How to Get Your ZZZ's: Pharmacologic Treatment Options for Insomnia

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Disclosure Statement

- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose

Learning Objectives

At the completion of this activity, the participant will be able to:

1. Identify causes and symptoms of insomnia
2. Compare and contrast pharmacologic and non-pharmacologic treatments for insomnia
3. Examine the therapeutic treatment plan for insomnia based on patient specific factors

Disease State Review

Prevalence

- Insomnia symptoms occur in approximately 33% -50% of the adult population
- 6-10% of adults have insomnia disorder
- More common in women and older adults
- Estimated $30- $107 billion is spent on insomnia each year
- Estimated $63.2 billion lost in terms of workplace productivity in 2009

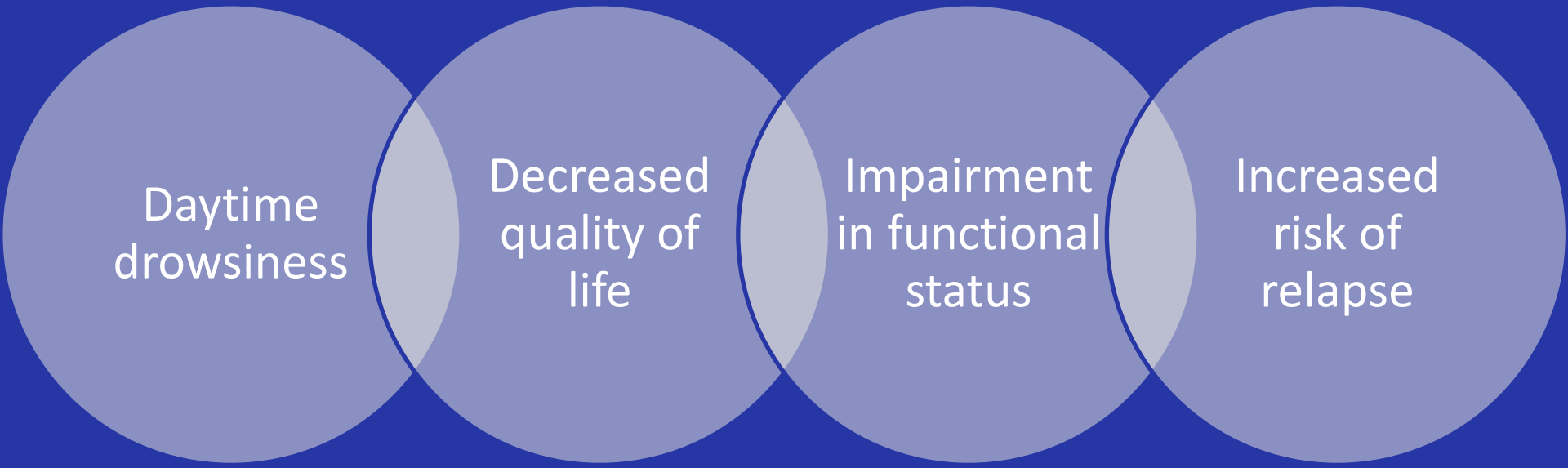
Physiology of Sleep

Non-rapid eye movement (NREM) sleep	• ~75% of total sleep • Heart rate and respiratory rate slow and regular
Rapid eye movement (REM) sleep	• ~25% of total sleep time • Heart rate, respiratory rate, and blood pressure may be irregular

Sleep Requirements

- Varies per individual
- Adults (18-64 yo) are recommended to sleep at least 7 hours/night
  - Less than 6 hours is associated with worsening health outcomes
    - Diabetes
    - Obesity
    - Heart disease
    - Depression
- 65+ should get at least 7-8 hours of sleep

Why is Insomnia a Concern?



Diagnosis

Initial Evaluation

- General medical/psychiatric questionnaire
- 2-week sleep log and sleep diary data
- Epworth sleepiness scale or other sleepiness assessment
- Assessment: symptom review, bed partner interview

Sleep Diary

- Time to bed
- Time falling asleep and waking
- Daytime napping
- Caffeine intake and time
- Alcohol consumption
- Medications
- Exercise routine

Signs and Symptoms

Nighttime complaints	Daytime complaints
• Difficulty falling asleep • Maintaining sleep • Waking multiple times a night • Waking too early	• Not feeling rested • Excessive daytime sleepiness • Fatigue • Lack of concentration • Memory impairment

Epworth Sleepiness Scale

ProHealth PHYSICIANS
Part of OptumCare®

ProHealthMD.com

The Epworth Sleepiness Scale

Name: _____ Today's date: _____

Date of birth: _____

How likely are you to doze off or fall asleep in the situations listed below, in contrast to feeling just tired? This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing (0–3)
1. Sitting and reading	_____
2. Watching TV	_____
3. Sitting, inactive, in a public place (for example, in a movie theatre or meeting)	_____
4. As a passenger in a car for an hour without a break	_____
5. Lying down to rest in the afternoon, when permissible	_____
6. Sitting and talking to someone	_____
7. Sitting quietly after a meal without alcohol	_____
8. In a car, while stopped for a few minutes in traffic	_____

About the Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) was developed in 1990 by Dr. Murray Johns of Melbourne, Australia. He was the first person in Australia to earn a Ph.D. in sleep medicine and the first to start a private practice focused on sleep medicine. His interest in drowsiness led him to create the ESS. Since then, it's become a worldwide standard method for measuring a person's inclination to sleep during the day.

DSM-5 Insomnia Disorder

- Dissatisfaction with quantity or quality of sleep at least 3 nights a week for at least 3 months and associated with 1 or 2 of the following
  - Difficulty falling asleep
  - Difficulty staying asleep
  - Early morning awakenings
- Causes clinically significant distress or impairment
- Occurs even when there is enough time for sleep
- Does not occur exclusively during narcolepsy, breathing-related sleeping disorders, circadian rhythm sleep disorders, or parasomnia
- Does not occur exclusively during the course of another mental disorder
- Not due to the direct psychologic effects of a substance

Treatment

Treatment

Goals

- Improve sleep quality and quantity
- Alleviate distress or dysfunction

Strategies

- Identify and resolve reversible causes
- Mix of psychological therapies, pharmacologic therapy, or a combination of both

Differential Diagnosis

- Co-occurring disorders
- Psychiatric illness
- Sleep hygiene practices
- Circadian rhythm changes
- Medications

Conditions Associated with Insomnia

Psychiatric Disorders	Substances	Sleep Disorders	Other Disorders
• Anxiety • Dementia • Mood disorders	• Alcohol • Stimulants • Nicotine	• Restless legs syndrome • Sleep apnea	• Asthma • Epilepsy • Heart failure • GERD

GERD: Gastroesophageal reflux disease

Contributing Medications

Antidepressants	• SSRI, SNRIs, bupropion, monoamine oxidase inhibitors
Stimulants	• Caffeine, methylphenidate, amphetamine derivatives, ephedrine
Decongestants	• Pseudoephedrine, phenylephrine, and phenylpropanolamine
Narcotic analgesics	• Oxycodone, codeine, propoxyphene
Cardiovascular	• Beta blockers, alpha receptor agonist and antagonists, diuretics
Pulmonary	• Theophylline, albuterol, and steroids

SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitors

Nonpharmacologic Therapy

Behavioral Interventions: Initial Approach

Cognitive behavioral therapy (CBT)	• In-person or group therapy • Comparable efficacy to pharmacological therapy short-term
Brief behavioral treatment for insomnia	• Shorter duration than CBT • 4 weekly sessions • Sleep restriction and stimulus control
Stimulus control	• Establish consistency in sleep patterns • Only go to sleep when tired
Relaxation strategies	• Guided imagery • Abdominal breathing • Muscle relaxation

Overall Sleep Hygiene

- Regular time to bed and for waking
- Dedicate time to wind-down before bed
- Exercise during day, limit exercise at night
- Avoid late, heavy meals
- Bedroom for sleep
- Minimize caffeine and alcohol in evenings

Pharmacotherapy

Classes of Medications

Benzodiazepine receptor agonists (nonbenzodiazepines and benzodiazepines)

Melatonin receptor agonist

Histamine receptor antagonist

Dual orexin receptor antagonist (DORAs)

Benzodiazepines (BZRAs)

Name	Dosing	Use	Comments
Temazepam	Usual: 15-30 mg nightly Elderly or debilitated: 7.5 mg nightly	• Sleep onset • Sleep maintenance/ mixed insomnia	• Short to intermediate acting • Take immediately before bed • Do not take with or right after a meal
Triazolam	Usual: 0.25 mg nightly Max 0.5 mg nightly Elderly: 0.125 mg nightly Max 0.25 mg nightly	• Sleep onset	• Short acting • Take immediately before bed • Do not take with or right after a meal

BZRA Class Effects

Drug interactions	Adverse effects	Warnings/ precautions
• Avoid in combination with CYP3A4 inhibitors, avoid alcohol and other sedatives	• Somnolence, drowsiness, dizziness	• SUD, sleep walking, rebound insomnia • Tolerance can develop • Risk of dependence • Beers criteria list • Typically only used short-term

SUD: substance use disorders

Nonbenzodiazepines (NBRA)

Name	Dosing	Use	Comments
Eszopiclone	Usual: 2-3 mg nightly Elderly: 1 mg nightly (max 2)	• Sleep onset • Sleep maintenance/mixed	• Intermediate acting • No short term use restriction
Zolpidem IR	Usual: 10 mg nightly Elderly and females: 5 mg nightly	• Sleep onset • Intermezzo® (3-5 mg) for maintenance if >4 hours sleep remains	• Short to intermediate acting
Zolpidem CR	Usual: 12.5 mg nightly Elderly: 6.25 mg nightly	• Sleep onset • Sleep maintenance/mixed	• Controlled release so swallow whole • Typically use if failed zolpidem IR
Zaleplon	Usual: 10 mg nightly (max 20) Elderly: 5 mg daily	• Sleep onset • Sleep maintenance (if 4 hours remaining for further sleep)	• Use max 5 mg if patients are taking with cimetidine • Short acting

IR: immediate release; CR: controlled release

NBRA: Class Effects

Drug interactions	Adverse effects	Warnings/ precautions
• Avoid in combination with CYP3A4 inhibitors, avoid alcohol and other sedatives	• Somnolence, drowsiness, dizziness	• SUD • Complex sleep-related behavior • Rebound insomnia and anxiety

SUD: substance use disorders

Histamine Receptor Antagonist

Name	Dosing	Use	Comments
Doxepin	Usual: 6 mg nightly Elderly: 3 mg nightly	• Sleep maintenance/ mixed insomnia	• Take within 30 minutes of bedtime • Do not take within 3 hours of a meal

Histamine Receptor Antagonist

DDI	ADE	Warnings/ Precautions
• MAOIs • SSRIs • Anticholinergics	• Somnolence, nausea, anticholinergic side effects	• Avoid in patients with untreated angle-close glaucoma or severe urinary retention

SSRI: selective serotonin reuptake inhibitor; MAOIs: monoamine oxidase inhibitors; DDI: drug drug interaction; ADE: adverse drug events

Dual Orexin Receptor Antagonist (DORAs)

Name	Dosing	Use	Comments
Suvorexant	Usual: 10-20 mg daily Avoid in hepatic impaired	• Sleep onset • Sleep maintenance/ mixed insomnia	• Take immediately before bed • Plan for at least 7 hours before awakening
Lemborexant	Usual: 5-10 mg daily Max 5 mg in hepatic impaired	• Sleep onset • Sleep maintenance/ mixed insomnia	• Take within 30 minutes of going to bed • Plan for at least 7 hours before awakening
Daridorexant	Usual: 25-50 mg daily Max 25 mg in hepatic impaired	• Sleep onset • Sleep maintenance/ mixed insomnia	• Take within 30 minutes before going to bed • Plan for at least 7 hours before awakening

Dual Orexin Receptor Antagonist (DORAs)

DDI	ADE	Warnings/ precautions
• CYP3A4 inhibitors and inducers	• Somnolence, drowsiness, dizziness • Next day sleepiness due to duration of action	• Abnormal thinking • CNS depression • REM sleep effects • Depression

DDI: drug drug interaction; ADE: adverse drug event; CNS: central nervous system; REM: rapid eye movement

Melatonin Receptor Agonist

Name	Dosing	Use	Comments
Ramelteon	Usual: 8 mg nightly Severe hepatic impairment: Avoid	• Sleep onset	• No short-term use restriction • Avoid taking with or soon after a high fat meal • Take within 30 minutes of bed

Melatonin Receptor Agonist

DDI	ADE	Warning/ precautions
• Fluvoxamine • CYP1A2 inhibitors • CYP3A4 inhibitors and inducers	• Dizziness, somnolence, nausea, fatigue, prolactinoma	• Abnormal thinking • Sleep changes (sleep walking/sleep talking/cooking/ driving) • Depression

DDI: drug drug interaction; ADE: adverse drug event

Off Label Medications

Antidepressants and anxiolytics	Antiepileptics	Antihypertensives
Antipsychotics	OTC	Herbals

OTC: over the counter

Sedating Antidepressants

Primary role is the management of insomnia associated with depression

Trazodone

- Small improvement in sleep quality with short-term use vs placebo
- Most evidence is in patients with depression or those experiencing insomnia secondary to antidepressant treatment
- AASM and VA/DoD recommend against its use

Mirtazapine- lower doses may be more sedating

AASM: American Academy of Sleep Medicine; VA: Veterans Affairs

Antipsychotics

AASM, American Psychiatry Association, and ESRS recommend against routine use

Low-dose quetiapine at bedtime, although sedating, is not recommended for insomnia unless a comorbid psychiatric disorder exists

AASM: American Academy of Sleep Medicine; ESRS: European Sleep Research Society

OTC Antihistamine

Recommended against by several guidelines

Diphenhydramine and Doxylamine

If used avoid for longer than 3-4 days because tolerance to the hypnotic effect may develop

Particularly risky for older adults, anticholinergic (e.g., urinary retention, confusion, dry mouth) and CNS depression side effects possible

CNS: central nervous system

Natural Products

Melatonin

- Most promising but data not robust
- Well-tolerated and available over the counter

Valerian

- Insufficient evidence
- Abrupt withdrawal may mimic benzodiazepine withdrawal
- Reported cases of hepatoxicity

Chamomile

- Insufficient evidence
- Consider interactions with anticoagulants and antiplatelets

Kava Kava

- No longer recommended due to hepatotoxicity

Special Populations

Benefits in Older Adults

Eszopiclone	• Remission, total sleep time and wake after sleep onset
Ramelteon	• Reduced sleep onset latency
Zolpidem	• Reduced sleep onset latency
Suvorexant	• Increased treatment response, total sleep time
Doxepin	• Reduced sleep onset latency, total sleep time and wake after sleep onset

Pregnancy and lactation

Pregnancy

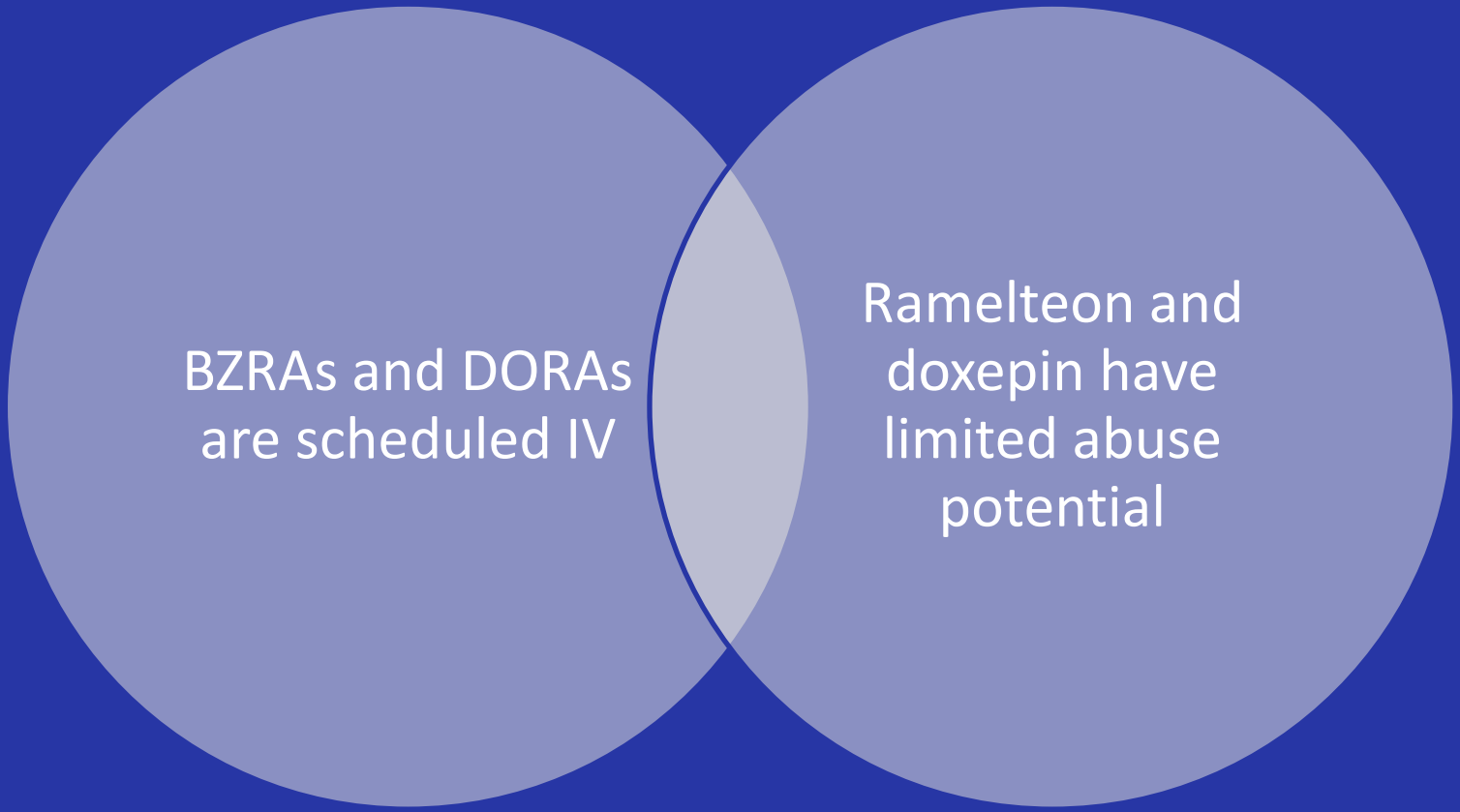
- Non-pharm methods preferred
- BZDs→ may cause congenital malformations
- NBRAs→ neonatal withdrawal symptoms possible
- Ramelteon → increases risk of structural abnormalities
- Suvorexant→ decreased body weight in animal trials

Lactation

- Non-pharm methods preferred
- BZDs→ temazepam decreases excretion into milk
- NBRAs→ not recommended
- Ramelteon→ unknown

BZDs: benzodiazepines; NBRAs: nonbenzodiazepine receptor agonists

Substance Use Disorders



BZDs: benzodiazepines; DORAs: dual orexin receptor antagonists

Choosing an Agent

Choosing an Agent: Factors to Consider

Type of insomnia: Sleep onset vs sleep maintenance vs both	Prior treatment response	Formulary/patient cost
Comorbid conditions	Side effects and contraindications	Patient preference

Choosing an Agent

Sleep onset	Sleep maintenance	Both
• Ramelteon • Zaleplon • Zolpidem IR • Triazolam	• Zolpidem CR • Middle of the night Intermezzo or Zaleplon dosing • Doxepin	• Eszopiclone • Temazepam • Suvorexant • Lemborexant

Follow-up

Follow-up

Sleep changes	Clinical reassessment	Long term
• Collect sleep diary during course of treatment and every 6 months thereafter	• Administer questionnaires, survey instruments every few weeks until stable	• Follow up at least every 6 months

Ineffective Therapy

Assess response

Reevaluate for comorbid disorders

Consider switching to another agent in the same class or use alternative first line agent

Combine BZRA or ramelteon AND sedating antidepressant

BZDs: benzodiazepines

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Need More Information?

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