Insomnia Pharmacotherapy
A Practical Guide for Primary Care

Fortis Spectrum is the educational partner for this session.
Session 7: Insomnia Pharmacotherapy: A Practical Guide for Primary Care

Learning Objectives

- 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

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Family Physician, Collegeville Family Practice
Medical Director, Ursinus College
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Paul P. Doghramji, MD, is cofounder of Brookside Family Practice & 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 has moved his practice location to Collegeville Family Practice in Collegeville, Pennsylvania, both subsidiaries of Pottstown Medical Specialists, Inc. Dr Doghramji received his medical degree from Jefferson Medical College in Philadelphia and completed his residency in family practice at Chestnut Hill Hospital, also in Philadelphia. He is a fellow of the American Academy of Family Physicians, a member of the National Headache Foundation and Chronic Fatigue and Immune Dysfunction Syndrome Association. He has been certified by the American Board of Family Practice in 1985, and has been recertified every six years since then.

Karl Doghramji, MD
Professor, Jefferson Medical College
Thomas Jefferson University
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Dr Doghramji is professor in the Department of Psychiatry and Human Behavior at Jefferson Medical College of Thomas Jefferson University in Philadelphia, Pennsylvania, and director of the Sleep Disorders Center at Thomas Jefferson University Hospital, also in Philadelphia. Dr Doghramji is also chair of the Albert M. Biele, MD, Memorial Lectureship in Psychiatry in the Department of Psychiatry and Human Behavior at Jefferson Medical College. Dr Doghramji received his medical degree from Jefferson Medical College and completed his internship in internal medicine at Presbyterian–University of Pennsylvania Medical Center in Philadelphia, his residency in psychiatry at Thomas Jefferson University Hospital, and his clinical research fellowship in sleep disorders medicine and polysomnography at Montefiore Medical Center/Albert Einstein College of Medicine in the Bronx, New York. He is also an Academic Associate in the Adult Division of the Institute of the Psychoanalytic Center of Philadelphia.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:

Dr Doghramji, MD, receives honoraria and speaker fees from Takeda Pharmaceuticals North America, Inc.; sanofi-aventis U.S.; and Sepracor, Inc.

Dr Doghramji receives speaker fees from GlaxoSmithKline; Boehringer Ingelheim Pharmaceuticals, Inc.; Jazz Pharmaceuticals; Takeda Pharmaceuticals North America, Inc.; sanofi-aventis U.S.; and Sepracor, Inc. He also receives consulting fees from sanofi-aventis, U.S. and owns stock in Merck & Co., Inc.

Education Partner Financial Disclosure Statements

The content collaborators at Fortis Spectrum have reported that they have no disclosures to report.

Drug List

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<td>Sonata</td>
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### Generic
- ramelteon
- tiagabine hydrochloride
- gabapentin
- pregabalin

### Trade
- Rozerem
- Gabitril
- Neurontin
- Lyrica

### Investigational
- agomelatine
- indiplon
- epilvanserin
- M100907
- ritanserin
- gaboxadol
- NGD96-3

### Off-Label
- Valdoxan
- trazodone
- nefazodone hydrochloride
- mirtazapine
- doxepin
- Desyrel
- Serzone
- Remeron
- Adapin, Sinequan

### 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%
- Other Sleep Disorders 9%
- Medical Disorders 11%
- No DSM-IV Diagnosis 24%

No DSM-IV Diagnosis 24%
Psychiatric Disorders 44%
Other Sleep Disorders 9%
Medical Disorders 11%
Primary Insomnia 16%

National Institutes of Health State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults June 13-15, Sleep 2005 Vol. 28

Ohayon MM. Sleep Medicine Review 2002; 6:97-111
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

Insomnia in Primary Care

Time to Response Based on Clinical Global Impression-Improvement Scale

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
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

*National Institutes of Health State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults June 13-15, Sleep 2005; Vol. 28

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

Morin et al., JAMA 1999;281:991-999

Efficacy of CBT

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

Pre-Treatment Post-Treatment
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”

Nutraceutical Therapies

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

Advantages:
- Prescription not needed

Disadvantages 1,2:
- Efficacy not consistent
- Limited supporting studies on efficacy in treating insomnia
- Potential for residual effects
- No well-defined effective dose
- Rapid onset of tolerance

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

Most Common Rx for Insomnia


**Diphenhydramine Tolerance**

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

Sleep latency = time required to fall asleep

**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**

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

*Median Sleep Latency*: Completed, Observed, and LOCF

*p<0.005; ESZ vs. PBO for all comparisons*

**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

**Insomnia Medications: Potential for Adverse Effects**

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

2. Krystal AD, Sleep Medicine Alert, National Sleep Foundation 2004 9:3

**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.

FDA Requests Label Change for All Sleep Disorder Drug Products, March 14, 2007
Melatonin and the Biological Clock

Adapted from Brzezinski 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; 48:301-310

Melatonin Agonists: Efficacy


Residual Pharmacologic Effects

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<td>3.5</td>
<td>3.6</td>
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</table>

All testing 1 hours post-dose. All comparisons N.S.

Emran M et al. Sleep Medicine. 7:17-24, 2006

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

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.

Two Questions to Ask All Patients....

1. Are you having difficulty sleeping?
2. If yes, does this problem affect you during the day?

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

Objective: Components of an Effect 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

Additional Tools for the Evaluation of Insomnia

- 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

My Patient has Insomnia. Now what?
If the problem is acute (< 4 weeks),
- Identify precipitant and reverse where possible (e.g., new medication, incomplete post-op pain control, acute stress)
- Education of sleep hygiene
- Short course of medications if insomnia is likely to pose risks
Case Study #1
Ellen – 80 Year-Old 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)

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. MelRA
  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

National Institutes of Health State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults June 13-15, Sleep 2005 Vol. 28
Specific Considerations for Insomnia Pharmacotherapy...

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

Case Study #2 Carolina – 29 Year-Old 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

- How would you manage this patient’s sleep complaint?
  1. Start anti-depressant medication and follow insomnia symptoms
  2. Start CBT for depression and insomnia
  3. Start anti-depressant and insomnia pharmacotherapy

Case Study #3 Allison – 35 Year-Old 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

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<td>Sonata</td>
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</table>

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

Pien GW and RJ Schwab, Sleep 2004 27(7): 1405-17

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Case Study #4
Liam – 50 Year-Old 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

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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

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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

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Try, Try Again?

- When should you try alternative pharmacotherapy?

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Approved BzRA Hypnotics

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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