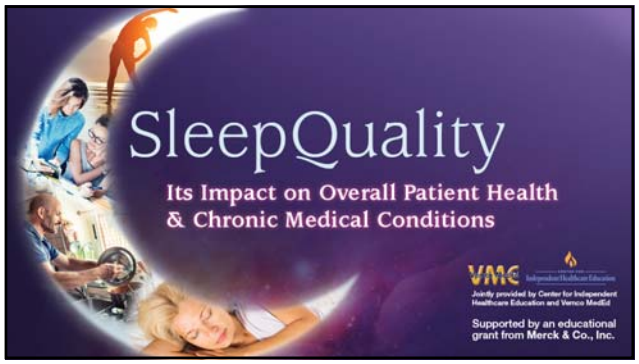


Why Should PCPs be Proactive in Evaluating SLEEP?

Sleep Problems…

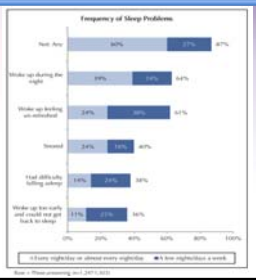
- …are very **prevalent** in primary care
  - But patients don't tell you
- …have **serious consequences**
  - Day-to-day life
  - Poor outcome on mental and physical health
- …are a **clue to other medical conditions**
  - Most insomnias are co-morbid
- …are **easy to identify**

Effective management may **improve outcomes**

- **Majority is done by PCPs**

Prevalence of Sleep Problems in America

Poll of 1503 individuals (age range of 13–64 years) reveals 87% report at least 1 sleep problem for at least a few nights/week.



National Sleep Foundation. 2011 Sleep in America Poll. Available at: https://sleepfoundation.org/sites/default/files/sleepinamericapoll/SIAP_2011_Summary_of_Findings.pdf

Epidemiology of Insomnia

Prevalence of insomnia

- 40–70 million adults in the United States have insomnia (approximately up to 30% of general population)
- 10% of population has associated symptoms of daytime functional impairment
- Up to 50% prevalence in clinical practices
- Greater prevalence in postmenopausal women

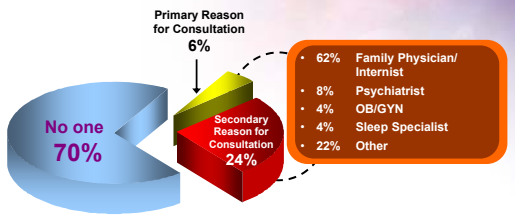
NIH. *NIH Consens State Sci Statements*. 2005;22(2):1-30.
Qaseem A, et al. *Ann Intern Med*. 2016;165:125-133.
Buscemi N, et al. Evidence report/technology assessment number 125. Rockville, MD: AHRQ. Publication 05-E021-2. June 2005. https://archive.ahrq.gov/clinic/epcsums/insomnsum.htm.

Risk Factors for Insomnia

- Age (greater prevalence in older individuals)
- Female gender (especially post-[a] and perimenopausal[b] females)
- Divorce/separation/widowhood
- Psychiatric illness (mood and anxiety disorders)
- Medical conditions
- Cigarette smoking
- Alcohol and coffee consumption
- Certain prescription drugs

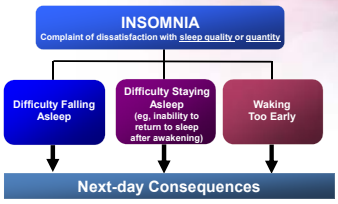
[a]*NIH Consens State Sci Statements*. 2005;22:1-30.
[b]Young T, et al. *Sleep*. 2003;26:667-672.
Buysse DJ. *JAMA*. 2013;309:706-16.

Where do Patients with Insomnia Go for Management?



Ancoli-Israel S, Roth T. *Sleep*. 1999;22:S347-S353.
The Gallup Organization for the National Sleep Foundation, 1995.

The Many Aspects of Insomnia Complaints



Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association Press, 2013.
The International Classification of Sleep Disorders: Diagnostic & Coding Manual, ICSD-3. 3rd ed. Westchester, IL: American Academy of Sleep Medicine, 2014.

Poor Sleep: Daytime Impact

- Feeling tired, fatigued, or "not up to par"
- Daytime sleepiness or excessive arousal
- Nodding off during daily activities such as driving
- Poor concentration
- Increased absence from work or events
- Decreased ability to accomplish tasks or an increased amount of errors
- Irritability
- Relationship problems, such as intimacy issues
- Diminished enjoyment of family and social life

NHLBI. Problem sleepiness in your patient. NIH Publication 97-4073; September 1997.
Shochat T, et al. *Sleep*. 1999;22(suppl 2):359-365.
Leger D, et al. *Curr Med Res Opin*. 2005;21:1785-1792.
Ohayon MM, et al. *Sleep Med*. 2005;6:435-441.

Poor Sleep (Insomnia): Societal Effects

- Decreased productivity
- Increased absenteeism
- Increased errors and accidents
- Increased health care costs
- Significant economic burden
  - Direct and indirect costs
  - Estimates of total U.S. annual costs for insomnia: $30–$107 billion

Simon GE, et al. Am *J Psychiatry*. 1997;154:1417-1423.
Qaseem A, et al. *Ann Intern Med*. 2016;165:125-133.

Sleep Disorders: Clinical Effects

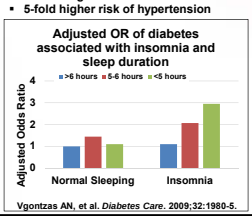
Sleep disorders associated with increased risk of various medical conditions, including:

- Increased risk of ischemic stroke
- Increased risk of heart disease
- Increased risk of obesity and metabolic syndrome
- Impaired glucose tolerance and increased risk of type 2 diabetes
- Increased cancer risk: breast, prostate, endometrial, colorectal

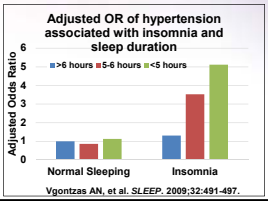
Luyster FS, et al. *Sleep*. 2012;35:727-34.
St-Onge MP, et al. *Circulation*. 2016;134:e367-86.

Insomnia Increases Risk for Diabetes and Hypertension

- Analysis of 1741 random adults from Central Pennsylvania who were studied in a sleep laboratory
  - Insomnia defined as complaint of insomnia with duration of at least 1 year
- Compared to normal sleeping, insomnia with a sleep duration of <5 hours was associated with:
  - ~3-fold higher risk of diabetes
  - 5-fold higher risk of hypertension

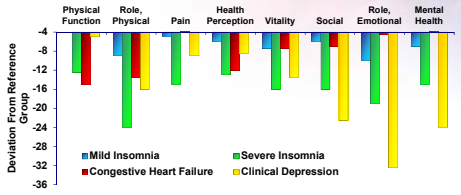


Vgontzas AN, et al. *Diabetes Care*. 2009;32:1980-5.



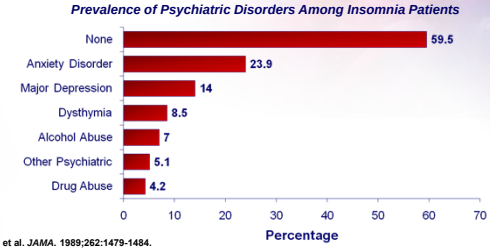
Vgontzas AN, et al. *SLEEP*. 2009;32:491-497.

Insomnia Is Associated With Reduced Mental Health, Vitality, and Social Functions



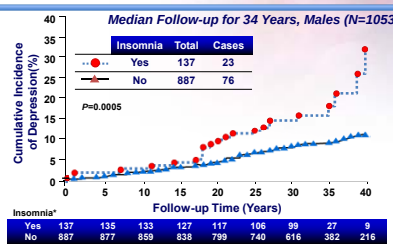
All comparisons with the reference group, $P \leq 0.001$, except congestive heart failure association with pain, emotional role, and mental health.
Katz DA, et al. *J Fam Pract.* 2002;51:229-235; graph adapted from Taylor DJ, et al. *Sleep.* 2005;28:1457-1464.

Insomnia and Psychiatric Disorders



Ford DE, et al. *JAMA.* 1989;262:1479-1484.

Insomnia History Predicts Future Depression

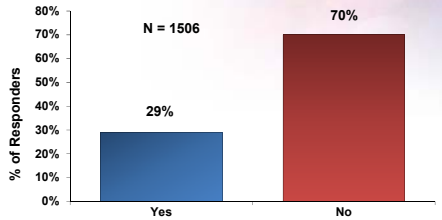


*Number of men included at each time point.
Chang P, et al. *Am J Epidemiol.* 1997;146:105-114.

Why the Urgent Need to Treat Sleep Disorders?

- Relieve an upsetting symptom
- Improve next-day consequences
- Improve outcome of co-morbidity
  - Psychiatric
  - Medical

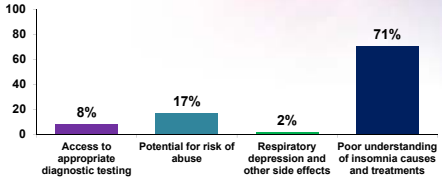
Patient Survey:
"Has your doctor ever asked you about sleep issues?"



National Sleep Foundation. "Sleep in America" Poll. March 2005. Available at: https://sleepfoundation.org/sleep-polls-data/sleep-in-america-poll/2005-adult-sleep-habits-and-styles.

Barriers to Identifying and Treating Sleep Disturbances: Physicians

PCP survey response to: "In your experience, which of the following is the largest barrier to the optimal and timely management of sleep disturbance?"



Winkelman JW. *A Primary Care Approach to Insomnia Management*, Medscape 2005. Available at: http://www.medscape.org/viewarticle/498167_5.

Sleep Quality Should be Evaluated at Nearly All Visits

- Acute care visit: “Does this problem affect your sleep?”
- Also ask patients with chronic conditions, especially those associated with sleep disturbances
- Yearly checkup, at review of systems:
  - “Do you have trouble getting to sleep or staying asleep?”
  - “Do you feel well rested throughout the day?”

Sleep Logs and Diaries

- Helpful in revealing patterns of sleep disturbance
  - Sleep onset
  - Sleep maintenance
  - Advanced or delayed sleep phase tendencies
  - Insufficient time in bed
- Helpful to monitor effects of treatment strategies
- Daily chart vs. graph approaches

Evaluation of Treatment of Sleep Disorders

- **Obtain feedback on therapy**
- **Compliance, perceived effects?**
- **Query mood disorder**
- **Request sleep diary***


National Sleep Foundation Sleep Diary

*Several sleep diaries are available from various sources.
National Sleep Foundation Sleep Diary. Available at: https://sleepfoundation.org/sites/default/files/SleepDiaryv6.pdf.

Approaches to Improve Sleep Quality

- Education
- Sleep hygiene measures
- Behavioral and cognitive therapy techniques
- Neurofeedback
- Pharmacotherapy
- Sleep medicine specialist consultation and sleep laboratory testing

Patient Education: The Most Powerful Tool

- Inform WHY management is so important
  - –Consequences
- Emphasize keeping regimented sleep schedule
  - –Wake up same time every day
  - –Naps usually not a good idea
- Emphasize sleeping long enough
  - –Can’t catch up on weekends
- Emphasize lifestyle measures
  - –Alcohol, exercise, smoking, caffeine, diet (no large meals)

Principles of Sleep Hygiene

- Regular sleep/wake cycle
- Regular exercise morning/afternoon
- Increase exposure to bright light during day
- Avoid exposure to bright light during night
- Avoid heavy meals/drinking <3 hours before bedtime
- Enhance sleep environment
- Avoid caffeine, alcohol, nicotine
- Relaxing routine

National Sleep Foundation. Sleep Hygiene. Available at: https://sleepfoundation.org/sleep-topics/sleep-hygiene.
Irish LA, et al. *Sleep Med Rev*. 2015;22:23-36.

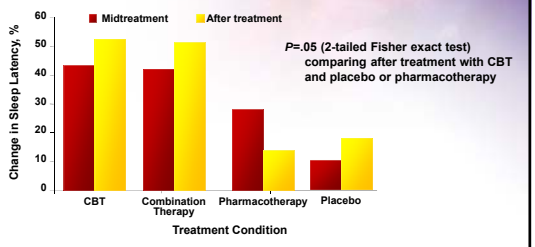
Cognitive Behavioral Therapy

- Multicomponent approach
  - Sleep education and sleep hygiene advice
  - Stimulus control and sleep restriction
  - Cognitive psychotherapy
- Individual or group format: 5–6 weekly sessions
- Numerous studies and meta-analyses demonstrate efficacy and long-term benefits
- Primarily relieves the PERPETUATING aspects of insomnia

Morin CM. *Insomnia: Psychological Assessment and Management*. New York, NY: The Guilford Press;1993.
Smith MT, et al. *Am J Psychiatry*. 2002;159:5-11.

National Sleep Foundation. Available at: https://sleepfoundation.org/sleep-news/cognitive-behavioral-therapy-insomnia.

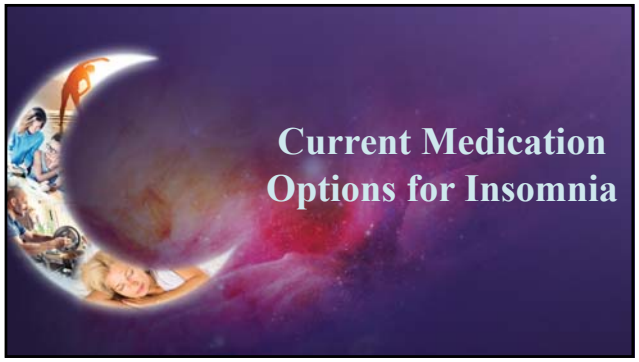
Cognitive Behavioral Therapy (CBT-I) Changes in Sleep-Onset Latency



Jacobs GD, et al. *Arch Intern Med*. 2004;164:1888-96.

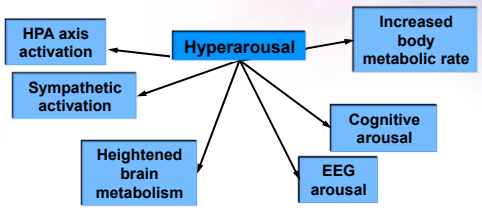
Summary

- Sleep disorders are highly prevalent and impact quality of life and increase the risk of comorbid conditions
- PCPs are at the forefront of managing sleep disorders and must take a proactive approach in evaluating patient sleep quality
  - Communication is key!
- Patient education on sleep hygiene and CBT options can be effective initial approaches in improving patient sleep quality

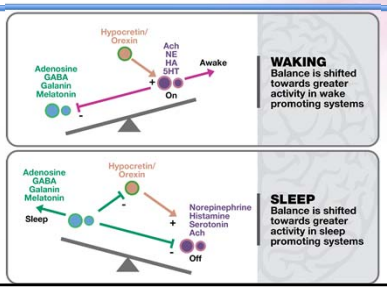


Pathophysiology of Insomnia

Factors Contributing to the Hyperarousal State



Neurotransmitters and the Sleep Arousal Switch



Adapted from Saper CB, et al. *Nature* 2005;437:1257-1263.

What do People Take to Improve Sleep Quality?

- Alcohol
- Herbals
- Melatonin
- Dietary supplements
- OTC sleep aids
- Antihistamines
- Antidepressants
- Assorted psychotropics
- Sedative-hypnotics

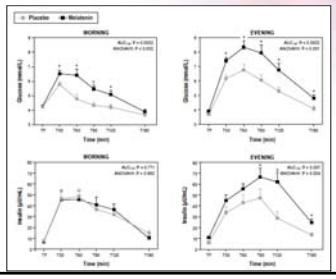
Roth T. *Primary Issues*. Oct. 2012. Available at: http://www.primaryissues.org/expertviews/EV_Sleep_toPCN_051614.pdf.

Melatonin Meta-Analysis in Primary Sleep Disorders

- 19 placebo-controlled studies, 1683 subjects. Melatonin demonstrated efficacy in:
  - Reducing sleep latency (WMD= 7.06 minutes)
  - Increasing total sleep time (WMD = 8.25 minutes)
    - Effects magnified with longer duration and higher doses
  - Improved sleep quality (standardized mean difference = 0.22)
    - No significant effects of trial duration and melatonin dose

Ferracioli-Oda E, et al. *PLoS One*. 2013;8:e63773.

Melatonin Impairs Glucose Tolerance



Rubio-Sastre P, et al. *Sleep*. 2014;37:1715-9.

When to Consider Pharmacotherapy vs. CBT-I

- Consider CBT
  - Specific cognitive or behavioral problem identified
  - Symptoms not pressing
  - Patient can actively participate in treatment
  - Multiple comorbidities and medications
  - Prior failure of pharmacotherapy
- Consider pharmacotherapy
  - Significant interference with daytime function
  - Need for rapid clinical improvement
  - CBT not available, not affordable, or previously failed
  - Lack of physician familiarity with CBT

Prescription Agents for Insomnia

- FDA-non-approved for insomnia
  - Sedating antidepressants
  - Antipsychotics like quetiapine
  - Anticonvulsants
- FDA-approved hypnotics
  - Benzodiazepine-receptor agonists (BzRAs)
    - Benzodiazepines
    - Non-benzodiazepines
  - Melatonin-receptor agonist
  - H1-receptor antagonist
  - Orexin-receptor antagonist

Low-Dose Sedating Antidepressants for Insomnia

Trazodone, doxepin, mirtazapine, paroxetine

- Advantages
  - Sedating side effects
  - Low abuse risk
  - Large dose range
- Disadvantages
  - Efficacy not well established for insomnia
  - Side effects include daytime sedation, anticholinergic effects, weight gain, drug-drug interactions

These agents are not FDA-approved for insomnia.
Kupfer DJ, Reynolds CF III. *N Engl J Med*. 1997;336:341-346.
Sharpley AL, et al. *Biol Psychiatry*. 2000;47:468-470.
Karam-Hage M, Brower KJ. *Psychiatry Clin Neurosci*. 2003;57:542-544.
National Institutes of Health. *Sleep*. 2005;28:1049-1057.

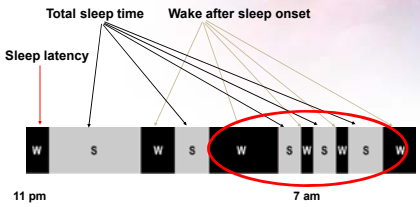
Low-Dose Atypical Antipsychotics for Insomnia

Quetiapine, olanzapine

- Advantages
  - At appropriate doses, effective for psychotic disorders
  - Low abuse potential
  - Sedation
- Disadvantages
  - Not well investigated in insomnia disorder
  - Daytime sedation, anticholinergic effects, weight gain
  - Risk of extrapyramidal symptoms, possible tardive dyskinesia
  - Glucose and lipid abnormalities

These agents are not FDA-approved for insomnia.
Kupfer DJ, Reynolds CF III. *N Engl J Med*. 1997;336:341-346.
Sharpley AL, et al. *Biol Psychiatry*. 2000;47:468-470.
Karam-Hage M, Brower KJ. *Psychiatry Clin Neurosci*. 2003;57:542-544.
National Institutes of Health. *Sleep*. 2005;28:1049-1057.

Clinically Relevant Sleep Variables



W = wake; S = sleep
Copyright: Karl Doghramji, MD.

Benzodiazepine-Receptor Agonists: The Benzodiazepines

Medication	Dosage Range† (mg)	Onset of Action	Half-life (h)	Short-term Limitation?
Estazolam	0.5 – 2	Rapid	10 - 24	Yes
Flurazepam	15 – 30	Rapid	47 - 100	Yes
Quazepam	7.5 – 15	Rapid	39 - 100	Yes
Temazepam	7.5 – 15	Slow-Intermediate	9.5 -12.4	Yes
Triazolam	0.25 – 0.50	Rapid	1.5 - 5.5	Yes

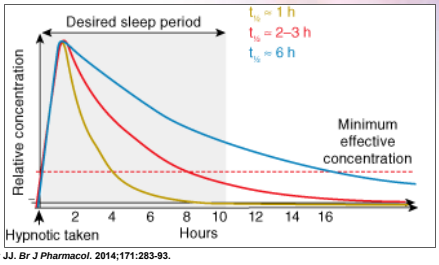
†Normal adult dose. Dosage may require individualization
MICROMEDEX. Available at: http://www.micromedex.com.
Prescriber's Digital Reference. Available at: www.PDR.net.

Selective Benzodiazepine-Receptor Agonists

	Zaleplon	Zolpidem	Zolpidem ER	Eszopiclone
Dose – mg [elderly]	5, 10, 20 [5]	5, 10 [5]	6.25, 12.5 [6.25]	1, 2, 3 [1]
T_{max} (hours)	1	1.6	1.5	1
Half-life [elderly] (hrs.)	1	2.5 [2.9]	2.8 [2.9]	6 [9]
Sleep latency	↓	↓	↓	↓
Wake After Sleep Onset	--	--	↓	↓
Total sleep time	↑ (20 mg)	↑	↑	↑
Schedule	IV	IV	IV	IV

Prescriber's Digital Reference. Available at: www.PDR.net.

Selecting an Appropriate Benzodiazepine: Consider Half-lives



Winrow CJ, Renger JJ. *Br J Pharmacol*. 2014;171:283-93.

Newer Hypnotics

	Ramelteon	Doxepin	Suvorexant
Mechanism	Melatonin agonist	H1 antagonist	Orexin antagonist
Dose – mg [elderly]	8	3, 6 [3]	10, 20
T_{max} (hours)	0.75	3.5	2
Half-life (hrs.)	1–2.6	15.3	12
Sleep latency	↓	--	↓
Wake After Sleep Onset	--	↓	↓
Total sleep time	--	--	↑
Schedule	None	None	IV

Prescriber's Digital Reference. Available at: www.PDR.net.

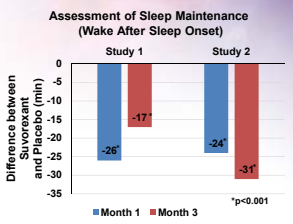
Suvorexant

- Novel mechanism of action
  - Highly selective antagonist of orexin receptors OX1R and OX2R
  - Orexin is a central promoter of wakefulness
- Approved for both help falling asleep (sleep onset) and maintaining sleep
- Dosing:
  - 10 mg within 30 minutes of going to bed with at least 7 hours remaining before awakening
  - Dosing can be adjusted to 20 mg if necessary
- Exposure to suvorexant is increased in:
  - Obese compared to non-obese patients
  - Women compared to men

Belsomra® (suvorexant) Prescribing Information. Merck & Co., Inc. Whitehouse Station, NJ. May 2016.

Suvorexant: Improvement in Sleep Maintenance

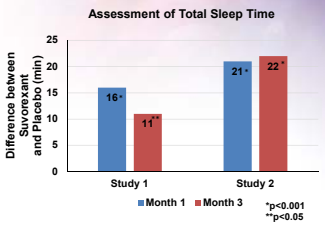
- Results from two phase 3 clinical trials comparing suvorexant vs. placebo
  - Dosing:
    Non-elderly: 20 mg
    Elderly: 15 mg
- **Improvement in Time to Sleep Onset at 1 month with suvorexant:**
  - 10 minutes (Study 1)
  - 8 minutes (Study 2)



Belsomra® (suvorexant) Prescribing Information. Merck & Co., Inc. Whitehouse Station, NJ. May 2016.
Herring WJ, et al. *Biol Psychiatry*. 2016;79:136-48.

Suvorexant: Improvement in Total Sleep Time

- Results from two phase 3 clinical trials comparing suvorexant vs. placebo
  - Dosing:
    Non-elderly: 20 mg
    Elderly: 15 mg



Belsomra® (suvorexant) Prescribing Information. Merck & Co., Inc. Whitehouse Station, NJ. May 2016.
Herring WJ, et al. *Biol Psychiatry*. 2016;79:136-48.

Patient Case: Gary S.

A 48-year-old attorney complains of sleep difficulties.

He says it usually takes him over 30 minutes each night to fall asleep.

Once he falls asleep, he wakes up multiple times during the night with some difficulty returning to sleep.

He has previously tried some OTC medications with little effect.

You decide to treat with a hypnotic agent.

Patient Case (cont'd)

The most appropriate medication choice would be?

1. Zaleplon
2. Zolpidem
3. Ramelteon
4. Low-dose doxepin
5. Suvorexant

Newer Agents to Tailor Medication Selection by Sleep Complaint

- Sleep onset:
  - Eszopiclone, zaleplon, zolpidem
  - Ramelteon
  - Suvorexant
- Sleep maintenance:
  - Eszopiclone, zolpidem ER
  - Doxepin
  - Suvorexant
- Onset *and* maintenance:
  - Zolpidem ER, eszopiclone, suvorexant

Prescriber's Digital Reference. Available at: www.PDR.net.

Selected Guidelines for Hypnotic Use

- Comprehensive evaluation; specific treatment for comorbidities
- Caution in patients with respiratory and hepatic impairment, substance use disorders, or who are already taking sedatives; avoid alcohol; not approved for children; avoid during pregnancy
- Use lowest effective dose, lower dose in elderly (and in women for certain compounds)
- Take at bedtime (or MOTN for zolpidem SL low dose)
- 7–8 hours in bed (or minimum of 4 hours for zolpidem SL low dose)
- Efficacy may be improved on empty stomach
- Gradual discontinuation
- Follow-up visits to evaluate efficacy, adverse events; change therapy/adjust dose if necessary

MOTN, middle-of-the-night; SL, sub-lingual
Neubauer DN. Pharmacotherapeutic approach to insomnia in adults. In: Barkoukis et al, eds. *Therapy in Sleep Medicine*. Elsevier Saunders, 2012, pp. 172-180

Adverse Effects of Hypnotics

- **Benzodiazepine-receptor agonists**
  - Daytime sedation, psychomotor and cognitive impairment (depending on dose and half-life)
  - Rebound insomnia
  - Respiratory depression in vulnerable populations
- **Melatonin-receptor agonist**
  - Headache, somnolence, fatigue, dizziness
  - Not recommended for use with fluvoxamine due to CYP 1A2 interaction
- **H1-receptor antagonist**
  - Somnolence/sedation
  - Nausea
  - Upper respiratory tract infection
- **Orexin-receptor antagonist**
  - Somnolence
  - Risk of impaired alertness and motor coordination, including impaired driving; increases with dose
  - Contraindicated in narcolepsy

Mitler MM. *Sleep*. 2000;23:S39-S47.
Holbrook AM, et al. *CMAJ*. 2000;162:225-233.
MICROMEDEX. Available at: www.micromedex.com; Package inserts for various compounds.
Charney DS, et al. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. 2001:399-427.

Which of the Following Factors Enhances the Risk for Parasomnias and Amnestic Behaviors with Zolpidem?

1. Female gender
2. Older age
3. Lower socioeconomic status
4. Use of alcohol
5. History of major depression

Parasomnias Associated with Zolpidem Use

- Limited to spontaneous reports
- Sleep-driving, ie, driving while not fully awake; preparing and eating food, making phone calls, or having sex
- Amnesia for events
- Risk factors
  - Co-use of alcohol or sedatives
  - Use at doses exceeding the maximum recommended dose
  - Sleep disorder: OSA or PLMS
  - H/O parasomnia such as sleep-walking
  - Ingestion at unusual bedtime
  - Ingestion while agitated or not typically asleep
  - Ingestion when sleep deprived
  - Poor management of pill bottles
  - Living alone
- FDA label change applies to all manufacturers of sedative hypnotic drugs

Poceta JS. *J Clin Sleep Med*. 2011;7(6):632-638.
FDA. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm334033.htm.

Selected Considerations in Choosing a Hypnotic Agent

- Insomnia therapy needs to be tailored to meet patient's expectations and needs
  - Consider half-life (benzodiazepines), mechanism of action, adverse effects
  - Age and co-morbidities
- Respiratory compromise; safety in mild to moderate OSA/COPD
  - Ramelteon, suvorexant
- Abuse potential
  - Lowest: Ramelteon, doxepin
- Prior failure of selected medications
- Patient preference

Prescriber's Digital Reference. Available at: www.PDR.net.
Sun H, et al. *J Clin Sleep Med*. 2016;12(1):9–17.
Kryger M, et al. *Sleep Breath*. 2007;11:159–164.

Take-Home Messages

- Insomnia is highly prevalent and can impact the general well-being of patients
  - Poor sleep quality can increase the risk of chronic medical conditions (e.g., diabetes, hypertension, depression)
- Evaluation of sleep should be a routine part of acute care and well visits
- Patient education and non-pharmacologic approaches can be an effective initial strategy to improve sleep
- When needed, pharmacologic therapy should be tailored to a patient's needs and preferences
- Follow-up and therapeutic adjustment is an important part of sleep management