, diabetes
- Primary sleep disorders, e.g., sleep apnea, restless legs syndrome

Roth T. and T. Roehrs, Clinical Cornerstone 2003 5(3): 5-15

Insomnia and Comorbid Disease: A Circular Relationship

Insomnia

Comorbid Disease

Insomnia & Major Depressive Disorder

Consequences of Insomnia

- Increased risk of psychiatric disorders
- Increased pain sensitivity
- Decreased quality of life (QOL)
- Motor vehicle and workplace accidents
- Falls and hip fractures
- Mortality

Fava M et al.; Biological Psychology 2006:59:1052-1060

Time to Response Based on Clinical Global Impression-Improvement Scale

Eszopiclone in Patients with Insomnia Related to Major Depressive Disorder

Treatment
- Eszopiclone 3 mg
- Placebo

PBO + FLX

ESZ + FLX

P<0.002

Days to Onset of Response

Estimated Cumulative Probability of Onset

Fava M et al.; Biological Psychology 2006:59:1052-1060

Consequences of Insomnia

- Increased risk of psychiatric disorders
- Increased pain sensitivity
- Decreased quality of life (QOL)
- Motor vehicle and workplace accidents
- Falls and hip fractures
- Mortality

Fava M et al.; Biological Psychology 2006:59:1052-1060
Part II: Insomnia Therapy

Recommended Insomnia Therapy

Chronic insomnia is a major public health problem affecting millions of individuals, along with their families and communities.*

- Behavioral therapy - e.g., sleep hygiene, cognitive behavioral therapy (CBT)
- Approved pharmacological therapy


Sleep Hygiene: An Essential Component of All Insomnia Treatment

- Regular sleep-wake cycle
- Regular exercise in the morning and/or afternoon
- Increase exposure to bright light during the day
- Minimize exposure to bright light at night
- Avoid heavy meals or drinking within 3 hours of bedtime
- Enhance sleep environment
- Avoid caffeine, alcohol and nicotine


Sleep Hygiene Patient Resource

www.SleepFoundation.org

Cognitive Behavioral Therapy for Insomnia

- Addresses the multiple factors that perpetuate insomnia
- An ideal CBT approach incorporates multiple modalities
- Success depends on trained therapist

Efficacy of CBT

WASO = Wake after sleep onset; CBT = cognitive behavioral therapy; PCT = pharmacotherapy

Morin et al., JAMA 1999;281:981-989
**Insomnia Pharmacotherapy in 2008**

- Nutraceuticals
- OTC agents
- Off-label prescriptive agents
- Approved prescriptive agents

**Nutraceutical Therapies**

- "Internet therapies"
- No FDA oversight and fewer data
- Many GABA-ergic
- An incomplete list:
  - Lavender
  - German chamomile
  - Mimosa blossoms
  - Melatonin
  - Valerian Root
  - "Sleeping Buddha"

**FDA WARNS CONSUMERS AGAINST TAKING DIETARY SUPPLEMENT "SLEEPING BUDDHA"**


**Most Common Rx for Insomnia**

![Bar graph showing the most commonly prescribed medications for insomnia](image)

**Sedating Antidepressants**

- Most commonly used agent in U.S. is trazodone
- No positive efficacy data in non-depressed patients
- Can cause daytime sedation
- Potentially significant adverse effects raising concerns about the risk-benefit ratio

**Over the Counter Sleep Agents (e.g., Diphenhydramine)**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages 1,2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription not needed</td>
<td>Efficacy not consistent</td>
</tr>
<tr>
<td>Limited supporting studies on efficacy in treating insomnia</td>
<td>Potential for residual effects</td>
</tr>
<tr>
<td>No well-defined effective dose</td>
<td>Rapid onset of tolerance</td>
</tr>
</tbody>
</table>
**Diphenhydramine Tolerance**

![Graph showing sleep latency over days](image)

Sleep latency = time required to fall asleep

Richardson et al., Clinical Psychopharmacology 2002 22:511-515

---

**BzRA Hypnotics: Mechanism**

- Principal CNS GABA receptor
- Pentamer constructed from 3 types of subunit (α, β, and γ)
- Binding sites for multiple modulators (including Bz)
- α subunit has 6 forms (α₁ - α₆) thought to confer specificity of Bz action

---

**BzRA Efficacy: Nocturnal Sleep**

![Graph showing median sleep latency over months](image)

* median sleep latency: time required to fall asleep

Krystal et al., Sleep 2003 26; 793-799

---

**BzRA Efficacy: Daytime Improvements**

- Recent studies with intermediate-acting BzRAs (e.g., eszopiclone and zolpidem CR) document that these drugs can improve daytime function (e.g., alertness) in patients with insomnia relative to placebo.

Krystal et al., 2003 Sleep Vol. 26., No. 7
Krystal et al., 2008 Sleep Vol. 30, No. 1

---

**Insomnia Medications: Potential for Adverse Effects**

- Daytime drowsiness
- Cognitive and psychomotor impairment
- Dependence
- Rebound insomnia


---

**Insomnia Medications: Recent Concerns**

- Allergic reaction including angioedema
- Complex sleep-related behaviors (CSB). Wake-like behavior, e.g., driving, performed without full cognitive awareness and for which the patient is subsequently amnestic. Incident and relationship to specific drugs or drug classes is unknown.

Melatonin and the Biological Clock

Adapted from Breslinski A. New England Journal Medicine 1997; 336:186-195

Melatonin Agonists: Ramelteon

- High selectivity and potency for MT1/MT2
- Negligible affinity for other active binding sites, including Bz, DA, and opiate receptors

Ramelteon should not be used in patients with severe hepatic impairment or in combination with fluvoxamine.

Kato K et al. Neuropsychopharmacology 2005; 28:301-310

Melatonin Agonists: Efficacy


Residual Pharmacologic Effects

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=103)</th>
<th>Ram 4mg (N=103)</th>
<th>Ram 8mg (N=103)</th>
<th>Ram 16mg (N=106)</th>
<th>Ram 32mg (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Week 3</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Week 5</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

** P<0.05 (LS means for LOCF data)


Abuse Liability of Hypnotics

- Abuse liability assessed as:
- Likelihood of abuse
- Consequences of abuse (toxicity)
- All BzRAs = class IV controlled substances
- MelRAs = non-scheduled


Part III: Treating Insomnia in the Primary Care Setting

Part III: Treating Insomnia in the Primary Care Setting
Defining Success...

- Insomnia patients suffer from a range of daytime deficits, health and quality of life impairments
- Treating sleep symptoms has been shown to improve daytime function, perceived health, and quality of life

ARS: What are the First Questions You Should Ask of All Your Patients to Help You Uncover Sleep Problems?

1. Do you have any health conditions that affect your sleep and, if so, do you have a family history of sleep problems?
2. Are you having difficulty falling asleep and, if so, does it affect you during the day?
3. Are you taking any medications that interfere with your sleep or help you sleep?
4. How long does it take you to fall asleep and how much sleep do you get each night?

Two Questions to Ask All Patients....

1. Do you have any health conditions that affect your sleep and, if so, do you have a family history of sleep problems?
2. Are you having difficulty falling asleep and, if so, does it affect you during the day?
3. Are you taking any medications that interfere with your sleep or help you sleep?
4. How long does it take you to fall asleep and how much sleep do you get each night?

Follow-Up Questions

For patients answering “yes” to 1 and 2:
- How does it affect you during the day?
- How long has this been a problem?
- Are you taking anything to help with this? If so, what?

Why Can't My Patient Sleep?

- Medications
- Are all comorbidities accounted for?
- Depression
- Substance abuse
- Primary sleep disorder

Insomnia Management: Where Do I Start?

Considerations for patient care include:
- Duration of treatment – long-term or short?
- Patient’s participation – is the patient likely to comply with behavioral interventions?
- Potential for adverse effects
- Abuse liability
Consider Likely Duration of Treatment?

- Acute insomnia (<4 weeks) can often be managed with a short course of hypnotics as the acute stress is resolved.
- Treatment of chronic insomnia often involves multiple types of therapy (e.g., hypnotics, CBT).

Objective: Practice Parameters to Enhance the Diagnosis and Treatment of Insomnia

1. Add sleep to ROS in order to identify patients presenting with other complaints
2. Facilitate patient education about sleep hygiene (e.g., handouts, Web pages)
3. Develop protocols to utilize full range of available treatments as well as fall-back strategies when initial therapy fails

Additional Tools for the Evaluation ofInsomnia

- Sleep diaries – having patients keep a sleep diary for two weeks can help identify sleep symptoms as well as precipitating factors.
- Polysomnography – for patients who snore and suffer from daytime sleepiness, polysomnography (overnight sleep study) can identify sleep disordered breathing.

Online Sleep Education Resources

Visit SleepFoundation.org for:

- Articles on sleep disorders such as insomnia and sleep apnea as well as a range of topics that may affect sleep (aging, depression, COPD, pain, fibromyalgia, pregnancy, etc.)
- Sleep-themed games, quizzes, and other interactive educational tools
- Downloadable sleep diaries

Broad Approaches to Insomnia Treatment:

- Sleep hygiene education only
- Combination of behavioral/pharmacological
- Pharmacotherapy only

Objective: Components of an Effective Risk-Benefit Analysis Leading to an Insomnia Treatment Plan

1. Complete a thorough evaluation, including history and physical exam
2. Assess degree of functional impairment
3. Consider the risks/benefits of alternative therapies
4. Weigh the risks/benefits against those of pharmacotherapy based on available data
5. Assess abuse potential and adverse events
My Patient has Insomnia. Now what?

If the problem is acute (< 4 weeks),
  a. Identify precipitant and reverse where possible (e.g., new medication, incomplete post-op pain control, acute stress)
  b. Education of sleep hygiene
  c. Short course of medications if insomnia is likely to pose risks

Case Study #1
Ellen – 80 yo Female

- Presenting complaint: worsening insomnia and fatigue over the past two years
- Suffers from chronic arthritis
- Poor sleep 4-7 nights per week
- Fatigue is worse after poor night of sleep
- Difficulty falling asleep most prominent, but also wakes too early (3-4 AM)

Case Study #1 Considerations for Treatment

- Sleep symptoms
- Daytime deficits
- Comorbidity
- Adverse effects with BzRAs (e.g., dependence, psychomotor impairment)

Case Study #1 – Question 1

How would you manage this patient’s sleep complaint?

1. BzRA
2. MeIRA
3. CBT
4. Observation/reassurance

For Chronic or Recurrent Insomnia...

Develop a longer-term strategy:
  a. Identify precipitants/exacerbants and reverse where possible (e.g., medications)
  b. Identify comorbidities and optimize current treatment (e.g., DM, depression)
  c. Educate on sleep hygiene
  d. If another sleep disorder is suspected or patient fails to respond to therapy, consider polysomnography

Are Daytime Symptoms Present?

- If there are no evident daytime consequences, educate on sleep hygiene and follow conservatively
- If daytime symptoms are present,
  a. Consider behavioral therapy in all patients with chronic insomnia, but particularly in those who will not or should not take hypnotics
  b. Consider pharmacologic therapy
When Selecting Pharmacotherapy for Insomnia, Consider that…

- Approved agents are preferable to off-label agents
- Newer BzRAs are preferable to older ones

Specific Considerations for Insomnia Pharmacotherapy...

- Age of the patient
- Sleep maintenance insomnia
- Respiratory compromise
- History of substance abuse

Case Study #2

Carolina – 29 yo Female

- Presents with sleep onset insomnia since a break-up six months ago
- Reports feeling “very sad”
- Uses alcohol as a sleep aid
- Medical history non-contributory
- Family history of depression

Case Study #2 - Question 1

- At this point in the evaluation, the most likely diagnosis for this patient is:
  1. Primary insomnia
  2. Insomnia comorbid with alcoholism
  3. Insomnia comorbid with depression

Case Study #2 - Question 2

- What is the appropriate management strategy for a patient with comorbid depression and chronic insomnia?
  1. Manage the depression first, then the insomnia.
  2. Manage the insomnia first, then the depression.
  3. Manage the depression and insomnia concurrently.
  4. Refer to a psychiatrist and a sleep specialist.

Case Study #3

Allison – 35 yo Female

- Eight months pregnant
- Presents with insomnia due to anxiety about pregnancy, labor, birth, and motherhood
Case Study #3 – Question 1

If pregnancy-specific approaches & sleep hygiene are inadequate, how would you manage this patient’s sleep complaints?
1. Reassure patient that this is a “normal part of pregnancy”
2. Add diphenhydramine 25-50 mg qhs
3. Add zolpidem 10 mg qhs prn
4. Add temazepam 7.5-30 mg qhs prn

Pregnancy Safety Classification - Commonly Used Medications for Sleep Disorders

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>B</td>
</tr>
<tr>
<td>Z-Drugs</td>
<td>B</td>
</tr>
<tr>
<td>Melatonin</td>
<td>C</td>
</tr>
<tr>
<td>褪黑素受体激动剂</td>
<td>C</td>
</tr>
<tr>
<td>褪黑素受体拮抗剂</td>
<td>C</td>
</tr>
<tr>
<td>褪黑素受体激动剂</td>
<td>C</td>
</tr>
</tbody>
</table>

Note: ramelteon is Pregnancy Category C (Physicians Desk Reference)

Case Study #4

Liam – 50 yo Male

New patient reports history of chronic insomnia
Prescribed zolpidem 10 mg qhs since divorce almost three years ago
Recently discontinued because of lapsed prescription – recurrence of symptoms x 2 nights
Medical history includes hypertension, hypercholesterolemia, GERD

Case Study #4 Question 1

Based on this patient’s clinical presentation, how do you proceed?
1. Resume BzRA
2. Discontinue BzRA, initiate CBT
3. Discontinue BzRA, observe/re-evaluate
4. Evaluate for possible primary sleep disorder

Alternate Treatment Approaches

- Inadequate efficacy:
  - Review sleep hygiene, add CBT?
  - Alternate drug class
- Daytime sedation, psychomotor symptoms:
  - Reconsider CBT
  - Switch to MelRA
- "Pharmacokinetic failure:"
  - Tailor duration of action to sleep complaint and morning function
Approved BzRA Hypnotics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg)</th>
<th>Half-life (h)</th>
<th>Class</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flurazepam HCL</td>
<td>15 or 30</td>
<td>47-100</td>
<td>BZDP</td>
<td>1970</td>
</tr>
<tr>
<td>Quazepam</td>
<td>7.5 or 15</td>
<td>39-73</td>
<td>BZDP</td>
<td>1979</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5, 15 or 30</td>
<td>3.5-18.4</td>
<td>BZDP</td>
<td>1982</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1, 2, or 3</td>
<td>6.0</td>
<td>NON-BZDP</td>
<td>2004</td>
</tr>
<tr>
<td>Zolpidem MR</td>
<td>6.25 or 12.5</td>
<td>1.4-4.5*</td>
<td>NON-BZDP</td>
<td>2005</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125 or 0.25</td>
<td>1.5-5.5</td>
<td>BZDP</td>
<td>1979</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5 or 10</td>
<td>1.4-4.5</td>
<td>NON-BZDP</td>
<td>1993</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>5 or 10</td>
<td>1.0</td>
<td>NON-BZDP</td>
<td>1997</td>
</tr>
</tbody>
</table>

*Modified absorption prolongs duration of action.

Summary

- Insomnia is a common complaint associated with daytime impairment
- Insomnia is most often comorbid with other conditions
- Insomnia has independent effects on comorbid conditions, daytime function, and QOL, and merits treatment
- New developments in therapy provide a wide range of empirically supported treatment options