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Understanding Insomnia:
A Chronic Sleep-Wake Disorder With Significant Unmet Medical Need

Introduction to content

Topics of discussion in today's presentation:

- Insomnia Disorder Overview
- Economic Burden of Insomnia
- Unmet Medical Need

Our speakers will not be discussing or addressing questions about product related information in this presentation

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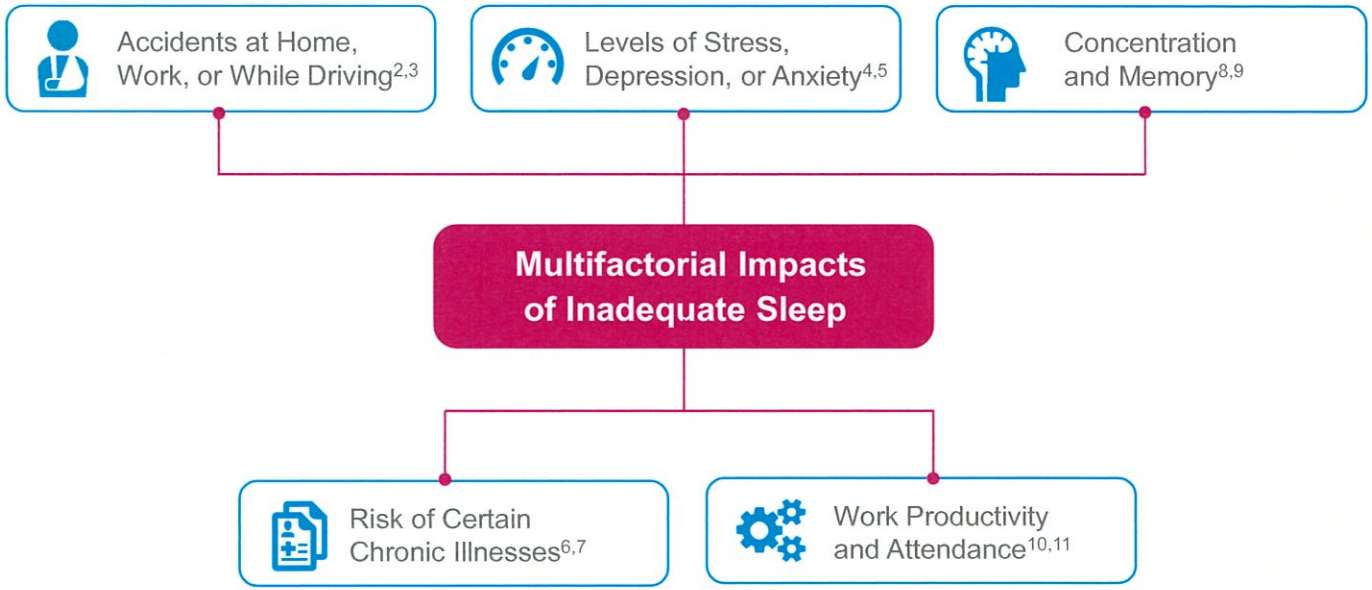
Insomnia Disorder Overview

Adequate Sleep Is a Fundamental and Critical Component of Good Health

The American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS) recommend at least

7 hours of sleep

each night for adults 18-60 years to promote optimal **health**[1]



References: 1. Watson NF et al. *J Clin Sleep Med*. 2015;11(8):931-952. **2.** Kessler RC et al. *Sleep*. 2012;1;35(6):825-834. **3.** Léger D et al. *J Sleep Res*. 2014;23(2):143-152. **4.** Goldstein AN, Walker MP. *Annu Rev Clin Psychol*. 2014;10:679-708. **5.** Zhai L et al. *Depress Anxiety*. 2015;32(9):664-670. **6.** Shan Z et al. *Diabetes Care*. 2015;38(3):529-537. **7.** Sofi F et al. *Eur J Prev Cardiol*. 2014;21(1):57-64. **8.** Ackermann S, Rasch B. *Curr Neurol Neurosci Rep*. 2014;14(2):430. **9.** Raven F et al. *Sleep Med Rev*. 2018; 39:3-11. **10.** Lallukka T et al. *Sleep*. 2014;37(9):1413-1425. **11.** DiBonaventura M et al. *PLoS One*. 2015;10(10):e0137117.

Clear, Defined Criteria Exist for the Diagnosis of Insomnia Disorder

Insomnia disorder is characterized by difficulty falling sleep, staying asleep, or both, despite an adequate opportunity to sleep, which can **lead to daytime consequences** such as fatigue, difficulty concentrating, and irritability[1,2]

DSM-5
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[3]

ICSD-3
International Classification of Sleep Disorders, Third Edition[4]

Diagnostic Criteria for Insomnia (DSM-5/ICSD-3) Include[3,4]:

Symptoms + **Impairment** + **Chronicity**

- Sleep difficulty and associated consequence occur for at least a 3-month duration with 3 times per week as the minimum frequency
- Distress or impairment that is caused by the insomnia
- The problem occurs despite ample opportunity to sleep
- The difficulty cannot be better explained by other physical, mental, or sleep-wake disorders
- The problem cannot be attributed to substance use or medication

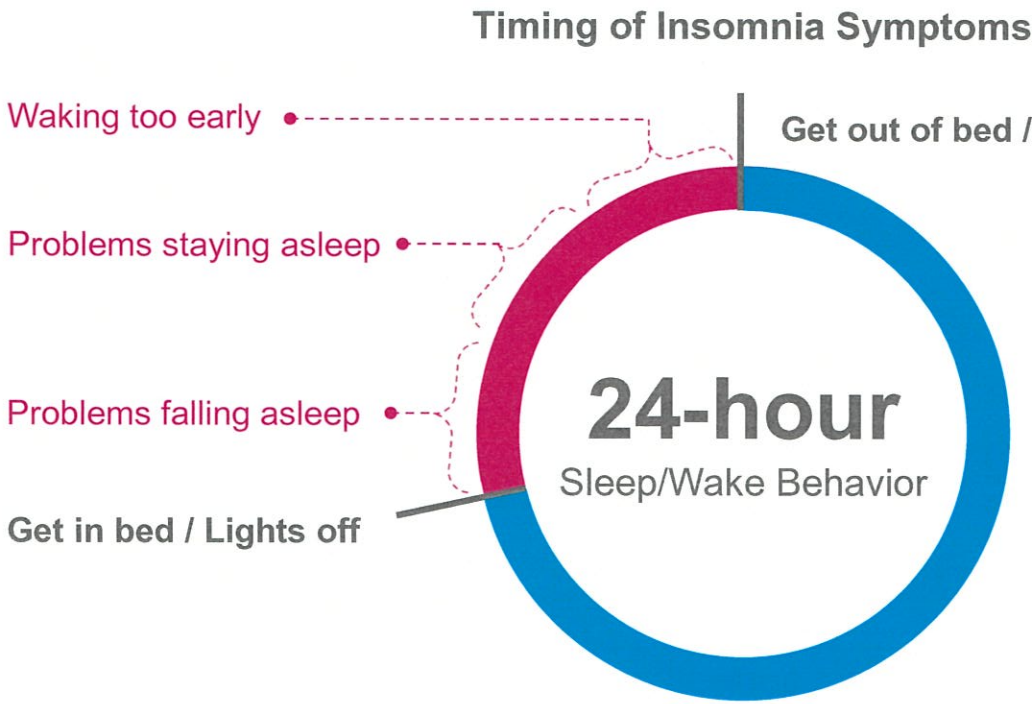
References: 1. Institute of Medicine. Sleep disorders and sleep deprivation: an unmet public health problem. Washington, DC: National Academies Press; 2006. **2.** Ohayon MM. *Sleep Med Rev.* 2002;6(2):97-111. **3.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013. **4.** Kryger MH et al. *Principles and Practice of Sleep Medicine*. 6th ed. Philadelphia, PA:Elsevier; 2017.

Although Many Adults Experience Insomnia Symptoms, Only a Small Percentage Meet Diagnostic Criteria for Insomnia Disorder

Prevalence of Insomnia Symptoms and Diagnosis in the Adult Population

Reference: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

Insomnia Can Manifest at Different Times of the Sleep Cycle and Cause Daytime Impairments[1,2]



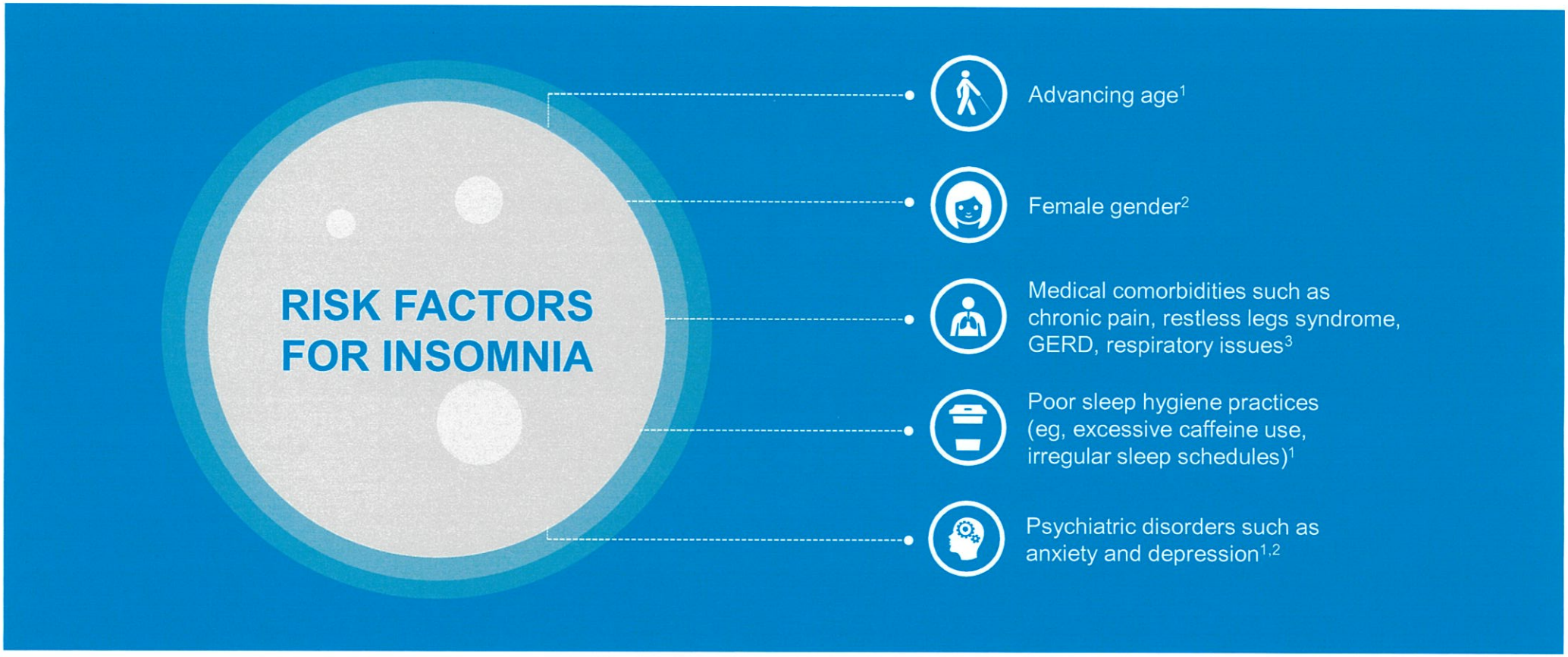
Daytime Impairments (Wake Behavior):

- Fatigue
- Daytime sleepiness
- Impairment in cognitive performance
- Mood disturbances
- Depressive or anxiety symptoms

The goal of insomnia therapy is to allow patients to fall asleep, stay asleep, wake, and function well

References: 1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013. **2.** Misra AK et al. *J Assoc Physicians India*. 2017;65(4):43-47.

While the Etiology Is Not Fully Understood, Insomnia Is Associated With Several Risk Factors



References: 1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013. **2.** Ohayon MM. *Sleep Med Rev*. 2002;6(2):97-111. **3.** Kaur H, Bollu PC. Chronic Insomnia. [Updated 2019 Feb 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK526136/. Accessed June 10, 2019.

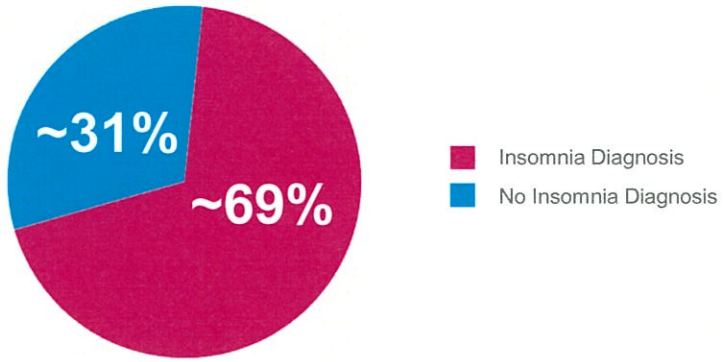
Insomnia Is Associated With Increased Risk for Certain Comorbidities

References: 1. Hertenstein E et al. *Sleep Med Rev*. 2019;43:96-105. **2.** LeBlanc ES et al. *BMJ Open Diabetes Res Care*. 2018;6(1):e000604. **3.** Li M et al. *Int J Cardiol*. 2014;176(3):1044-1047. **4.** Javaheri S, Redline S. *Chest*. 2017;152(2):435-444. **5.** Sen A et al. *Psychosom Med*. 2017;79(4):461-468. **6.** Garbarino S et al. *Int J Environ Res Public Health* 2016;13(8). **7.** Laugsand LE et al. *Eur Heart J*. 2014;35(21):1382-1393.

Insomnia Symptoms Have Been Associated With an Increased Risk of Motor Vehicle Accidents and Falls

Motor Vehicle Accidents

Motor Vehicle Accident (MVA)-Related Injuries in Active Component Service Members Between 2007–2016* (n=5,587)

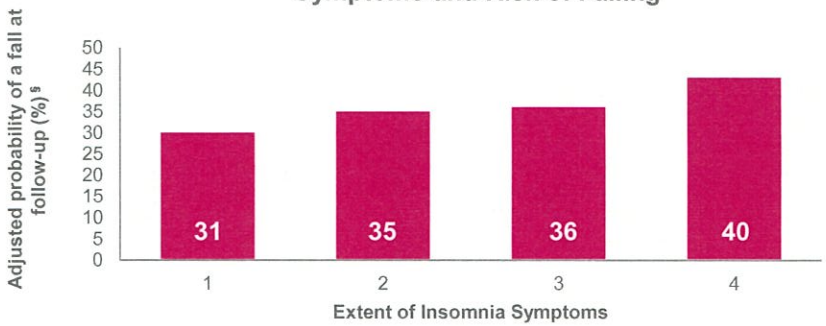


Service members with insomnia† had **more than double the rate of motor vehicle accident-related injuries**, compared to members without insomnia (aRR: 2.08; 95% CI: 1.95-2.22‡)

A retrospective cohort study compared incidence rates of MVA-related injuries between service members with diagnosed insomnia† and an unexposed cohort (N=172,062) (January 1, 2007–December 31, 2016)[1]

Falls

Positive Relationship of the Extent of Insomnia Symptoms and Risk of Falling



A composite score (0–4) for the number of insomnia symptoms was created. A higher score reflected a greater burden of insomnia symptoms.‖

Older **adults who fell reported a greater number of insomnia symptoms** compared with those who did not fall

Data from the Health and Retirement Study (HRS) patients were asked about their extent of insomnia symptoms (n=6,882) (2006–2014)[2]

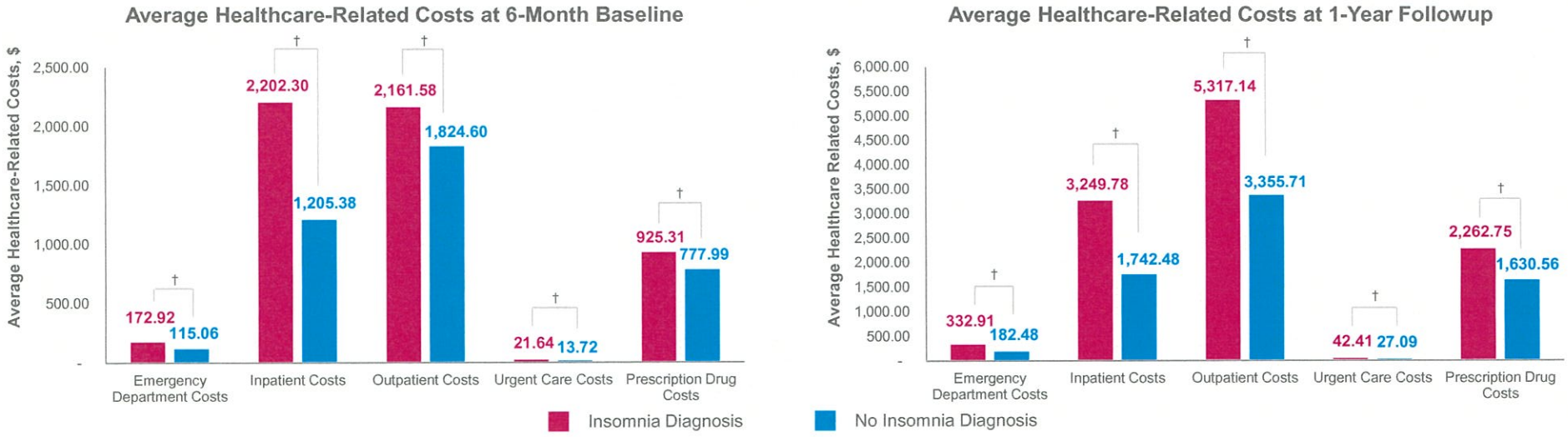
aRR, adjusted incidence rate ratio.
*MVA-related injury during the 365-day follow-up period was defined as an outpatient or inpatient encounter that included any of the MVA-related ICD-9 or ICD-10 external cause of injury codes, or NATO Standardization Agreement (STANAG 2050) hospitalization cause of injury and trauma codes.
†An incident case of insomnia was defined by records of two outpatient medical encounters within 90 days of each other or one hospitalization with a diagnosis of insomnia in any diagnostic position, in a non-deployed healthcare setting using ICD-9 or ICD-10 codes.
‡Adjusted for covariates.
§Adjusted for age, any fall, balance, walking speed, and vision, at baseline, and race and sex.
‖Participants were asked how often they had trouble with "falling asleep," "waking up during the night," and "waking up too early and not being able to fall asleep again."

References: 1. Erickson EA et al. *MSMR*. 2017;24(12):2-11. **2.** Chen TY, Lee S, Buxton OM. *Sleep*. 2017;40(11).

Economic Burden

Healthcare Costs Are Higher in Adults With Insomnia Compared to Adults Without Insomnia

Data from a retrospective observational study in a Midwestern health plan cohort of 7,647 adult members with insomnia* compared with an equally matched cohort of health plan members without insomnia (January 1, 2003–December 31, 2006)



†$p<0.0001$

Baseline, 6 months before insomnia diagnosis or index date; follow-up, 12 months after insomnia diagnosis or index date.

- An insomnia diagnosis was associated with higher costs in all healthcare categories at baseline and at followup
- Average costs at:
  - 6-month baseline period: **Insomnia cohort $5,484 vs $3,937 for the control cohort**; $p<0.0001$
  - In the year-long follow-up period: **Insomnia cohort $11,206 vs $6,939 for the control cohort**; $p<0.0001$

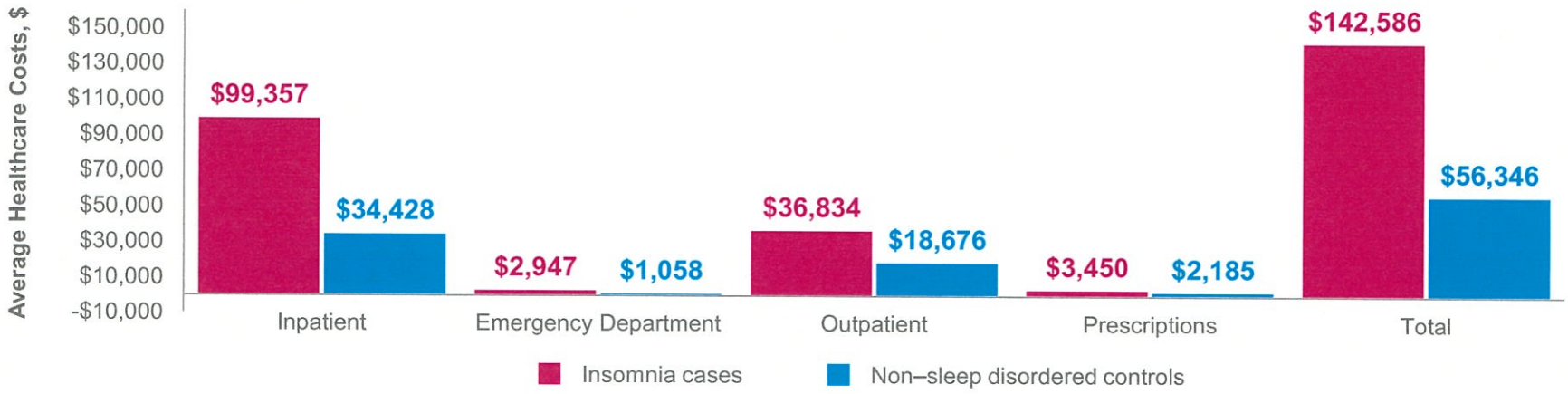
*Members were considered to have insomnia if they had a qualifying insomnia diagnosis code from January 1, 2004, to December 31, 2005, preceded by a 6-month period free of an insomnia diagnosis (baseline period) and if they remained in the plan for at least 12 months after the diagnosis (follow-up period).

Reference: Anderson LH et al. *Am J Manag Care*. 2014;20(5):e157-165.

Healthcare Costs Are Higher Among Medicare Beneficiaries With Insomnia Compared to Controls

Data from a random 5% sample of Medicare administrative data for 2006–2013 were evaluated, and a total of 151,668 beneficiaries were found to have untreated insomnia compared to non–sleep disordered controls (n=333,038)

Annual all-cause health care costs in the year prior to insomnia diagnosis or matched index date among Medicare beneficiaries



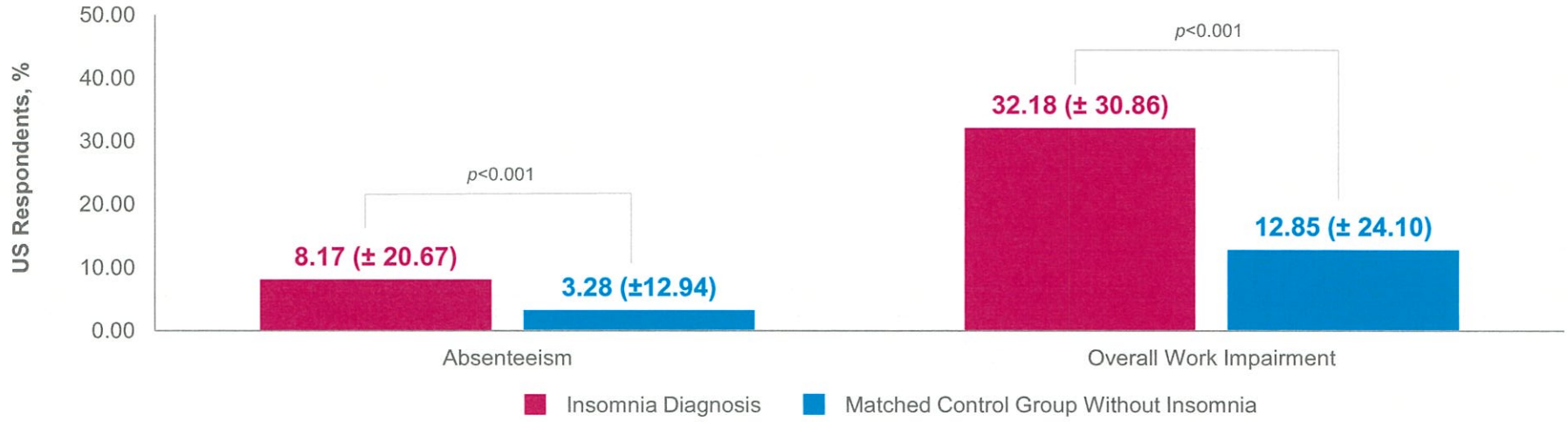
Medicare beneficiaries with untreated insomnia demonstrated $63,607 (95% CI $60,532, $66,685) higher all-cause costs compared to non–sleep disordered controls

Reference: Wickwire EM et al. *Sleep J.* 2019;42(4):1-8.

Insomnia Is Associated With Impaired Workplace Productivity

Data from US respondents of the 2013 National Health and Wellness Survey (NHWS), an internet-based health questionnaire administered to a nationwide sample of adults (aged 18 or older) in the US (N=75,000) and Western Europe (N=62,000)

Health Outcome Differences Between US Respondents With Insomnia* and Matched Controls (N=4517 in each arm)†



On average, respondents with insomnia reported approximately 2.5 times more absenteeism and overall work impairment compared to matched controls ($p<0.001$)

*If respondents reported a diagnosis of insomnia and the use of a prescription medication, they were considered to have insomnia regardless of their symptom experience (because it is possible the treatment was successful at reducing the impact and frequency of their symptoms). If they did not report a diagnosis, insomnia was defined using the DSM-V criteria.

†Data from a total of 4517 adults (6.0% of the US sample) who met criteria for insomnia and matched controls.

Reference: DiBonaventura M et al. *PLoS One.* 2015;10(10):e0137117.

Insomnia Is Associated With Costly Workplace Accidents and Errors

Workplace Accidents and Errors in Individuals With Insomnia*
The America Insomnia Survey (N=4991)†

Insomnia sufferers are **40% more** likely to experience a **workplace accident** compared to those without insomnia [OR 1.4; 95% CI 1.0-2.0]

The population-attributable risk proportion (PARP)‡ showed that:

- **14.5%** of all costly workplace accidents, **6.7%** of all costly workplace errors, and **8%** of accidents and/or errors are associated with insomnia
  - The total costs of insomnia-related accidents and errors were higher than those of other workplace accidents and errors by an average of **$10,428** per incident§

*Insomnia was assessed by the Brief Insomnia Questionnaire (BIQ) developed for the America Insomnia Survey, a national cross-sectional telephone survey of commercially insured health plan members selected from the more than 34 million in the HealthCore Integrated Research Database. Insomnia was defined according to DSM-IV-TR, ICD-10, and RDC/ICSD-2 classification systems.
†The data shown are from the comorbidity subsample (N=4991).
‡PARP is defined as the proportion of observed costly accidents or errors that would not have occurred if insomnia had not occurred or had been effectively treated. PARP data shown are uncontrolled for comorbidities.
§Without controls for comorbidity.

Reference: Shahly V et al. *Arch Gen Psychiatry*. 2012;69(10):1054-1063.

Unmet Medical Need

Cognitive Behavioral Therapy for Insomnia (CBT-I) Is the Recommended Primary Intervention for the Treatment of Chronic Insomnia in Adults

The American College of Physicians (ACP) and the American Academy of Sleep Medicine (AASM) recommend CBT-I as initial treatment in adults with chronic insomnia[1,2]

CBT-I consists of a combination of treatments[1,2]

Cognitive therapy around sleep

Behavioral interventions (eg, sleep restriction and stimulus control)

Sleep hygiene education[2]

References: 1. Sateia MJ et al. *J Clin Sleep Med*. 2017;13(2):307-349. **2.** Qaseem A et al. *Ann Intern Med*. 2016;165(2):125-133.

Despite the Reported Effectiveness of CBT-I, Several Barriers Exist to Insomnia Patient Access to This Treatment Option[1]

Knowledge Gap	Lack of Trained Sleep Specialists	Patients' Acceptability, and Adherence to Treatment	Insurance Coverage
• Both the general public and healthcare professionals lack knowledge regarding CBT-I	• Few sleep training programs exist, and even fewer provide CBT-I training • Not all sleep disorder centers employ staff trained in CBT-I	• Treatment success is dependent on the patient's willingness to accept and adhere to CBT-I treatment recommendations and to implement them in their daily lives as solutions for their sleep difficulties	• Insurance coverage limitations for CBT-I in the United States may pose a financial barrier to patients

Pharmacotherapy can be used as an adjunct to CBT-I treatment in cases where CBT-I alone has not been successful[2,3]

References: **1.** Edinger JD et al. *Clin Psychol Rev.* 2005;25(5):539-558. **2.** Sateia MJ et al. *J Clin Sleep Med.* 2017;13(2):307-349. **3.** Qaseem A et al. *Ann Intern Med.* 2016;165(2):125-133.

AASM Guidelines Recommend Different Treatment Agents Depending on the Type of Insomnia Manifestation in Patients

Year Introduced		For Sleep Onset[1]	For Sleep Maintenance[1]	Strength of Recommendation[1]*	Quality of Evidence[1]	Benefits Outweigh Harms[1]	Indicated for Insomnia
1960	**Benzodiazepines**						
	Triazolam	✓		WEAK	HIGH	✓	✓
	Temazepam	✓	✓	WEAK	MODERATE	✓	✓
1988	**Benzodiazepine Receptor Agonists**						
	Eszopiclone[2]	✓	✓	WEAK	VERY LOW	✓	✓
	Zaleplon[2]	✓		WEAK	LOW	✓	✓
	Zolpidem[2]	✓	✓	WEAK	VERY LOW	✓	✓
1990	**Melatonin Receptor Agonists**						
	Ramelteon	✓		WEAK	VERY LOW	✓	✓
2014	**Orexin Receptor Antagonists**						
	Suvorexant		✓	WEAK	LOW	✓	✓
Various	**Heterocyclics**						
	Doxepin		✓	WEAK	LOW	✓	✓
	Trazodone			WEAK	MODERATE	Harms outweigh benefits	NO
	Anticonvulsants						
	Tiagabine			WEAK	VERY LOW	Harms outweigh benefits	NO

The **FDA** requires a new **boxed warning** regarding rare but serious injuries and deaths resulting from various complex sleep behaviors that have occurred with certain prescription insomnia medications.[2]

Approximately 80% of US adults taking medications for insomnia report experiencing negative next-day effects related to medication use[3]

*All recommendation categories in blue [including Quality of Evidence (Very low, Low, Moderate, High, and Very High) and Strength (Strong or Weak)] based on GRADE approach; for GRADE approach details, refer to Morgenthaler et al. *J Clin Sleep Med.* 2016:12(1):129-135.

References: 1. Sateia MJ et al. *J Clin Sleep Med.* 2017:13(2):307-349. **2.** FDA requires stronger warnings about rare but serious incidents related to certain prescription insomnia medicines [press release]. Food and Drug Administration. April 30, 2019. **3.** Fitzgerald T et al. *Sleep Disord.* 2015:2015:607148

Summary

Insomnia is a Chronic Sleep-Wake Disorder With a Significant Unmet Medical Need

Insomnia disorder is characterized by **difficulty falling asleep, staying asleep, or both, which can lead to daytime consequences**[1-3]

Insomnia is associated with:

- Elevated risk of several comorbidities[4-10]
- Increased risk of motor vehicle accidents and falls[11,12]
- Workplace impairment and costly workplace accidents and errors[13,14]

Insomnia is associated with a **substantial economic burden**

Healthcare costs are higher in adults with insomnia compared to those without insomnia[15]

The **goal of therapy** for insomnia is to improve the patient's ability to fall asleep, stay asleep, to wake and function well

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association: 2013. **2.** Ohayon MM. *Sleep Med Rev*. 2002;6(2):97-111. **3.** Institute of Medicine. Sleep disorders and sleep deprivation: An unmet public health problem. Washington, DC: National Academies Press; 2006. **4.** Hertenstein E et al. *Sleep Med Rev*. 2019;43:96-105. **5.** LeBlanc ES et al. *BMJ Open Diabetes Res Care*. 2018;6(1):e000604. **6.** Li M et al. *Int J Cardiol*. 2014;176(3):1044-1047. **7.** Javaheri S. *Chest*. 2017;152(2):435-444. **8.** Sen A et al. *Psychosom Med*. 2017;79(4):461-468. **9.** Garbarino S et al. *Int J Environ Res Public Health* 2016;13(8). **10.** Laugsand LE et al. *Eur Heart J*. 2014;35(21):1382-1393. **11.** Erickson EA et al. *MSMR*. 2017;24(12):2-11. **12.** Chen TY, Lee S, Buxton OM. *Sleep*. 2017;40(11). **13.** DiBonaventura M et al. *PLoS One*. 2015;10(10):e0137117. **14.** Shahly V et al. *Arch Gen Psychiatry*. 2012;69(10):1054-1063. **15.** Anderson LH et al. *Am J Manag Care*. 2014;20(5):e157-165.