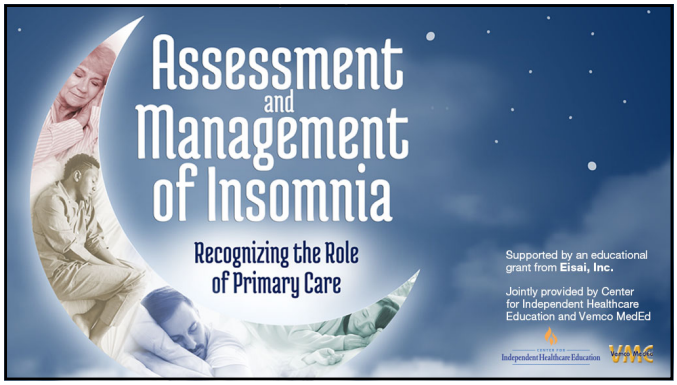


1

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**

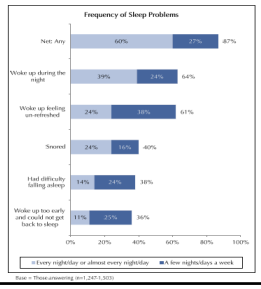
Effective management may **improve outcomes**

- **Majority is done by PCPs**

2

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

3

Epidemiology of Insomnia

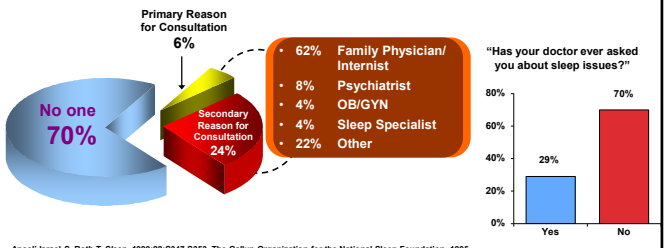
Prevalence of insomnia

- 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.

4

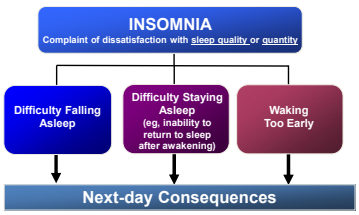
Where do Patients with Insomnia Go for Management?



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

5

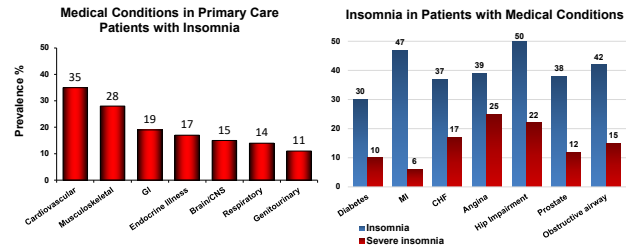
The Many Aspects of Insomnia Complaints



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.

6

How Frequent are Comorbidities in Patients?

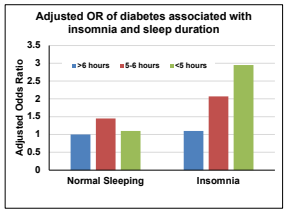


Terzano MG, et al. *Sleep Med.* 2004;5:67-75.
Katz DA, McHorney CA. *Arch Intern Med.* 1998;158:1099-1107.

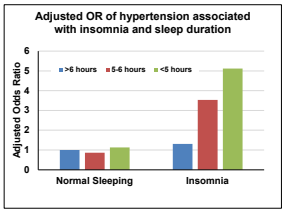
7

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



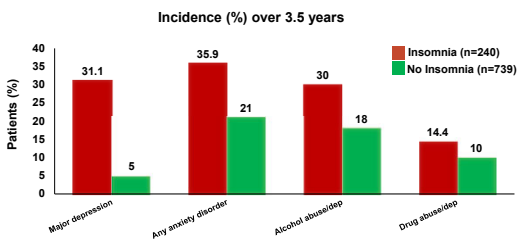
Vgontzas AN, et al. *Diabetes Care.* 2009;32:1980-5.



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

8

Does Insomnia Increase Risk for Psychiatric Disorders?



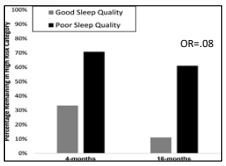
Breslau N, et al. *Biol Psychiatry.* 1996;39:411-8.

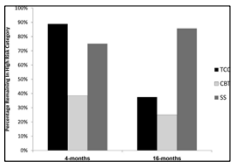
9

Does Treating Insomnia Improve Comorbidities?

2-hour group sessions weekly over 4 months with a 16-month evaluation

Cognitive Behavioral Therapy (CBT), Tai Chi chih (TCC), Sleep Seminar control (SS)





	4 months
CBT	OR=.21 (.03-1.47), p<.10
TCC	NS
	16 months
CBT	OR=.06 (.005-.669), p<.01
TCC	OR=.10 (.008-1.29), p<.05

Risk score based on 8 biomarkers:

- **High-density lipoprotein, low-density lipoprotein, triglycerides, C-reactive protein, fibrinogen**
- **Hemoglobin A1c, glucose, insulin**
- **High risk = 4 or more abnormal biomarkers**

Carroll, JE, et al. *Psychoneuroendocrinology.* 2015;55:184-92.

10

When Do You Ask About Sleep Problems?

- When applicable
  - During **Acute Visit**
  - During **Follow-up Visit**
- During **Periodic Health Assessment Visit**
- During Review of Systems
  - **Case Finding Initial Questions**
- Sleep Schedule:
  - Do you have trouble getting to sleep, staying asleep, or waking up too early?
- Daytime consequences:
  - Do you feel like you have slept well throughout the day?

Risk Factors

- Age (↑ in older individuals)
- Female gender (especially post- and peri-menopausal females)
- Divorce/separation/widowhood
- Psychiatric illness
- Medical conditions
- Cigarette smoking
- Alcohol and coffee consumption
- Certain prescription drugs

NIH Consens State Sci Statements. 2005;22:1-30. Young T, et al. *Sleep.* 2003;26:667-672. Sateia MJ, et al. *Sleep.* 2000;23:1-66.
Erman MK. In: *Sleep Disorders: Diagnosis and Treatment.* Totowa, NY: Humana Press; 1998; pp. 21-51.

11

Follow-Up Questions

- **Sleep timing:**
  - When do you go to bed? …Wake up? …Middle of the night awakening? …How long does it take you to fall back to sleep?
- **Duration, frequency, prior such:**
  - How long has this been going on?...How often have you had this sleep problem?...Have you had it before?...
- **Any sleep hygiene/lifestyle issues?**
  - Sleep environment? Alcohol? Smoking? Exercise? Medications?
- **Medical/psychiatric associations**
- **Treatments:**
  - What remedies have you tried? Any previous Rx's?
- **Other sleep disorders**
  - Snoring, daytime sleepiness, restless legs
- **Family History of sleep difficulties**

12

Approaches to Improve Sleep Quality

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

13

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)

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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.

15

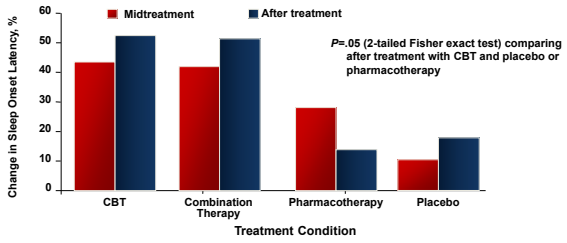
Cognitive Behavioral Therapy

- 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.

16

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



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

17

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

18

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

19

Pharmacologic Management of Insomnia

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What do People Take to Improve Sleep Quality?

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

21

Dietary Supplement Sleep Aids

- Dietary supplements, herbal preparations, homeopathic formulations
- Often considered complementary and alternative medicine
- Two broad types
  - Melatonin
  - Everything else (eg, valerian)
- Limited efficacy data
- Few safety concerns
- Huge number of products marketed as sleep aids

22

Dietary Supplement Sleep Aids (cont)

- None are regulated by the FDA
- Safety questions
  - Purity
  - Concentration
  - Toxicity

23

23

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.

24

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

25

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.

26

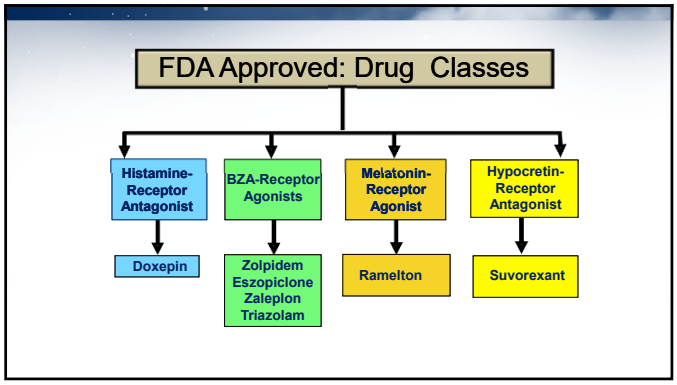
Low-Dose Atypical Antipsychotics for Insomnia

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.

27



28

2017 AASM Treatment Recommendations

USE

1. Suvorexant as a treatment for sleep maintenance insomnia.
2. Eszopiclone as a treatment for sleep onset and sleep maintenance insomnia.
3. Zaleplon as a treatment for sleep onset insomnia.
4. Zolpidem as a treatment for sleep onset and sleep maintenance insomnia.
5. Triazolam as a treatment for sleep onset insomnia.
6. Temazepam as a treatment for sleep onset and sleep maintenance insomnia.
7. Ramelteon as a treatment for sleep onset insomnia.
8. Doxepin as a treatment for sleep maintenance insomnia

DO NOT USE:

1. Trazodone as a treatment for sleep onset or sleep maintenance insomnia.
2. Tiagabine as a treatment for sleep onset or sleep maintenance insomnia.
3. Diphenhydramine as a treatment for sleep onset and sleep maintenance insomnia.
4. Melatonin as a treatment for sleep onset or sleep maintenance insomnia.
5. Tryptophan as a treatment for sleep onset or sleep maintenance insomnia.
6. Valerian as a treatment for sleep onset or sleep maintenance insomnia.

Data Compares: Versus no treatment, in adults. Level of Evidence: WEAK

Sateia MJ, et al. *J Clin Sleep Med.* 2017;13:307-49.

29

AASM Chronic Insomnia Clinical Guideline Consensus Recommendations

- Not Recommended: OTC antihistamine, barbiturates, chloral hydrate for the treatment of insomnia.
- Use: lowest effective maintenance dosage, taper Rx when conditions allow.
- Chronic hypnotic Rx: Severe/refractory insomnia or chronic comorbid illness
- Long-term use may be nightly, intermittent, or as needed in an "on demand pattern."

Schutte-Rodin S, et al. *J Clin Sleep Med.* 2008;4:487-504.

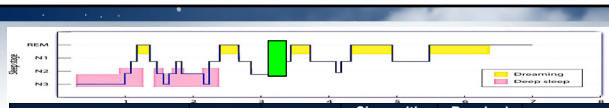
30

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.

31



Agent	Initiates Sleep	Maintains Sleep	Sleep with limited opportunity	Required Inactivity (hr)	Dose (mg)
Eszopiclone	√	√		8+	1,2,3
Zaleplon	√		√	4	5,10
Zolpidem	√			7-8	5,10
Extended release	√	√		7-8	6.25, 12.5
Intermezzo (Sublingual)		√	√ (4 hrs)	4	1.75, 3.5
Zolpimist (oral spray)	√			4	5, 10
Elduar (Sublingual)	√			4	5, 10
Doxepin (Ultra-low dose)		√		7-8	3, 6
Ramelteon	√			-	8
Suvorexant	√	√		7	5, 10, 15, 20

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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.

33

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

Miller 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.

34

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.

35

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.

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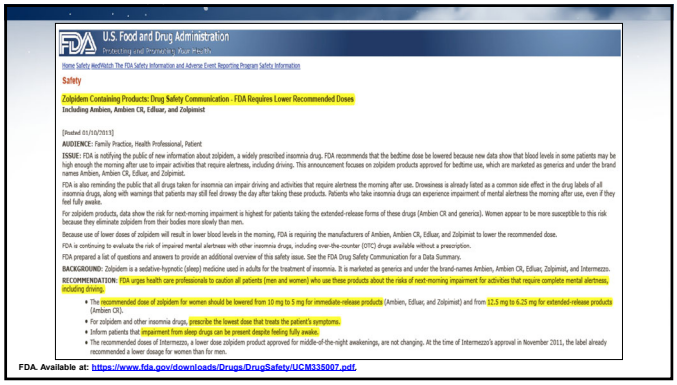

U.S. Food and Drug Administration

Protecting and Promoting Your Health

Home Safety MedWatch The FDA Safety Information and Adverse Event Reporting Program Safety Information

Safety

Zolpidem Containing Products: Drug Safety Communication - FDA Requires Lower Recommended Doses

Including Ambien, Ambien CR, Edluar, and Zolpimist

[Posted 01/10/2013]

AUDIENCE: Family Practice, Health Professional, Patient

ISSUE: FDA is notifying the public of new information about zolpidem, a widely prescribed insomnia drug. FDA recommends that the bedtime dose be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. This announcement focuses on zolpidem products approved for bedtime use, which are marketed as generics and under the brand names Ambien, Ambien CR, Edluar, and Zolpimist.

FDA is also reminding the public that all drugs taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the drug labels of all insomnia drugs, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia drugs can experience impairment of mental alertness the morning after use, even if they feel fully awake.

For zolpidem products, data show the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men.

Because use of lower doses of zolpidem will result in lower blood levels in the morning, FDA is requiring the manufacturers of Ambien, Ambien CR, Edluar, and Zolpimist to lower the recommended dose.

FDA is continuing to evaluate the risk of impaired mental alertness with other insomnia drugs, including over-the-counter (OTC) drugs available without a prescription.

FDA prepared a list of questions and answers to provide an additional overview of this safety issue. See the FDA Drug Safety Communication for a Data Summary.

BACKGROUND: Zolpidem is a sedative-hypnotic (sleep) medicine used in adults for the treatment of insomnia. It is marketed as generics and under the brand-names Ambien, Ambien CR, Edluar, Zolpimist, and Intermezzo.

RECOMMENDATION: FDA urges health care professionals to caution all patients (men and women) who use these products about the risks of next-morning impairment for activities that require complete mental alertness, including driving.

- The recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR).
- For zolpidem and other insomnia drugs, prescribe the lowest dose that treats the patient's symptoms.
- Inform patients that impairment from sleep drugs can be present despite feeling fully awake.
- The recommended doses of Intermezzo, a lower dose zolpidem product approved for middle-of-the-night awakenings, are not changing. At the time of Intermezzo's approval in November 2011, the label already recommended a lower dosage for women than for men.

FDA. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM335007.pdf.

37

FDA Drug Safety Communication for Other Sleep Products: 2014-2017 FDA Update

- Eszopiclone
  - FDA warns of next-day impairment with sleep aid eszopiclone (Lunesta) and lowers recommended dose (5/15/2014)
  - Recommends lower initial dose for men and women to be 1 mg at bedtime
  - "…the previously recommended dose of 3 mg can cause impairment to driving skills, memory, and coordination that can last more than 11 hours after receiving an evening dose "
  - Dosage may be increased to 2 or 3 mg at bedtime with caution
- Benzodiazepines
  - FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning (8/31/2016)
- Benzodiazepines
  - FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks (9/20/2017)

US Food and Drug Administration. MedWatch Safety Alerts for Human Medical Products. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sleep-disorder-sedative-hypnotic-drug-information.

38

Orexin (Hypocretin)

- **Hypothalamic peptides**
  - Localized in the dorsolateral hypothalamus
  - Wide projections throughout the brain
  - Projections found in the spinal column
- **Peptide neurotransmitters**
  - Arousal
  - Locomotion
  - Metabolism
  - Increase blood pressure/heart rate

Peyron et al. *J Neurosci.* 1998;18:9996.
Moore et al. *Arch Ital Biol.* 2001;139:195.
Silber and Rye. *Neurology.* 2001;56:1616.

39

Novel Agents for Insomnia: Clinical Application of Orexin Receptor Antagonists

- Single and dual orexin receptor antagonists (SORAs and DORAs, respectively) have been evaluated in animal models and shown to modulate sleep/wake states
- DORAs have progressed to clinical development as pharmaceutical candidates for insomnia
- Suvorexant is the first DORA FDA-approved for the treatment of insomnia
  - Safety, efficacy, and tolerability were demonstrated in phase 3 randomized, double-blind, placebo-controlled, parallel-group, 3-month trials in nonelderly (18-64 years) and elderly (≥65 years) patients with insomnia
  - Compared with placebo, suvorexant improved sleep onset and maintenance over 3 months of nightly treatment

Winrow CJ, Renger JJ. *Br J Pharmacol.* 2014;171:283-293.
BELSOMRA® (suvorexant) Prescribing information. Available at: https://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf.

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Emerging Agents for Insomnia: Orexin Receptor Antagonists – Lemborexant (LEM)

- LEM is a DORA in development for treatment of insomnia and irregular sleep-wake rhythm disorder
  - NDA submitted January 2019
- Two pivotal phase 3 trials:

SUNRISE-1:

- Efficacy and safety of LEM for the treatment of insomnia in older individuals ≥55yrs (ClinicalTrials.gov: NCT02783729) (N=1006)
  - Randomized, double-blind, double-dummy, parallel group, placebo-controlled, and active comparator (zolpidem ER) design. Duration 35 days
  - Subjects randomized (5:5:5:4 ratio) to receive LEM 5 mg, LEM 10 mg, zolpidem tartrate (ZOL) extended release 6.25 mg (ZOL; Ambien® CR), or PBO

LEM, Lemborexant; NDA, new drug application; PBO, placebo
Clinicaltrials.gov. https://www.clinicaltrials.gov/ct2/show/record/NCT02783729.
Press Release: Extensive analyses of phase 3 data for investigational lemborexant assess efficacy and safety profile for the potential treatment of insomnia in adults. http://eisai.mediaroom.com/2019-06-11-Extensive-Analyses-of-Phase-3-Data-for-Investigational-Lemborexant-Assess-Efficacy-and-Safety-Profile-for-the-Potential-Treatment-of-Insomnia-in-Adults.

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Emerging Agents for Insomnia: Orexin Receptor Antagonists - Lemborexant

- **SUNRISE-1 Results:**
  - LEM **significantly improved both sleep onset and sleep maintenance** compared with both PBO and ZOL
  - Improved sleep maintenance in the latter part of the sleep period
  - Improvements were observed at both the beginning and end of 1 month of treatment, indicating that LEM works immediately and over time
  - LEM significantly shortened awakenings during the night and increased total sleep time
  - LEM was well tolerated
    - The most common AEs were headache and somnolence

Press Release: Extensive analyses of phase 3 data for investigational lemborexant assess efficacy and safety profile for the potential treatment of insomnia in adults. http://eisai.mediaroom.com/2019-06-11-Extensive-Analyses-of-Phase-3-Data-for-Investigational-Lemborexant-Assess-Efficacy-and-Safety-Profile-for-the-Potential-Treatment-of-Insomnia-in-Adults.
Clinicaltrials.gov. https://www.clinicaltrials.gov/ct2/show/record/NCT02783729.

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Emerging Agents for Insomnia: Orexin Receptor Antagonists - Lemborexant

- **SUNRISE-2**:
  - Long-term (12 months) study of LEM in adults aged ≥18 y with insomnia disorder (NCT02952820)
  - Global, multicenter, randomized, PBO-controlled, double-blind, 2-dose, parallel-group study (N=959)
- **Results**:
  - LEM significantly improved sleep onset and sleep maintenance that persisted through 12 months
  - Subjects reported higher quality of sleep and morning alertness from baseline through 12 months
  - The most common treatment-emergent AE (>5%) was nasopharyngitis

Press Release, Three New Analyses of Data Expand Understanding of the Potential Role of Investigational Agent Lemborexant in Insomnia and Irregular Sleep-Wake Rhythm Disorder, September 2019, http://eisai.mediaroom.com/2019-09-27-Three-New-Analyses-of-Data-Expand-Understanding-of-the-Potential-Role-for-Investigational-Agent-Lemborexant-in-Insomnia-and-Irregular-Sleep-Wake-Rhythm-Disorder.
Yardley J, et al. Efficacy of Lemborexant Compared With Placebo in Adult and Elderly Subjects With Insomnia: Results From a Phase 3 Study (SUNRISE-2). Poster presented at the Advances in Sleep and Circadian Science (ASCS)/Sleep Research Society (SRS), February 1-4, 2019, Clearwater, FL. Abstract 10.

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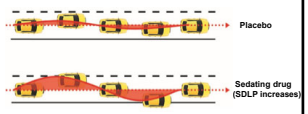
Standard Deviation of Lateral Position (SDLP): An Index of "Weaving" Is Lower With LEM

- Effect of lemborexant on next-morning driving performance was investigated in 48 healthy volunteers, 23 to 78 years (ClinicalTrials.gov: NCT02583451)
  - Randomized, double-blind, double-dummy placebo and active Increased errors and accidents
- Patients received at bedtime for 8 nights lemborexant, zopiclone, or placebo
- Drug-placebo difference in SDLP >2.4 cm considered as clinically meaningful driving impairment



- **No significant or clinically meaningful effects of single and repeated dose of LEM on next-morning driving performance**
- **Did not differ between adults and the elderly or between males and females**

Change in SDLP vs Placebo ≥2.4

	Day 2 N (%)	Day 9 N(%)
Lemborexant (10 mg)	6 (18.8) *P*=.51	6 (18.8) *P*=.51
Zopiclone (7.5 mg)	20 (41.7) *P*<.0001	24 (50) *P*<.0001

Zopiclone not available in the US.

Vermeeren A, Jongen S, Murphy P, et al., *Sleep*. 2019;42: pii: zsy260. doi: 10.1093/sleep/zsy260.

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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

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