Insomnia Across the Lifespan: Treating this common condition

Presented by:
Wendy L. Wright,
DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP

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Wendy L. Wright,
DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP

Owner and President:
Adult/Family Nurse Practitioner
Wright & Associates Family Healthcare, Amherst
Owner – Partners in Healthcare Education, LLC

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Disclosure

- Speaker Bureau
  - Sanofi-Pasteur, Merck, Pfizer – Vaccines
  - AbbVie and Biohaven – Migraines
  - Idorsia – Insomnia
- Consultant
  - Sanofi-Pasteur, Merck, Pfizer, Moderna, and Seqirus – Vaccines
  - GlaxoSmithKline – OA and Pain
  - Bayer – Chronic Kidney Disease
  - Idorsia – Insomnia
  - Shield Therapeutics – Iron Deficiency Anemia

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Objectives

- At the end of this presentation, the participant will be able to:

1. Discuss the incidence and prevalence of insomnia across the lifespan.
2. Identify the appropriate work-up of the individual with insomnia.
3. Compare nonpharmacological and pharmacological treatment options for the patient with insomnia.

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Tips

- References
  - Listed at the end of the presentation
- To facilitate your learning
  - Specific tables/images can be viewed full page at the end of your handout.

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What is insomnia?

Insomnia
- Difficulty initiating or maintaining sleep; sleep that is nonrestorative despite having an adequate opportunity and no abnormal environmental circumstances; and accompanied by daytime somnolence[1]

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What is insomnia? (continued)

- DSM-V definition[2]
  - Difficulty initiating ***and/or***
  - Difficulty maintaining ***and/or***
  - Waking earlier than desired ***AND***
  - Occurring at least 3 nights per week for at least 3 months ***AND***
  - Dissatisfaction with sleep

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DSM-5 Diagnostic Criteria[3]

Focus	Criteria
Sleep problem	A predominant complaint of dissatisfaction with sleep quantity or quality, associated with ≥1 of the following sxs: 1. Difficulty initiating sleep 2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakening 3. Early-morning awakening with inability to return to sleep
Functional effects	The sleep disturbance causes clinically significant distress or impairment in social, occupational, education, academic, behavioral, or other important areas of functioning
Frequency	The sleep difficulty occurs at least 3 nights per week
Duration	The sleep difficulty is present for at least 3 months
Further clarification	1. The sleep difficulty occurs despite adequate opportunity for sleep 2. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, breathing-related disorder, circadian rhythm, parasomnia) 3. The insomnia is not attributable to the physiologic effects of a substance 4. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia

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Eleven Sleep-Wake Disorders

- Insomnia disorder
- Hypersomnolence disorder
- Narcolepsy
- Obstructive sleep apnea hypopnea
- Central sleep apnea
- Sleep-related hypoventilation
- Circadian rhythm sleep-wake disorders
- Non–rapid eye movement (NREM) sleep arousal disorders
- Nightmare disorder
- Rapid eye movement (REM) sleep behavior disorder
- Restless legs syndrome and substance- /medication-induced sleep disorder

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Burden of Insomnia

- There are about 70 million Americans who have problems with sleep.
- Short-term insomnia affects 30–50% of the population.
- From 2013 U.S. Census Data, it is estimated that ~23.7 million people have symptoms consistent with the diagnosis of insomnia.[4,5]

Figure 1

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How common are the symptoms of insomnia?

- Affects up to 30–48% of the population
- 9–15% have daytime sleepiness and impairment
- Approximately 8–18% report unhappiness with sleep
- 6% meet DSM 5 Diagnostic Criteria

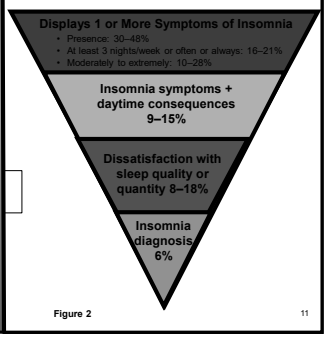

Figure 2

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Insomnia

- Insomnia is now a diagnosis of its own entity.
  - Prevalence is much higher in individuals with chronic medical or psychiatric conditions.
- It may or may not be caused by other conditions.

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Insomnia and the Older Adult

- Older patients with insomnia more often experience trouble sleeping through the night and waking up too early than difficulty falling asleep.[6]
- Insomnia is not inherent with older age, but advancing age is associated with changes in sleep physiology, including a decrease in total sleep time and increases in arousals and awakenings secondary to lighter and more fragmented sleep.[7]
- The elderly also experience a phase advance, or earlier bedtimes and earlier rise times.

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Insomnia and the Older Adult (continued)

- In addition, medications and medical and psychiatric disorders that are more prevalent in the older population may be interfering with the ability to fall or stay asleep.
- Most medications used to treat insomnia are found on the Beers criteria, thus limiting the clinician's desire to utilize them.

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Acute vs. Chronic Insomnia

- Insomnia can be either acute (short-term) or chronic.
  - Acute (short-term) – Lasts for up to three months
    - It occurs in 15 to 20 percent of people.
  - Chronic insomnia – Lasting longer than three months
    - It is associated with numerous effects on function, health, and quality of life.
    - Chronic insomnia is associated with an increased risk for developing mood disorders, relapsing depression and alcoholism, and hypertension.

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Insomnia Costs Society

- Insomnia costs about $16 billion each year in medical care.
- It is estimated that more than 25% of the population drives while drowsy or nods off while driving
- MVAs are more common in drowsy or sleep-deprived drivers.
- Occupational injuries are more common, as well.

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Typical Adult Sleep Pattern

- Duration
  - 7–8 hours
- Time awake after sleep (WASO)
  - Approximately 30 minutes or less
- Onset to fall asleep
  - 30 minutes or less
- Sleep efficiency
  - Approximately 85% (time asleep/time in bed)

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A Depiction of the Wake-Sleep Circuit

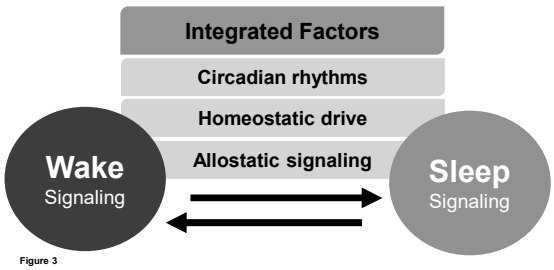

Figure 3

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Neurotransmitters Involved in Sleep and Wakefulness

Wakefulness	Sleep
• Monoamines ▪ Dopamine ▪ Norepinephrine ▪ Serotonin • Acetylcholine • Histamine • Orexin	• Adenosine • GABA • Melatonin • Galanin

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Sleep vs. Wakefulness

- Two interacting brain systems mediate wakefulness and sleep.
- Wakefulness is maintained by the ascending reticular activating system (ARAS) through input from cells that release acetylcholine and monoamine neurotransmitters, including norepinephrine, histamine, dopamine, and serotonin.
  - By acting on components of the ARAS, orexins, which are produced by neurons in the hypothalamus, also promote wakefulness.
- The neurotransmitters γ-aminobutyric acid (GABA) and galanin, which are released by cells in the anterior hypothalamus and basal forebrain, promote sleep by inhibiting the various wake-promoting cells.

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Screening

- Screening may be done with two simple questions
  - "Do you experience difficulty sleeping?"
  - "Do you have difficulty falling or staying asleep?"
- Recommend adding
  - Are you dissatisfied with your sleep?
  - Do you suffer daytime fatigue?
- Biggest issue
  - Clinicians don't want to ask or open pandora's box.

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Another Sleep Assessment Tool

BEARS
Sleep Assessment

B: Bedtime problems i.e., falling asleep
E: Excessive daytime drowsiness
A: Awakenings during the night
R: Regularity of sleep and duration (work schedules, infants, children)
S: Sleep disordered breathing (apnea)

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Work-up of Insomnia

- History
  - ROS
    - Do you suffer from daytime fatigue?
    - Do you snore or have episodes where you stop breathing?
    - Hours in bed, hours asleep; do you feel refreshed?
    - Restless leg symptoms?
    - Any sleep walking, vivid dreams? Night terrors?
    - Any sleep paralysis?

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Work-up of Insomnia (continued)

- History (cont.)
  - Social – Alcohol or drug use
  - Medications
    - Stimulants, decongestants, steroids
  - PMH
    - BPH, overactive bladder, pain, mental health disorders, fibromyalgia, hyperthyroidism, perimenopause, RLS
  - What has been tried?
    - OTC options
    - Alcohol
    - Prescription medications

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Sleep Apnea

- Common cause of insomnia in adults, particularly those who are overweight or obese
- Not all individuals with sleep apnea fit the typical profile.
- Associated with significant risks (i.e., MI, hypertension, obesity, CVA)
- Affects about 10% of the U.S. population
- Sleep study
  - Home sleep study
    - Some insurances now mandating this method
  - In-lab sleep study

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Recurrent Uvulitis – A Clue to Sleep Apnea

- Beefy uvula
- Recurrent sore throat
- Numerous causes but can be a sign of snoring and sleep apnea

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Restless Leg Syndrome

- Common cause of insomnia
- Prior to giving individual medication to treat insomnia or RLS, check ferritin.
- If ferritin <40–50 ng/mL (<90–112 pmol/L), start patient on ferrous sulfate or similar.
  - Ferrous sulfate 65 mg 1 pill BID-TID

- If not effective, consider
  - Ropinirole Hcl (Requip®)
  - Pramipexole (Mirapex®)
  - Gabapentin (Neurontin®)
  - Benzodiazepines

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Children/Young Adults

- Insomnia in children is often indicative of more serious pathology.

- Consider
  - Depression or anxiety
  - ADHD
  - Tonsillar or adenoid hyperplasia
  - Sleep apnea

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Pediatric Hypoventilation Syndrome

- Frequently overweight or obese
- Often diagnosed with ADHD
- Enuresis persistent in over 60% of children; also, **have seen this in adults.**
- May have persistent daytime fatigue
- Diagnosis – Sleep study

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Sleep State Misperception

- Individual believes that they are awake much of the night but actually sleep for a normal period of time each night.
  - They incorrectly believe it takes them an abnormally long time to fall asleep and/or they underestimate how long they remain asleep.
  - Have found the sleep study to be very helpful with identifying this

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Treatment of Insomnia

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Important to Treat Comorbid Conditions

- Pain
- BPH and urinary frequency
- Depression
- Anxiety
- Substances of abuse

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Sleep Hygiene

- Cognitive behavioral therapy
  - Cognitive Behavioral Therapy for Insomnia (CBT-I) that addresses sleep-disruptive beliefs, habits, and physiological factors is recommended as first-line intervention.[8]
  - In older adults, CBT-I has been shown to improve global and sleep outcomes and reduce wake after sleep onset.[8]
  - Difficult to access and expensive
  - Online options now available.

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Sleep Hygiene (continued)

- Sleep hygiene
  - Consistent bedtime
  - Daily exposure to sunlight
  - A quiet and dark room
  - Regular exercise
  - Minimize alcohol and regulate liquid intake.
  - Minimize phone or stimulating activity prior to bedtime.
  - Do not eat a heavy meal within a few hours of bedtime.

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Prescription Digital Therapeutic through CBTi (Somryst™)

- 22 years of age and older
- CBT program which is FDA approved

- Conducted through app/phone/trained providers
- Uses sleep “restriction” and sleep “consolidation”

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OTC and Pharmacologic Agents

Agents	
1. Diphenhydramine	8. Trazodone
2. Melatonin	9. Doxepin
3. Valerian root	10. Triazolam
4. Diphenhydramine	11. Zaleplon
5. Ramelteon	12. Zolpidem
6. Suvorexant	13. Eszopiclone
7. Temazepam	

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Sleep Medications

- Five classes of sleep medications
  - Orexin receptor antagonists
  - Histamine receptor antagonists
  - Non–benzodiazepine γ-aminobutyric acid A ($GABA_A$) agonists
  - Benzodiazepine $GABA_A$ receptor agonists
  - Melatonin receptor agonists

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Pharmacologic Options

- Numerous over-the-counter and prescription pharmacologic agents exist.
- All have varying degrees of efficacy and evidence.
- Unfortunately, many have adverse effects or precautions.

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Alcohol

- Most common “medication” to treat insomnia
- Alcohol used to induce sleep can be a cause of insomnia.
- Long-term alcohol use is associated with a decrease in **non-REM** stage 3 and 4 sleep, as well as suppression of **REM** and **REM** sleep fragmentation.
- Frequent moving between sleep stages occurs, with awakenings due to headaches, urination, dehydration, and sweating.

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Herbal Options

- Melatonin
  - Produced endogenously by the pineal glands
  - Believed to control the circadian pacemaker and promote sleep
  - Trials conducted using dosages of 2 mg
  - Weak efficacy with low quality of evidence (MIXED evidence)
  - 1–10 mg of melatonin dosed nightly

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Herbal Options (continued)

- Melatonin (cont.)
  - Adverse effects
    - Tachycardia, sedation, flushing, itching, headaches, vivid dreams
  - Interactions
    - Melatonin inhibits CYP1A2 substrates and may increase levels of drugs such as fluvoxamine; anticoagulants (increased risk of bleeding)
  - AASM
    - Does not recommend for sleep onset or sleep maintenance

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Herbal Options (continued)

- Valerian
  - Mechanism of action is unknown but is used for insomnia and anxiety.
  - Trials conducted with varying dosages
    - Weak efficacy with low quality of evidence
  - Cautions
    - Discontinue 1-week or more before surgery; interacts with anesthesia
    - Sedation
    - May experience a benzodiazepine like withdrawal after prolonged use

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Herbal Options (continued)

- Valerian (cont.)
  - Avoid in those with liver and pancreatic disease.
  - Avoid in pregnancy and lactation.
  - Drug-drug interactions
    - Benzos (increased effects), CYP2D6 and 3A4 inhibitor
  - AASM
    - Does not recommend for sleep onset or sleep maintenance

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Possible Herb-Drug Interactions

Herbal agent	Interacting drugs	Clinical effect
Danshen	Warfarin	Bleeding
Dong quai	Warfarin	Bleeding
Ephedra	Caffeine, decongestants	Sympathomimetic toxidrome
Garlic	Warfarin	Lowers blood levels
	Chlorpropamide	Hypoglycemia
Ginkgo biloba	ASA, clopidogrel, dipyridamole, warfarin, heparin	Bleeding
	Thiazide diuretic	Elevated blood pressure
	Trazodone	Coma
	Morphine	Lack of effect
Ginseng	Warfarin, ethanol	Lowers BP
	Phenelzine	Induces mania
Kava	Benzos, sedative-hypnotics	CNS depression
	Levodopa	Increased "off" periods
St. John's wort	Antidepressants	Serotonergic stimulation (theoretical)
	Cyclosporin	Decreased effect (CYP450 inducer)
	Digoxin	Decreased serum level
Valerian	Anxiolytics	CNS sedation

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OTC Options

- Diphenhydramine
  - Weak efficacy and low quality of evidence (AASM)
  - Not recommended for use, particularly in those >65 years of age
  - Adult dosing – 12.5–50 mg; maximum 300 mg/day
  - Children dosing – Ages 2 years and up
    - Ages 2–5 years: 6.25 mg PO; maximum 37.5 mg daily
    - Ages 6–11 years: 12.5–25 mg
    - Ages 12 years and older: 25–50 mg PO

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OTC Options (continued)

- Diphenhydramine (cont.)
  - Anticholinergic adverse effects
  - May be used during pregnancy but consider alternative in breastfeeding; may cause CNS depression in infant; may decrease breast milk
  - AASM
    - Does not recommend for sleep onset or sleep maintenance

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Melatonin Receptor Agonist

- Ramelteon (Rozerem®)
  - MOA
    - Binds to the melatonin MT1 and MT2 receptors to induce sleep (melatonin receptor agonist)
  - 8 mg dose
    - Avoid administration with a high fat meal; interferes with drugs absorption
  - Caution
    - Mild-moderate liver disease, caution if smoking habit changes, COPD

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Melatonin Receptor Agonist (continued)

- Ramelteon (Rozerem®) (cont.)
  - Avoid – Severe sleep apnea, avoid with severe impairment
  - Avoid pregnancy and lactation.
  - Based upon evidence – Sleep onset is best effect.
  - Benefits outweigh harm

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Trazodone (Serotonin Modulator)

- MOA – Exact unknown
  - Antagonizes serotonin 5-HT2A/C and alpha-1 adrenergic receptors
- Insomnia
  - Adult: 25–50 mg at bedtime; maximum 200 mg
  - Children: 6–12 years of age
    - 1.5–6 mg/kg/day (for depression only)
- Often used as an adjunct to SSRI treatment
- AASM
  - Does not recommend its use for sleep onset or maintenance

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Trazodone (Serotonin Modulator) (continued)

- Box warning re: suicidality
- Caution
  - Sedation, avoid abrupt withdrawal, alcohol abuse, elderly patients, long QT syndrome, glaucoma, priapism
- Adverse effects
  - Anticholinergic

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Prescription Options

- Tricyclic antidepressants
  - Doxepin (Silenor®)
    - 3–6 mg dosage available
    - 10–50 mg is traditional dose for insomnia. (**staying asleep**)
    - MOA – Antagonizes central H_1 receptors (H_1 receptor antagonist)
    - Carries a box warning because of its class (suicidality) in children and adolescents <24 years of age
    - Avoid in those with glaucoma.

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Prescription Options (cont.)

- Tricyclic antidepressants (cont.)
  - Doxepin (Silenor®) (cont.)
    - Anticholinergic properties, complex sleep-related behavior
    - Consider ECG – QT prolongation
    - Avoid eating within 3 hours of taking medication.
    - Possible teratogenicity based upon limited human data
    - AASM – Recommends for sleep maintenance

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Norepinephrine-Serotonin Modulator

- Mirtazapine (Remeron®)
- Enhances central noradrenergic and serotonergic activity
  - Potent H_1 receptor blocker
  - Dose range: 15–45 mg/day
  - Adverse effects
    - Sedation
    - Increased appetite
    - Weight gain
    - Dizziness
    - Anticholinergic effects

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Controlled Substances

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Prescription Options

- Suvorexant (orexin receptor agent) – Schedule IV
  - Better option for sleep maintenance than sleep onset although indicated for both
  - 5–20 mg; 10 mg is usual starting dose; may take up to 7 nights for benefit
  - Has been studied in adults over age 65 years
  - Maximum – 20 mg per day
  - Give without food for quicker onset of action.
  - Not recommended in severe liver disease
  - Not on the Beers Criteria
  - New indication – Insomnia in patients with Alzheimer's dementia

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Lemborexant (Dayvigo®)[9]

- Indication – Insomnia characterized by difficulties with sleep onset or sleep maintenance.
- Class
  - Orexin receptor antagonist
  - Competition – Suvorexant (Belsomra®) – Schedule IV
- Dosage
  - 5 mg and 10 mg
- Schedule IV
- CYP3A4 substrate (avoid with mod-strong inhibitors)

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Daridorexant (Quviviq™)[10]

- Class
  - Orexin antagonist
- Indication
  - Treatment of individuals with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
- Dosage
  - 25 mg and 50 mg
  - Approved and now available

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Daridorexant[10] (continued)

- 50 mg dose
  - Reduced time to fall asleep by 30 minutes
  - Reduced time await during night by 60 minutes
  - Improved scores on daytime sleepiness
  - Improved over 1-month and continued to improve for 1-year

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Daridorexant[10] (continued)

- Adverse events
  - Headache (6%, 7% vs. 5% placebo)
  - Fatigue (2%, 3% vs. 1% placebo)
  - Nausea (0, 3% vs. 1% placebo)
  - Dizziness (2%, 3%, vs. 2%)

- To prescribe
  - RX needs to be sent to Vita Care Pharmacy in Boca Raton, Florida
  - Not available in pharmacies

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Benzodiazepine receptor agonists (Nonbenzodiazepine hypnotic)

Eszopiclone (Lunesta™) – Schedule IV

- GABA-BZD receptor complex agonist
- 1–3 mg at bedtime
  - Maximum 3 mg
- Maximum 2 mg per day in elderly patient
- Avoid high fat meal.
  - Enhances absorption
- Not indicated in children

- Consider different medication in pregnancy and lactation.
- Taper dose to avoid withdrawal.
- CYP3A4 Substrate
- Avoid in pregnancy and lactation.
- AASM
  - Recommends use for sleep onset and sleep maintenance

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Benzodiazepine receptor agonists (Nonbenzodiazepine hypnotic) (continued)

Zaleplon (Sonata®) – Schedule IV

- GABA-BZD receptor complex agonist
- 5–10 mg
  - Maximum 20 mg at bedtime
- Elderly patients
  - Maximum 10 mg at bedtime
- Mild-moderate liver disease
  - 5 mg maximum
- Avoid with high-fat meal.
- Gradual taper to avoid withdrawal after prolonged use.
- Lactation – May use
- Pregnancy – Avoid use.
- AASM
  - Recommend use for sleep onset.

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Benzodiazepine Receptor Agonists (Nonbenzodiazepine Hypnotic) (continued)

Zolpidem (Ambien®) – Schedule IV

- BZD $GABA_A$receptor agonist
- Women
  - 5 mg at bedtime with maximum of 10 mg
    - 5 mg preferred
  - Should have a minimum of 7 hours of planned "in-bed" time
  - 5 mg maximum in older adults
- Women (cont.)
  - Take on an empty stomach.
  - Gradual taper
  - Avoid in pregnancy.
    - Embryo-fetal toxicity at 25× manufacturers dosing and neonatal withdrawal
    - May use while breastfeeding

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Benzodiazepine Receptor Agonists (Nonbenzodiazepine Hypnotic) (continued)

Zolpidem (Ambien®) – Schedule IV (cont.)

- Men
  - 5–10 mg; maximum 10 mg/day
- Caution
  - Mild-moderate hepatic impairment – Maximum 5 mg
- AASM
  - Recommends for sleep onset and sleep maintenance

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Concerns

- Short-term
  - Complex sleep behaviors
  - Next day sedation
- Long-term
  - Amnesia
  - Dementia
  - Rebound insomnia
  - Withdrawal symptoms if abruptly discontinued after prolonged use

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Benzodiazepines

Temazepam (Restoril™) – Schedule IV

- MOA
  - Binds to benzodiazepine receptors to enhance GABA effects
- Dosage
  - 7.5–30 mg at bedtime
- Sleep terrors
  - 15–30 mg at bedtime
- AASM
  - Recommends use for sleep onset and sleep maintenance
- Caution
  - Respiratory depression, COPD, elderly
- LFTs
  - If using for prolonged period of time; increased AST and ALT
- Lactation
  - May use short-term
  - Avoid use in pregnancy.

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Benzodiazepines (continued)

Triazolam (Halcion®) – Schedule IV

- MOA
  - Binds to benzodiazepine receptors to enhance GABA effects
- Dosing
  - 0.125–0.5 mg at bedtime
- AASM
  - Recommends use for sleep onset
- Avoid use with opioids due to CNS and respiratory depression.
- Caution
  - Taper patients who have used medication for prolonged time; AST and ALT elevation.
- Gastric pH sensitive
  - Medications which alter gastric pH (i.e., PPIs can affect absorption).
- Avoid in both pregnancy and lactation.

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Follow-up

- Patients and providers should not expect to find an effective solution for insomnia in a single visit.
- Early follow-up after medication is started is needed to assess the response.
- Patients should return for follow-up after 4 to 8 weeks for evaluation of efficacy, safety, and the need for ongoing treatment.
- American College of Physician guidelines recommend that patients who require medication for longer than 4–5 weeks should be assessed regularly for the need to continue therapy.

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Conclusions

- Insomnia affects millions of individuals.
- Costs to the individual and society are significant.
- Comprehensive history and PE are essential to rule out secondary causes.
- Numerous treatment options exist.
- Must balance the benefits vs. risks of all treatments.

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I would be happy to entertain any questions you have!

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End of Presentation!
Thank you for your time, attention.

Wendy L. Wright,
DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP

WendyARNP@aol.com

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Image Sources

Figure 1 Microsoft stock image

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