Managing Obstructive Sleep Apnea:
New Developments and Recommendations to Enhance Managed Care Outcomes

Jointly provided by:

Impact Education LLC

PIM Postgraduate Institute for Medicine

This activity is supported by an independent educational grant from Jazz Pharmaceuticals, Inc.

Learning Objectives

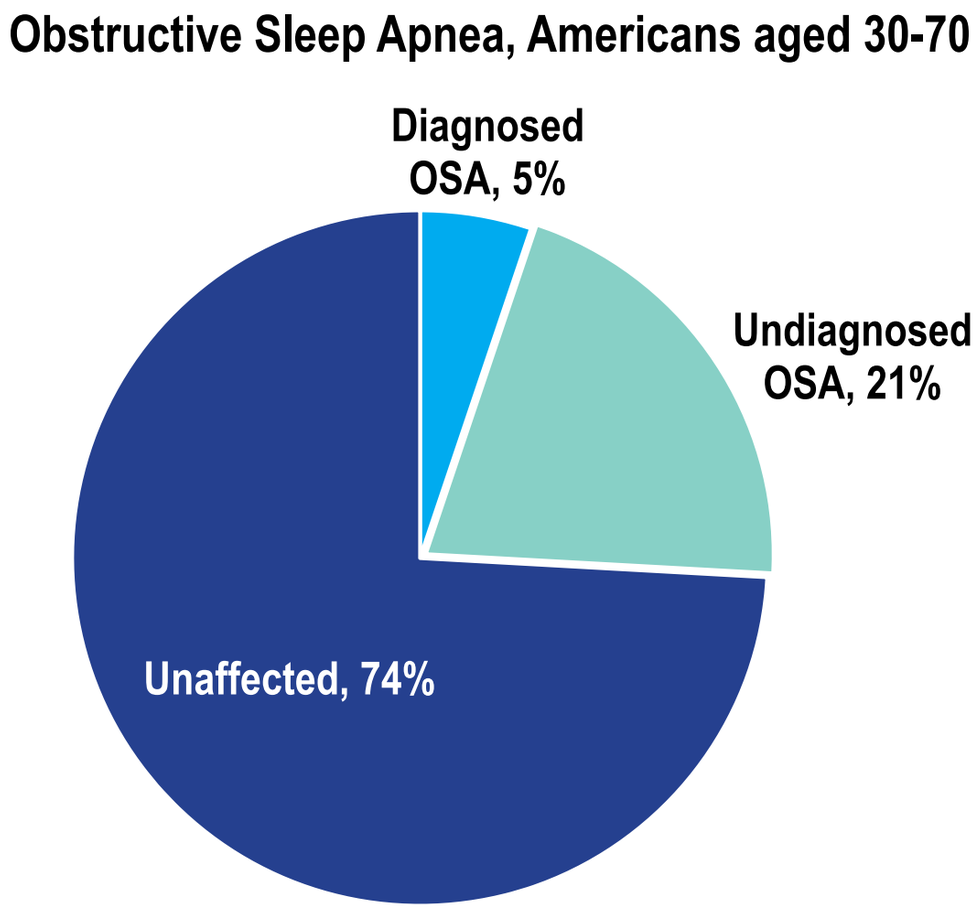
- Characterize the clinical and economic burden of both diagnosed and undiagnosed OSA as it pertains to comorbid conditions and EDS
- Describe potential cost offsets garnered through appropriate therapeutic interventions for OSA
- Utilize available criteria, risk factors, and clinical indicators for the timely and accurate diagnosis of OSA
- Review available OSA screening methodology for dissemination and standardized use among network providers
- Outline the available treatment modalities for OSA in terms of outcomes and patient adherence
- Evaluate the efficacy and safety data associated with available and emerging pharmacotherapies for the management of EDS in patients with OSA as they pertain to benefit design and coverage considerations including potential prior authorization criteria

Assessment Methodologies, Diagnostic Criteria and Recommended Treatment for OSA

Phyllis Zee, MD, PhD
Benjamin and Virginia Professor in Neurology
Chief, Division of Sleep Medicine
Director, Center for Circadian and Sleep Medicine
Northwestern University Feinberg School of Medicine

Epidemiology of Obstructive Sleep Apnea (OSA)

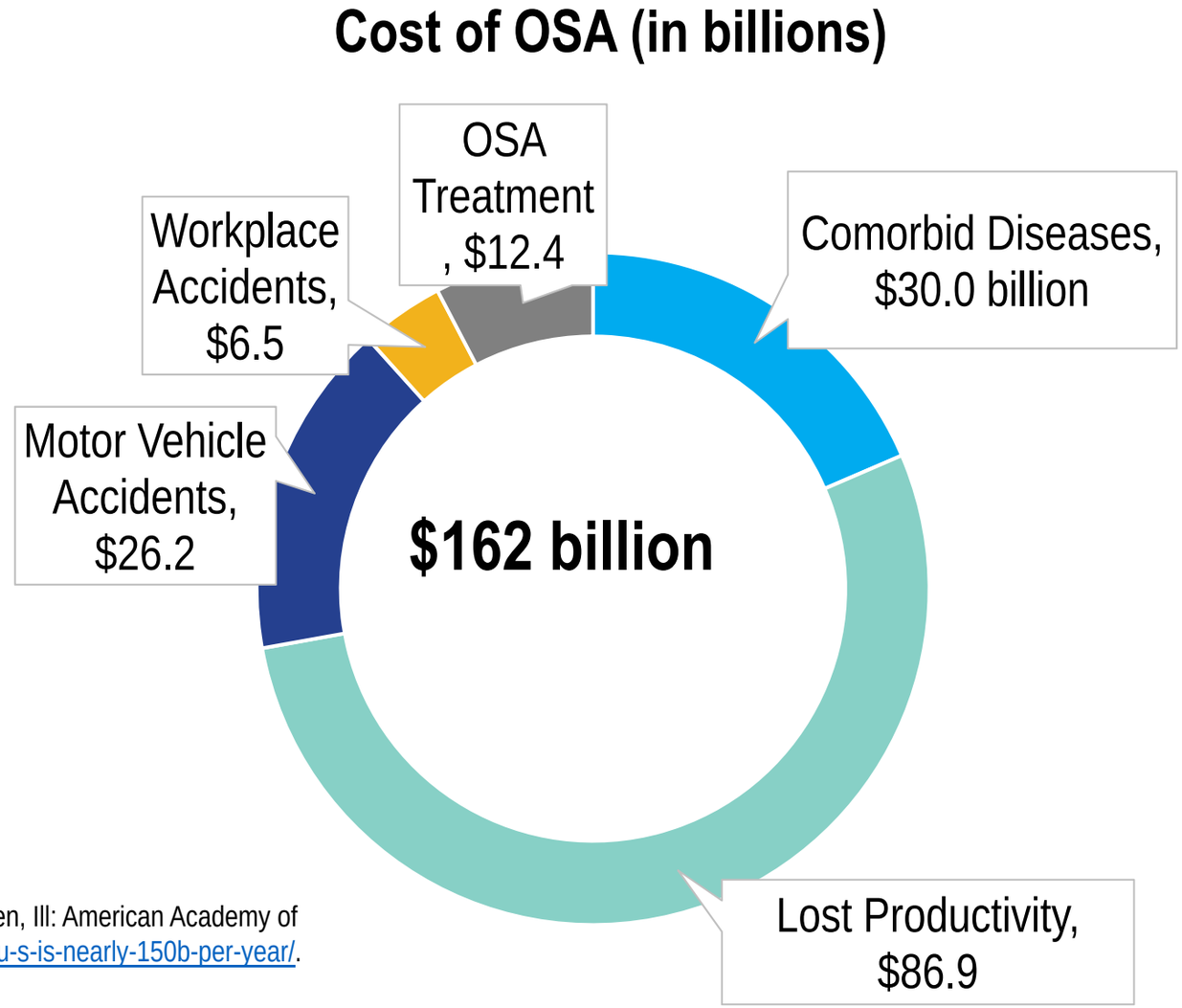
- Obstructive sleep apnea affects approximately 26% of adults aged 30-70.
- About 13% of men and 6% of women aged 30-70 have moderate to severe OSA.
- Only 20% of people with OSA have been diagnosed.



Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. 2013;177(9):1006-14.
Resident population of the United States by sex and age as of July 1, 2017. Statista. June 2018.

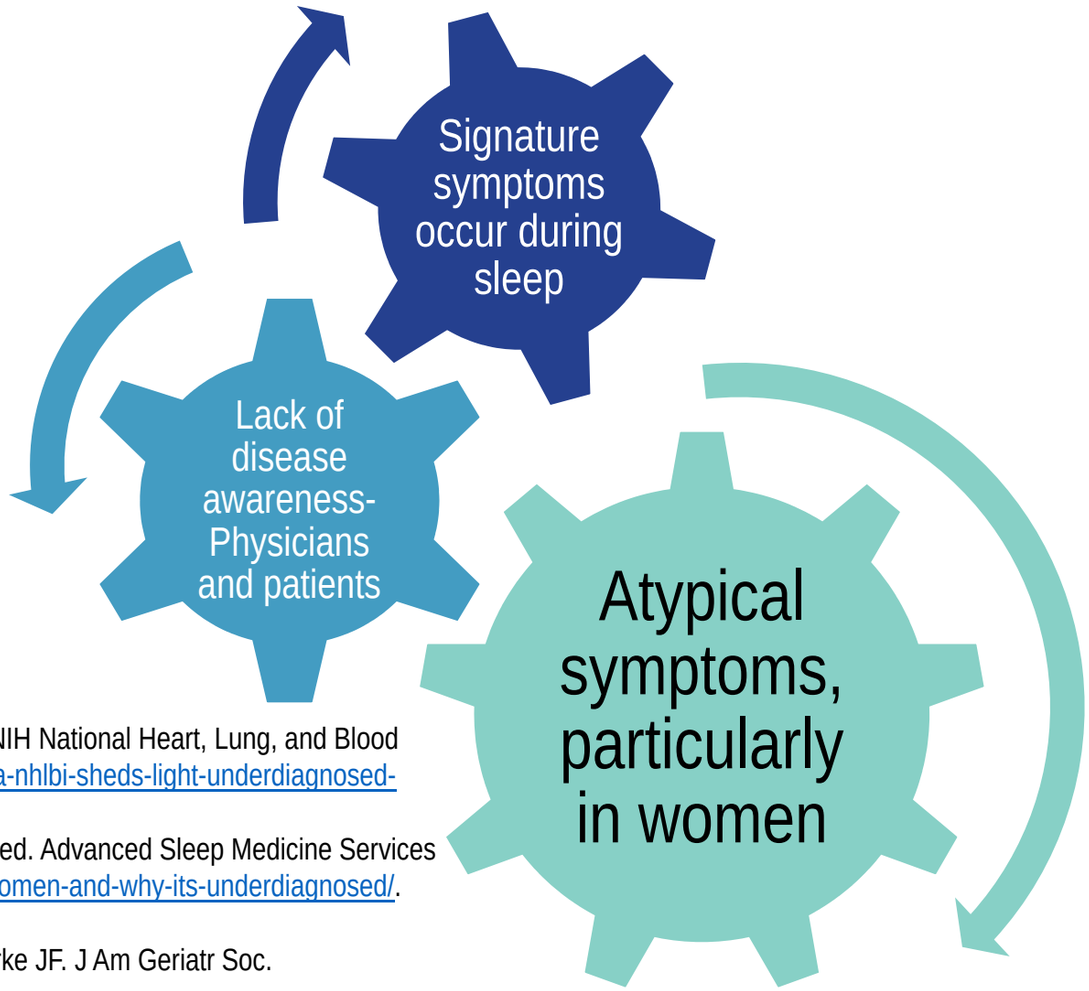
Cost of Undiagnosed Sleep Apnea

Of the $162 billion in estimated annual costs attributed to OSA, $149.6 billion (92%) is the result of undiagnosed and untreated OSA.



Economic burden of undiagnosed sleep apnea in U.S. is nearly $150B per year [news release]. Darien, Ill: American Academy of Sleep Medicine; August 8, 2016. https://aasm.org/economic-burden-of-undiagnosed-sleep-apnea-in-u-s-is-nearly-150b-per-year/. Accessed December 2018.

Why is OSA so Underdiagnosed?



Sleep Apnea: NHLBI sheds light on an underdiagnosed disorder. NIH National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/news/2017/sleep-apnea-nhlbi-sheds-light-underdiagnosed-disorder. August 22, 2017.
Fessenden M. Sleep Apnea in Women and Why It's Underdiagnosed. Advanced Sleep Medicine Services website. https://www.sleepdr.com/the-sleep-blog/sleep-apnea-in-women-and-why-its-underdiagnosed/. Accessed December 2018.
Braley TJ, Dunietz GL, Chervin RD, Lisabeth LD, Skolarus LE, Burke JF. J Am Geriatr Soc. 2018;66(7):1296-1302.

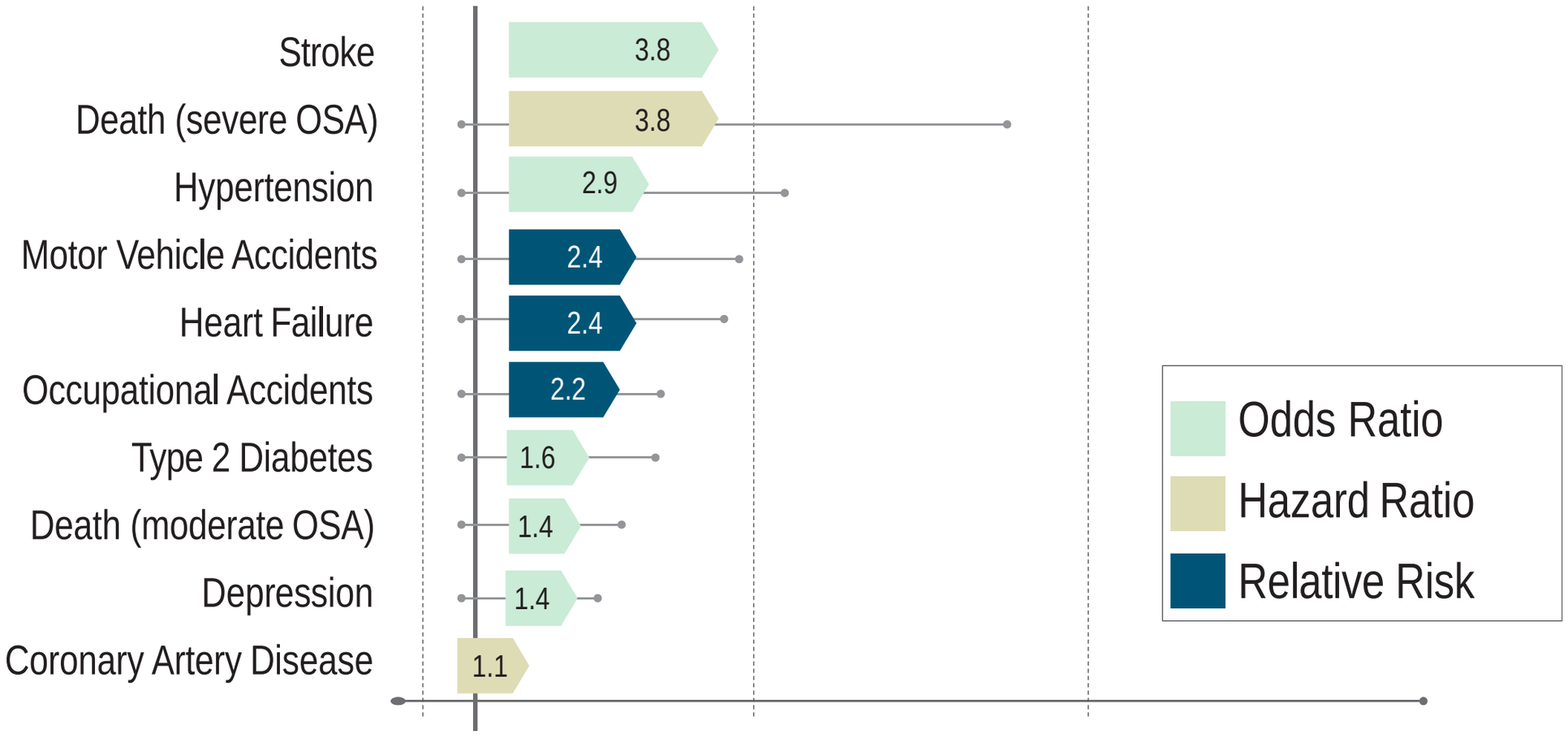
Importance of Diagnosis

- Reduce morbidity and consequences associated with excessive daytime sleepiness.
- Mitigate potential long-term complications related to:
  - Depression
  - Obesity
  - Metabolic syndrome
  - T2DM
  - CVD

Watson NF. J Clin Sleep Med. 2016;12(8):1075-7.

Consequences of Untreated OSA

Increased Risk of Morbidity and Mortality Associated With Untreated OSA



Knauert M, Naik S, Gillespie MB, Kryger M. *World J Otorhinolaryngol Head Neck Surg*. 2015;1(1):17-27.

Assessment and Diagnosis

Suspect OSA in individuals with these clinical indicators:

- Male gender
- Severe snoring
- History of apnea
- Older age
- Post-menopausal female
- High waist-to-hip ratio

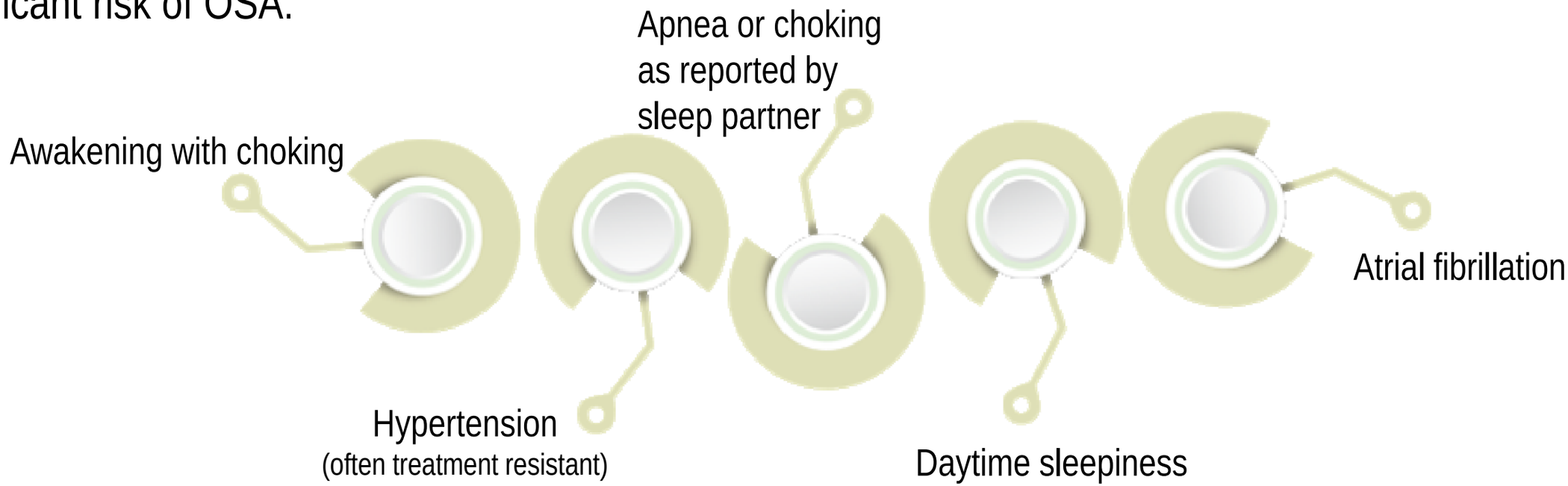
Body habitus

- High body mass index (30+) or
- Neck circumference of 17” or more for men, 16” or more for women

Balk EM, et al. Diagnosis and Treatment of Obstructive Sleep Apnea in Adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Jul.

Other Clinical Symptoms of OSA

According to the Institute for Clinical Systems Improvement, these characteristics also suggest a significant risk of OSA:



Institute for Clinical Systems Improvement. Diagnosis and treatment of obstructive sleep apnea. 6th ed. Bloomington, Minn.: Institute for Clinical Systems Improvement; June 2008.

Recommended Primary Care Screening

STOP Sleep Apnea Questionnaire

S: Snore loudly?

T: Tired, fatigued or sleepy during the day?

O: Observed stopping breathing during sleep?

P: High blood **Pressure?**

Two or more positive answers indicates high risk of OSA.

Chung F, Yegneswaran B, Liao P, et al. *Anesthesiology*. 2008;108(5):812-21.

Sleep Study

Definitive diagnosis of OSA requires evaluation from a sleep specialist of objective information from a sleep study:

- Take-home (preferred): limited channel testing (LCT)
- Overnight polysomnography (PSG)

Obstructive sleep apnea: Diagnosis. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/obstructive-sleep-apnea/diagnosis-treatment/drc-20352095. Accessed December 2018.

Sleep Studies Evaluate Multiple Factors

Sleep Studies Evaluate Multiple Factors

HOME TESTING MEASURES:

Blood oxygen levels

Airflow

Respiratory effort

May underestimate apnea-hypopnea index (AHI): the number of apnea and hypopnea (partial inhalation) incidents the sleeper experiences per hour

Board-certified sleep specialists should evaluate sleep test results and make treatment recommendations.

PSG MEASURES:

Blood oxygen levels

Airflow

Respiratory effort

Leg movements

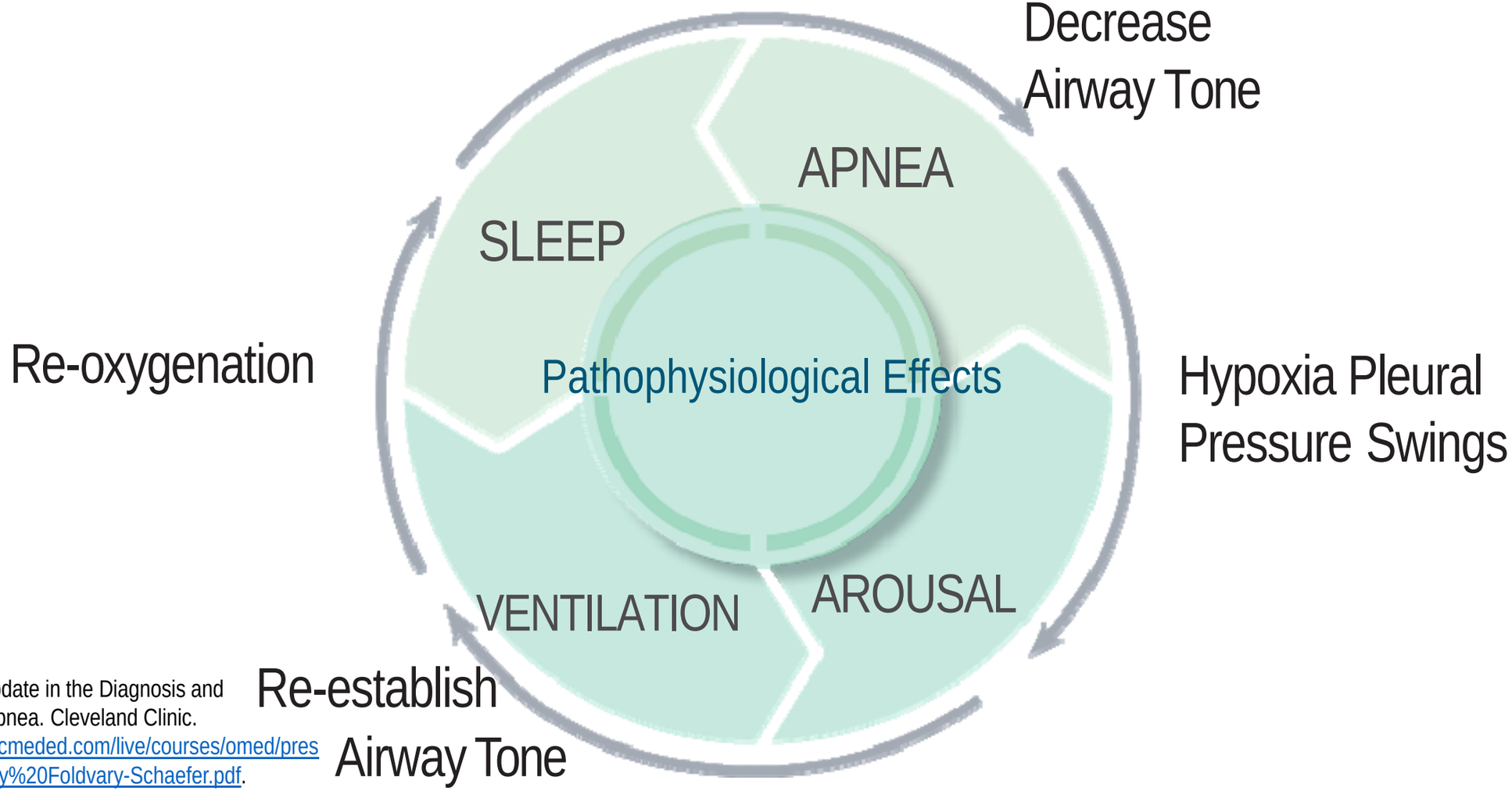
AHI

Cardiovascular function

Brain-wave activity

Chesson AL, Berry RB, Pack A. *Sleep*. 2003;26(7):907-13.
Collop NA, Tracy SL, Kapur V, et al. *J Clin Sleep Med*. 2011;7(5):531-48.
Collop NA, Anderson WM, Boehlecke B, et al. *J Clin Sleep Med*. 2007;3(7):737-47.

Sleep Studies Reveal Pattern of Apnea



Foldvary-Schaefer N. Update in the Diagnosis and Management of Sleep Apnea. Cleveland Clinic. http://www.clevelandclinicmeded.com/live/courses/omed/presentations/0800%20Nancy%20Foldvary-Schaefer.pdf. Accessed December 2018.

Conservative Treatment: Lifestyle Changes

Avoidance of alcohol and sedatives for 4 to 6 hours prior to bedtime

Weight loss

Sleeping on one's side rather than on the stomach or back

Smoking cessation

Memon J, Manganaro SN. Apnea, Snoring and Obstructive Sleeps, CPAP. StatPearls [Internet]. June 3, 2018.

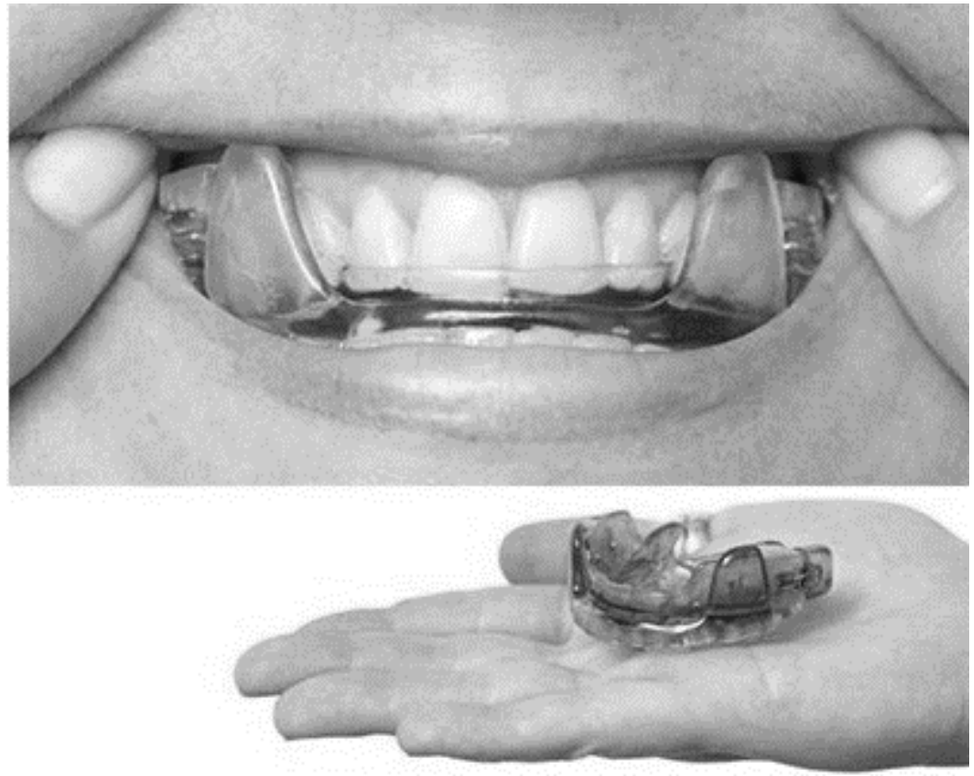
Non-pharmacological Treatment

- Treating nasal obstruction may help mild apnea.
- Oral appliances may suffice for mild to moderate apnea.
- Moderate-to-severe apnea usually requires continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP).
- Surgery is an option for patients who fail other therapies, but has mixed results.
- Hypoglossal nerve stimulation is an alternative for severe apnea.

Memon J, Manganaro SN. Apnea, Snoring and Obstructive Sleeps, CPAP. StatPearls [Internet]. June 3, 2018.
Foldvary-Schaefer N. Update in the Diagnosis and Management of Sleep Apnea. Cleveland Clinic. http://www.clevelandclinicmeded.com/live/courses/omed/presentations/0800%20Nancy%20Foldvary-Schaefer.pdf. Accessed December 2018.

Oral Appliances

- An oral appliance can help mild OSA and may be preferred by patients resistant to CPAP devices.
- A mandibular advancement device holds the jaw forward to help keep upper airway open.
- Tongue retaining mouthpieces hold the tongue forward with gentle suction to keep it from collapsing into the airway. They are an option for patients whose jaws are not held forward sufficiently by mandibular advancement devices.



Hines, J. Dental Appliances for Sleep Apnea: Pros and Cons of Dental Devices. Alaska Sleep Education Center. https://www.alaskasleep.com/blog/dental-appliances-for-sleep-apnea. Published June 26, 2018. Accessed December 2018.

Oral Appliance Studies

- Four randomized controlled studies found oral appliances improved AHI, arousal index and oxygen saturation, though the degree differed substantially.
- All reported significant reduction in snoring.
- Up to 99% of patients expressed interest in continuing oral appliance use at study conclusion and most studies found a high degree of compliance in usage.
- Patients experienced some jaw discomfort in the morning and excessive salivation at night.

40-60%	• Mean Apnea-Hypopnea Index decline
30-50%	• Reduction in hourly arousals
23-66%	• ESS score drop
3-4%	• Oxygenation improvement

Blanco J, Zamarrón C, Abeleira pazos MT, Lamela C, Suarez quintanilla D. *Sleep Breath*. 2005;9(1):20-5.
Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. *Am J Respir Crit Care Med*. 2001;163(6):1457-61.
Gotsopoulos H, Chen C, Qian J, Cistulli PA. *Am J Respir Crit Care Med*. 2002;166(5):743-8.

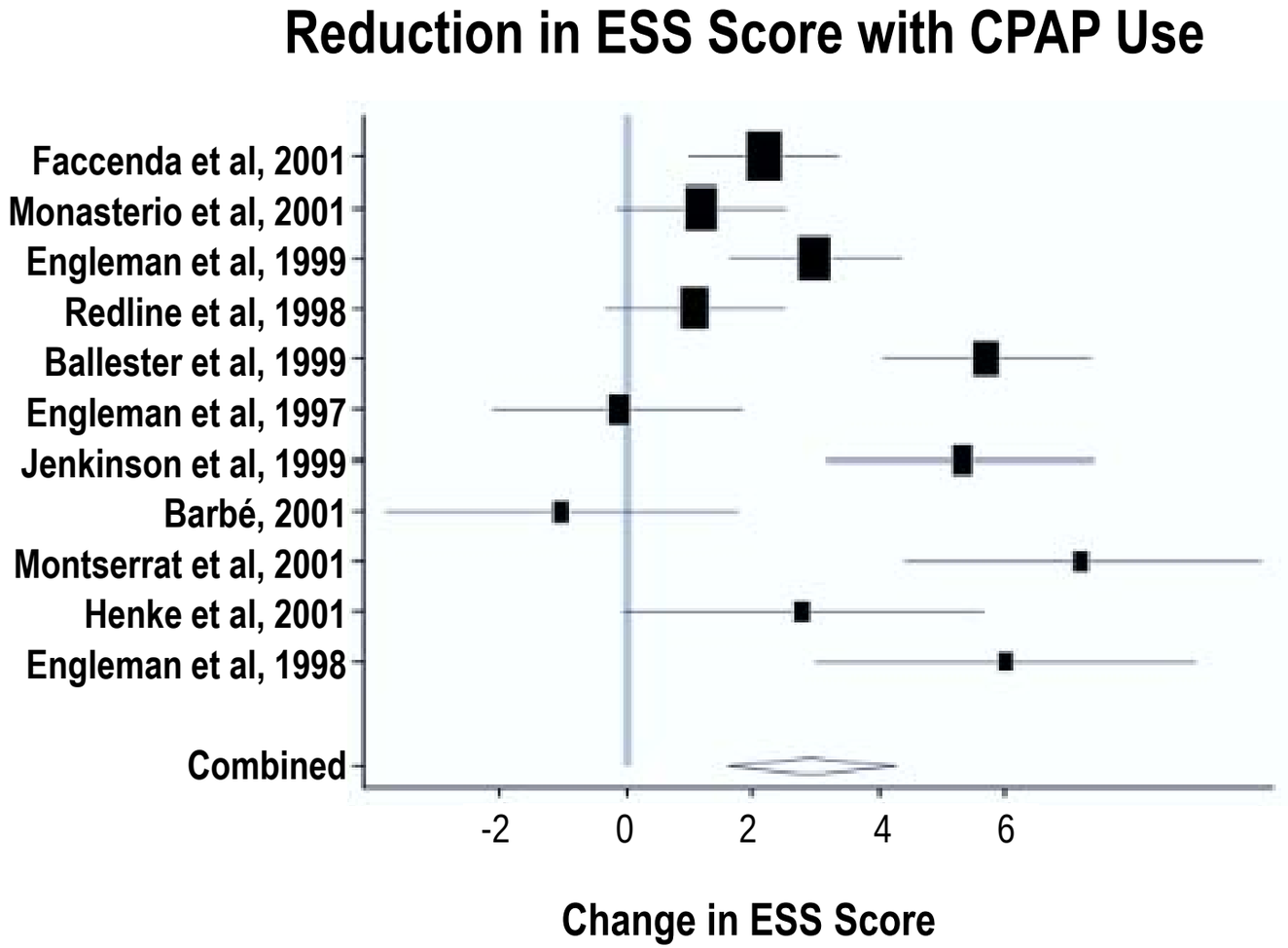
CPAP Function

- First-line medical therapy.
- Blows air into the nose and throat through a mask.
- Creates positive pressure to keep upper airway open during sleep, eliminating obstruction that causes apnea.
- Permits unrestricted airflow to lungs.
- Reduces frequency of respiratory events during sleep, decreases daytime sleepiness, improves systemic blood pressure, improves quality of life.

Redline S. *JAMA*. 2017;317(4):368-370.

CPAP Benefits Some More Than Others

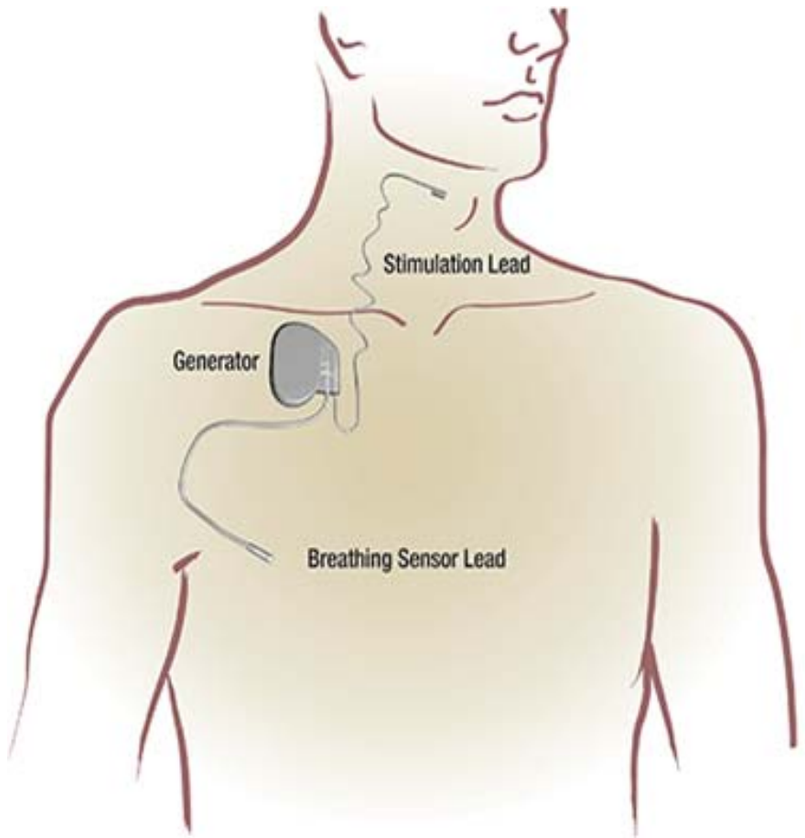
- Meta-analysis of 11 studies of patients with OSA found CPAP reduced Epworth Sleepiness Scale (ESS) score by a mean of 2.94 points more than placebo.
- 6 studies that recruited only patients with severe OSA and ESS scores greater than 11, had mean ESS score reduction of 4.75 associated with CPAP usage.
- Excluding those studies, the mean reduction in ESS was 1.1 points, which was not statistically significant.



Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. *Arch Intern Med*. 2003;163(5):565-71.

Electrical Stimulation of Hypoglossal Nerve

- Surgically implanted device stimulates the hypoglossal nerve when respiratory pressure changes.
- Stimulation tightens tongue and upper airway, improving air flow and reducing episodes of apnea.
- Recommended for adults with AHI of 15 or more who failed CPAP therapy and have BMI below 32.



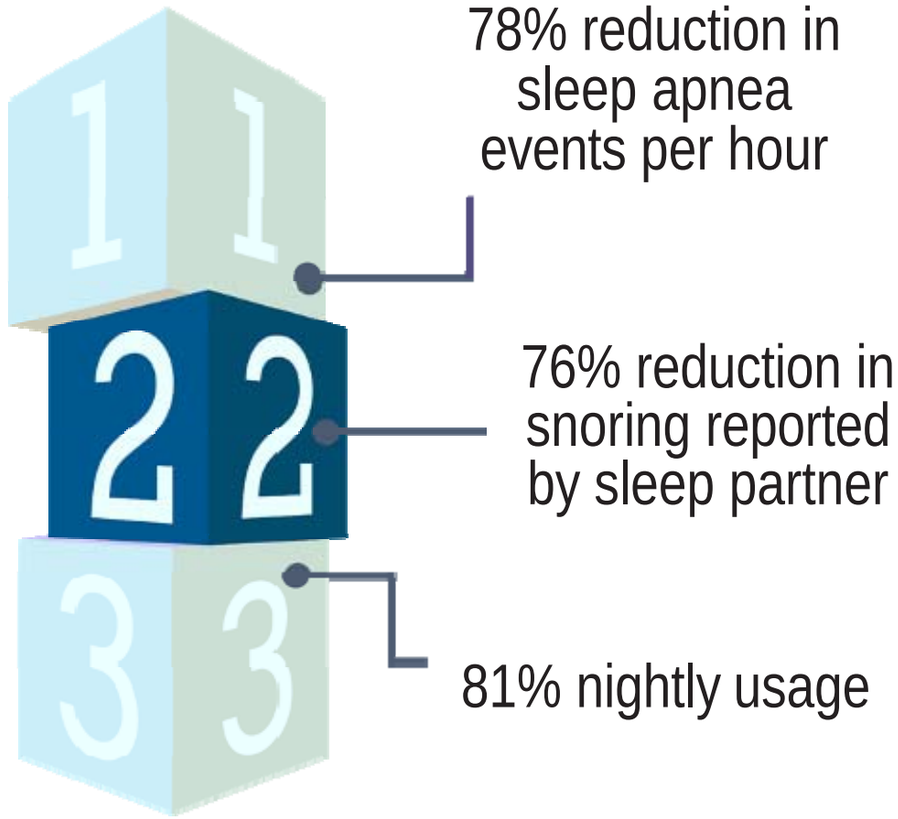
Stimulation Lead
Delivers mild stimulation to maintain multilevel airway patency during sleep

Generator
Monitors breathing patterns

Breathing Sensor Lead
Senses breathing patterns

Star Trial: Inspire Hypoglossal Nerve Stimulation

STAR enrolled 126 patients with OSA to evaluate hypoglossal nerve stimulation system (Inspire). Based on results published in *New England Journal of Medicine*, FDA approved the device for OSA.



Woodson BT, Soose RJ, Gillespie MB, et al. *Otolaryngol Head Neck Surg*. 2016;154(1):181-8.
Woodson BT, Strohl KP, Soose RJ, et al. *Otolaryngol Head Neck Surg*. 2018;159(1):194-202.

Challenges In OSA Treatment

- CPAP and surgery can cure OSA for some patients.
- Other patients find the devices burdensome or ineffective.

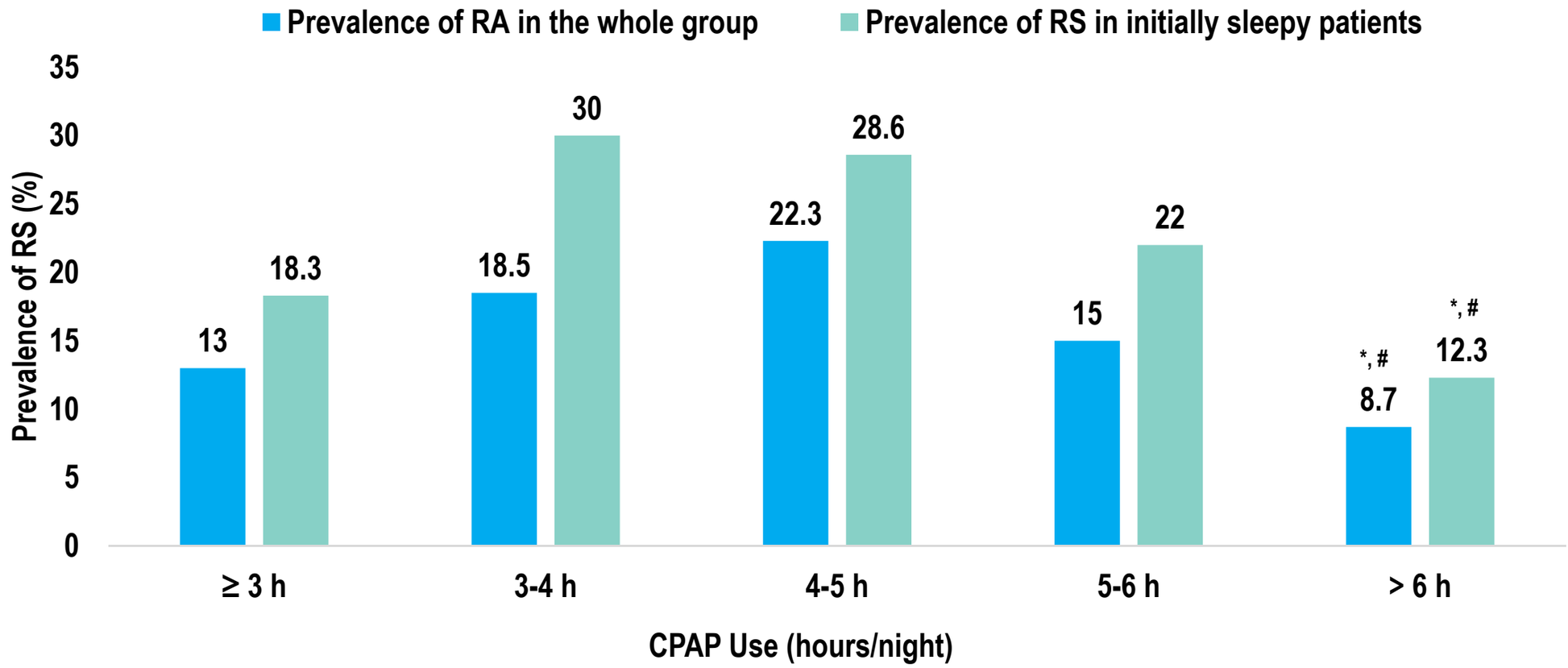
Up to one-third of OSA patients report excessive sleepiness despite compliance with CPAP.

32% of patients who use CPAP 6+ hours reported functional impairment.

Half of patients do not consistently use CPAP devices at 3 months.

Weaver TE, Maislin G, Dinges DF, et al. *Sleep*. 2007;30(6):711-9.
Antic NA, Catcheside P, Buchan C, et al. *Sleep*. 2011;34(1):111-9.
Weaver TE, Kribbs NB, Pack AI, et al. *Sleep*. 1997;20(4):278-83.

CPAP Compliance and Residual Excessive Sleepiness



*, #: significant differences for comparison with 3-4 and 4-5 hr, respectively.

Gasa M, et al, *J Sleep Res*, 2013.

Summary

The majority of individuals with OSA are undiagnosed.

Undiagnosed OSA is associated with increased healthcare costs and risk of significant comorbidities.

Specific patient characteristics should raise suspicion of OSA.

Primary care physicians can quickly conduct the STOP questionnaire to screen at-risk patients for OSA.

A sleep study can provide a definitive diagnosis.

Treatment varies with severity and response to behavioral changes and use of appliances and other devices.

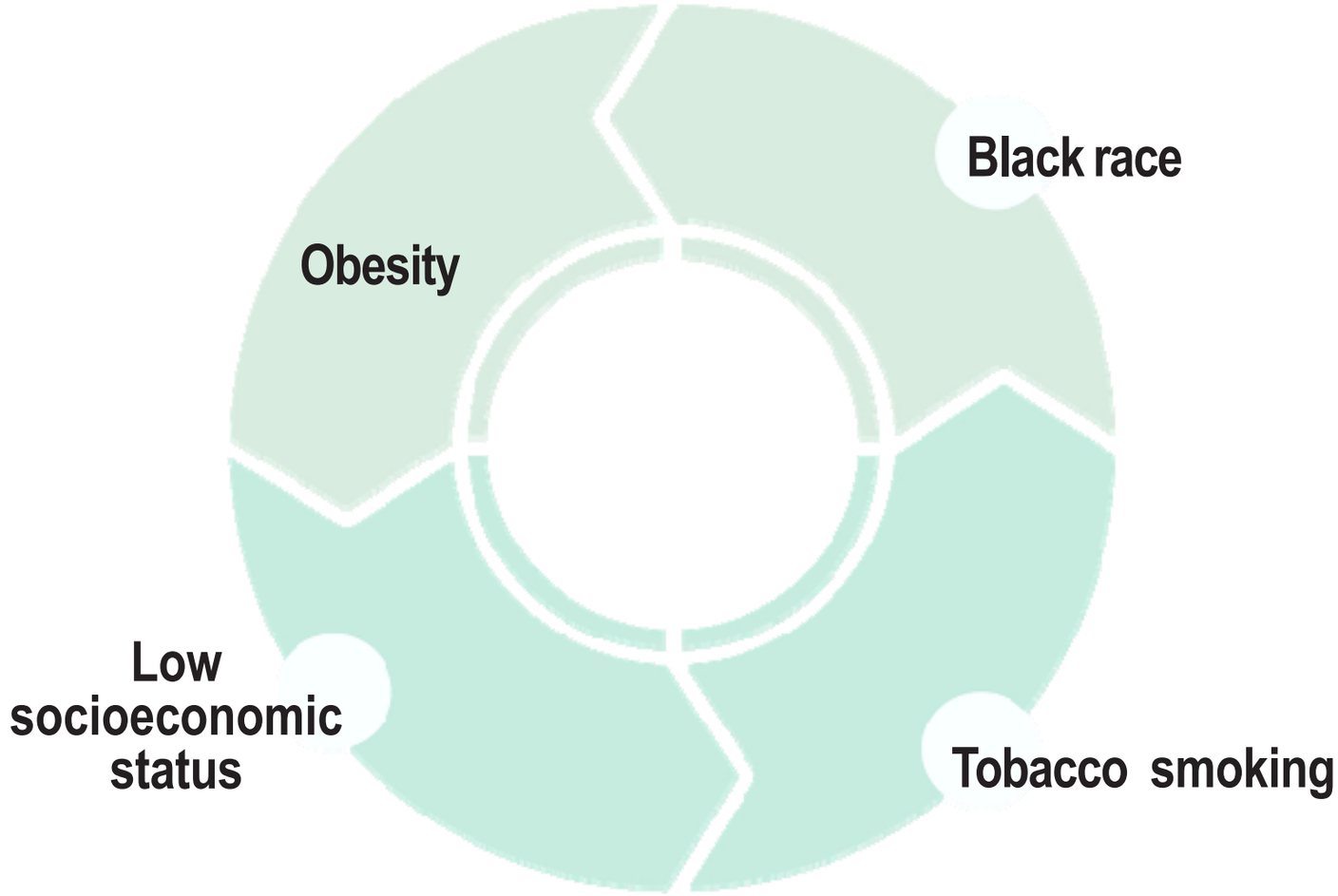
Pharmacologic Therapy Review for the Management of OSA

Edmund Pezalla, MD, MPH

CEO, Enlightenment Bioconsult, LLC

High Risk and Low Compliance

Many risk factors for OSA and resultant CVD also increase the risk of poor CPAP adherence.

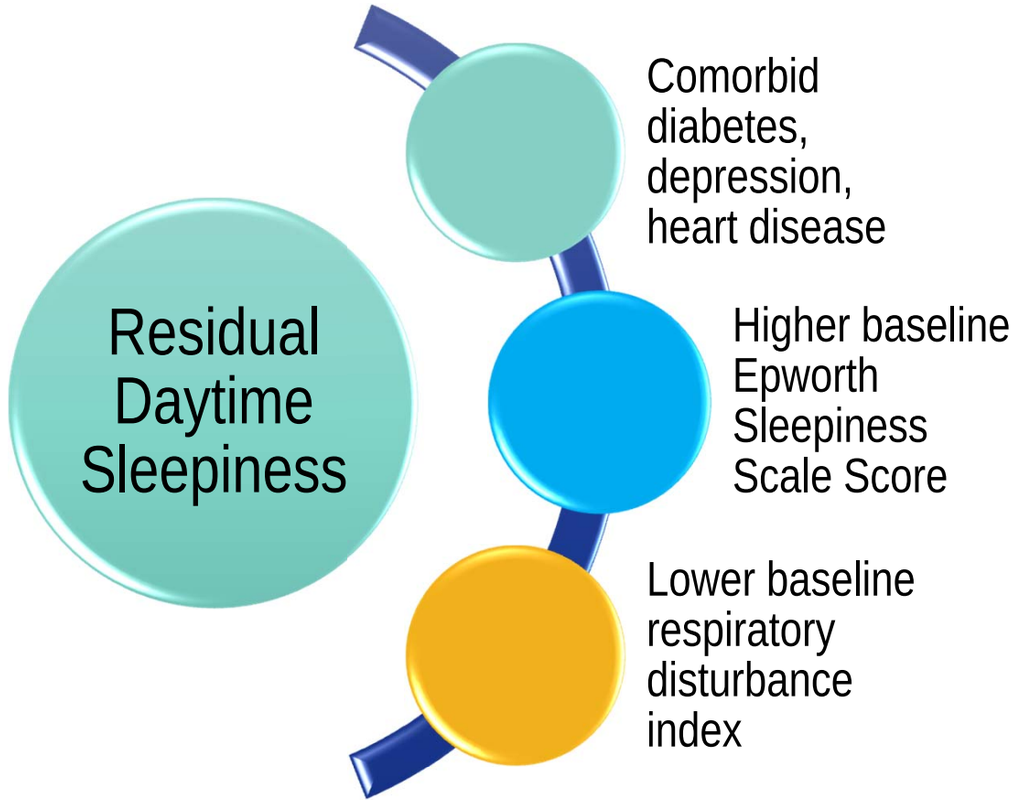


Billings ME, Auckley D, Benca R, et al. *Sleep*. 2011;34(12):1653-8.

Persistent Daytime Sleepiness

- 10% of *optimally* treated patients with OSA continue to experience excessive daytime sleepiness.
- 55% of those with “good” compliance (more than 4 hours per day, at least 5 nights per week) continue to report excessive daytime sleepiness.

Factors in Persistent Sleepiness with Optimal CPAP Use



Koutsourelakis I, Perraki E, Economou NT, et al. *Eur Respir J*. 2009;34(3):687-93.
Launois SH, Tamisier R, Lévy P, Pépin JL. *Curr Opin Pulm Med*. 2013;19(6):601-8.

Multiple Causes for Excessive Daytime Sleepiness (EDS)

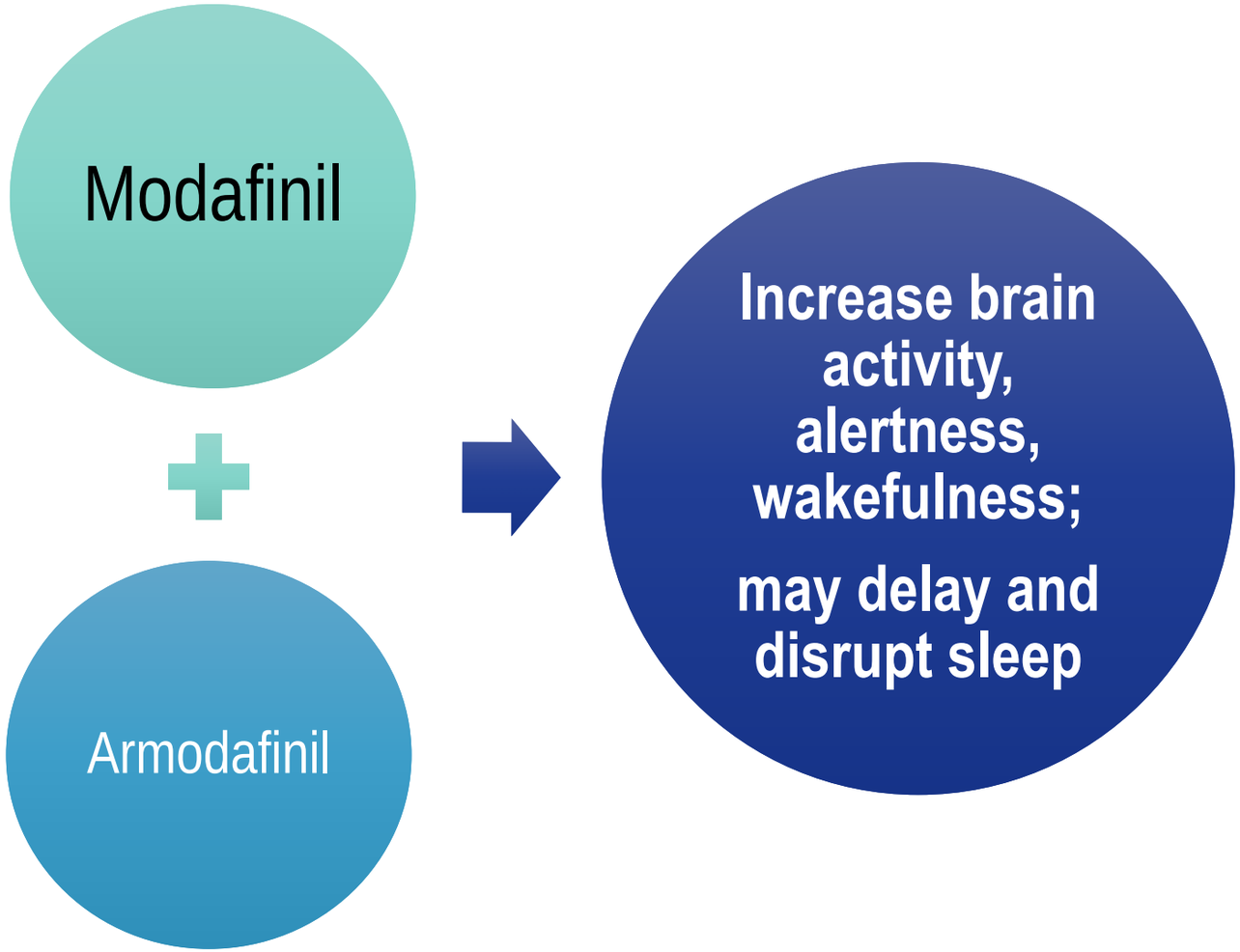
In mild-to-moderate sleep apnea, daytime sleepiness may be caused by other sleep disorders not addressed by CPAP usage.

- Periodic limb movement
- Chronic sleep deprivation
- Undiagnosed narcolepsy
- Idiopathic hypersomnolence

Schweitzer PK, Rosenberg R, Zammit G.K., et al. *Sleep Medicine*. December 2017;40(S1):e298.

Pharmacological Treatment of EDS in OSA

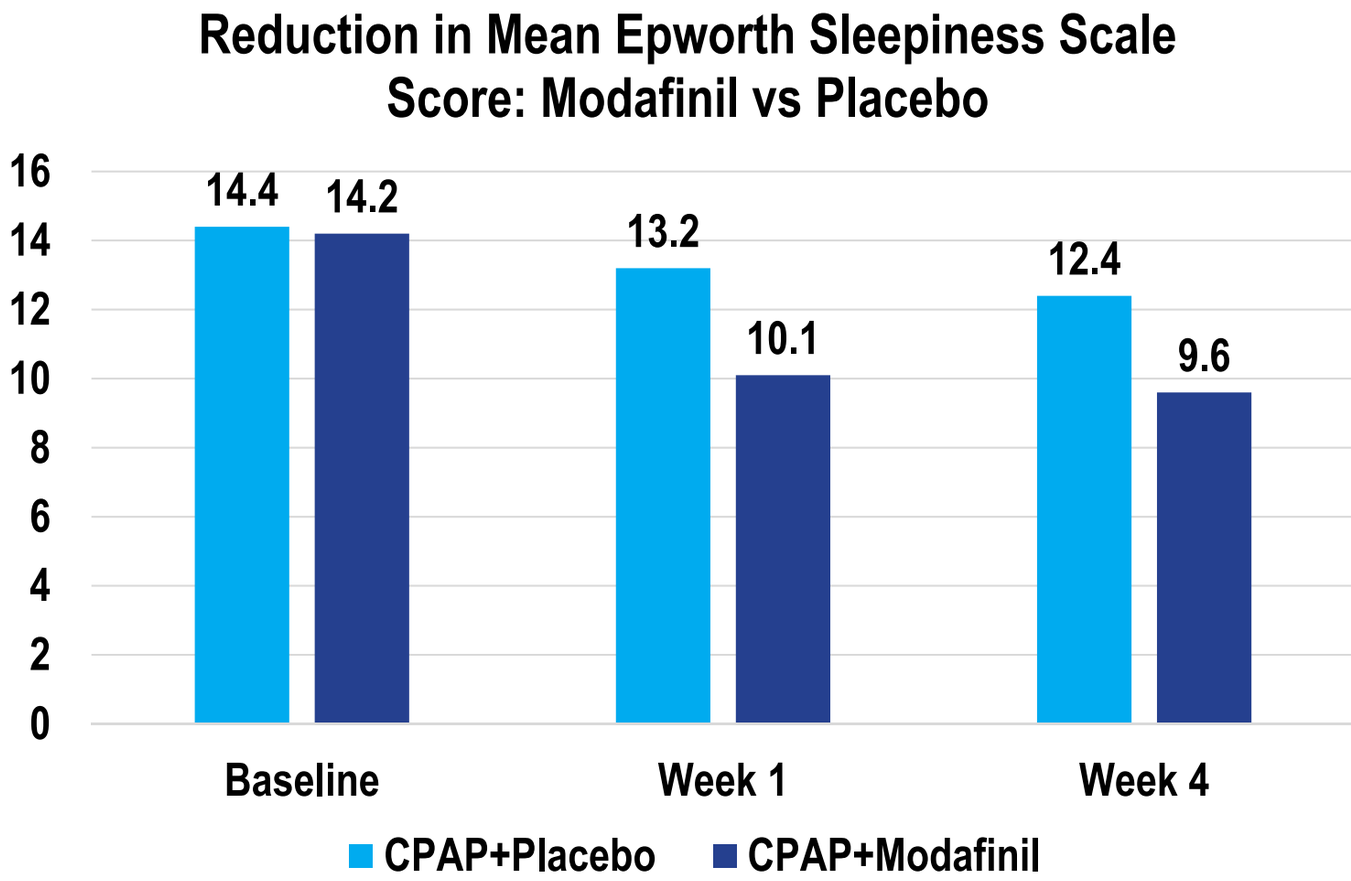
Two FDA-approved stimulant medications for residual sleepiness despite optimal CPAP use are recommended by the American Academy of Sleep Medicine—modafinil and armodafinil.



Kuan YC, Wu D, Huang KW, et al. *Clin Ther*. 2016;38(4):874-88.

Modafinil: Residual Excessive Daytime Sleepiness

Modafinil and its R-enantiomer armodafinil reduce sleepiness 2.8 points more than placebo in patients with EDS despite CPAP use.



Pack AI, Black JE, Schwartz JR, Matheson JK. *Am J Respir Crit Care Med.* 2001;164(9):1675-81.

Risks of Modafinil and Armodafinil

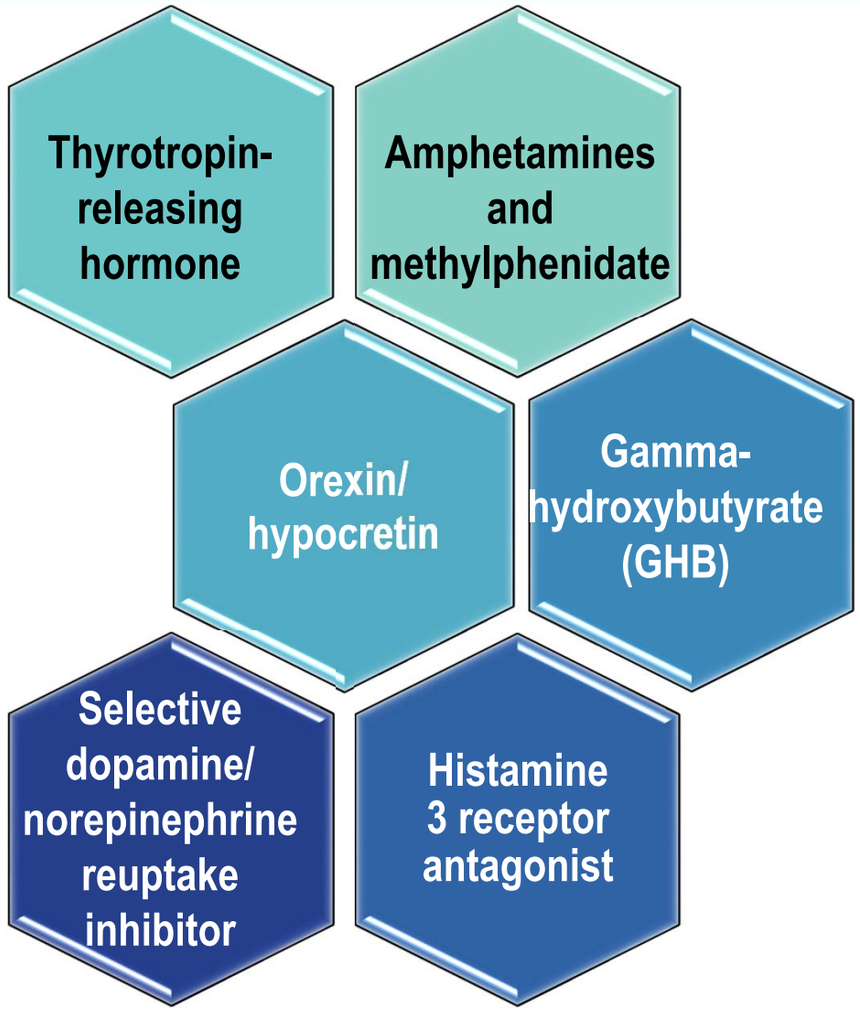
Risks associated with modafinil/armodafinil caused the FDA to classify them as controlled substances and the European Medicines Agency to reverse their approval for use in OSA.

- **Linked to life-threatening skin reactions**
- **Adverse psychiatric reactions—suicidal thoughts, depression, psychosis**
- **Cardiovascular adverse reactions—hypertension, irregular heart beat**
- **Schedule IV controlled substances based on potential for abuse and addiction**

Modafinil. European Medicines Agency. https://www.ema.europa.eu/medicines/human/referrals/modafinil. Published November 11, 2010. Updated April 26, 2011. Accessed December 2018.

Investigational Agents for EDS in OSA

A number of new agents and some existing agents are in clinical development to address excessive daytime sleepiness in OSA.



Schweitzer PK, Rosenberg R, Zammit G.K., et al. *Sleep Medicine*. December 2017;40(S1):e298.

Phase III Investigational Therapies For Excessive Daytime Sleepiness (EDS)

Solriamfetol

- Selective dopamine and norepinephrine reuptake inhibitor
- In Phase III trials for EDS in OSA
- Unlike CNS stimulants, does not promote hyperactivity, disrupt sleep or cause rebound hypersomnia
- Low risk of abuse

Pitolisant:

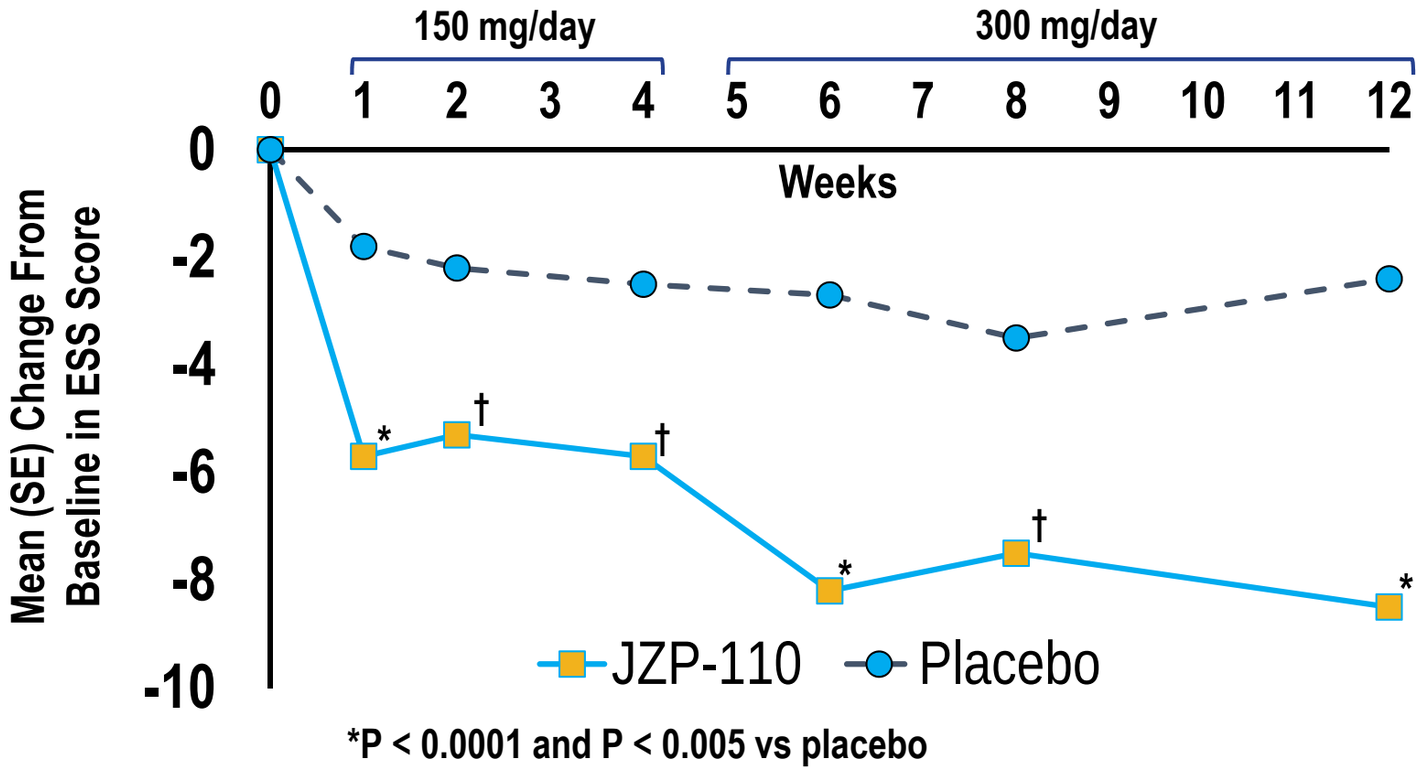
- Selective inverse agonist of the histamine H3 receptor
- In Phase III trials for treatment of hypersomnia

Schweitzer PK, Rosenberg R, Zammit G.K., et al. *Sleep Medicine*. December 2017;40(S1):e298.
Leu-semenescu S, Nittur N, Golmard JL, Arnulf I. *Sleep Med*. 2014;15(6):681-7.
JZP-110 May Have Low Potential for Abuse. *Neurology Reviews*. 2016 September;24(9):26.

Solriamfetol: Excessive Daytime Sleepiness

- Solriamfetol (JZP-110) reduced patients' Epworth Sleepiness Scale (ESS) score by more than 8 points at week 12.
- ESS asks patients to assess their likelihood of dozing off in eight common situations such as watching TV or traveling in a car. Scaled from 0-24, a score above 10 is considered excessive daytime sleepiness.

Reduction in Epworth Sleepiness Scale (ESS) Score: Solriamfetol and Placebo

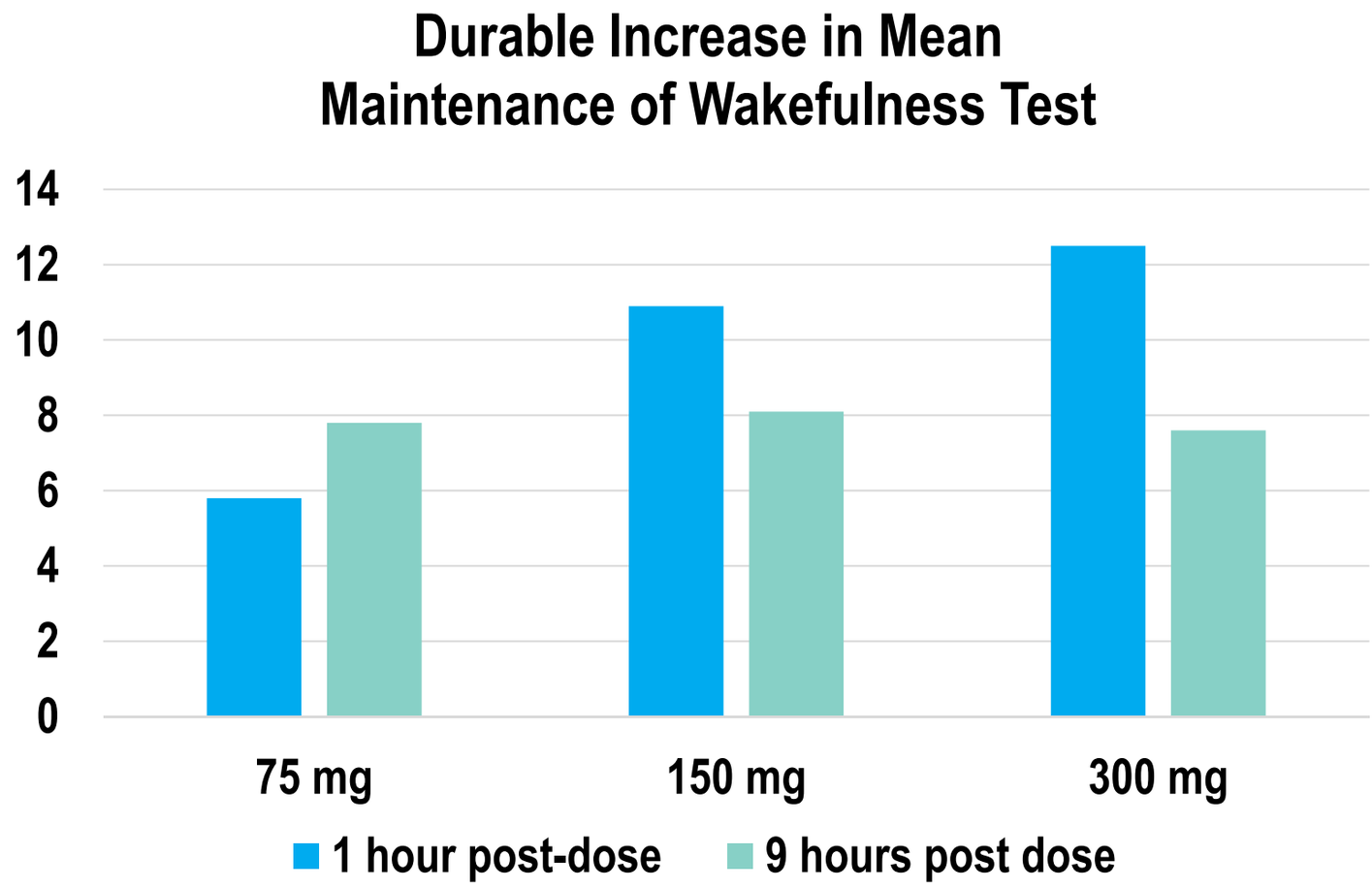


*P < 0.0001 and P < 0.005 vs placebo

Ruoff C, Swick TJ, Doekel R, et al. *Sleep*. 2016;39(7):1379-87.

Solriamfetol: Long-lasting Increase in Daily Wakefulness

- Solriamfetol extended sleep latency by more than 11 minutes on Maintenance of Wakefulness Test at 150 mg and 300 mg doses.
- Increased wakefulness continued for more than 9 hours.

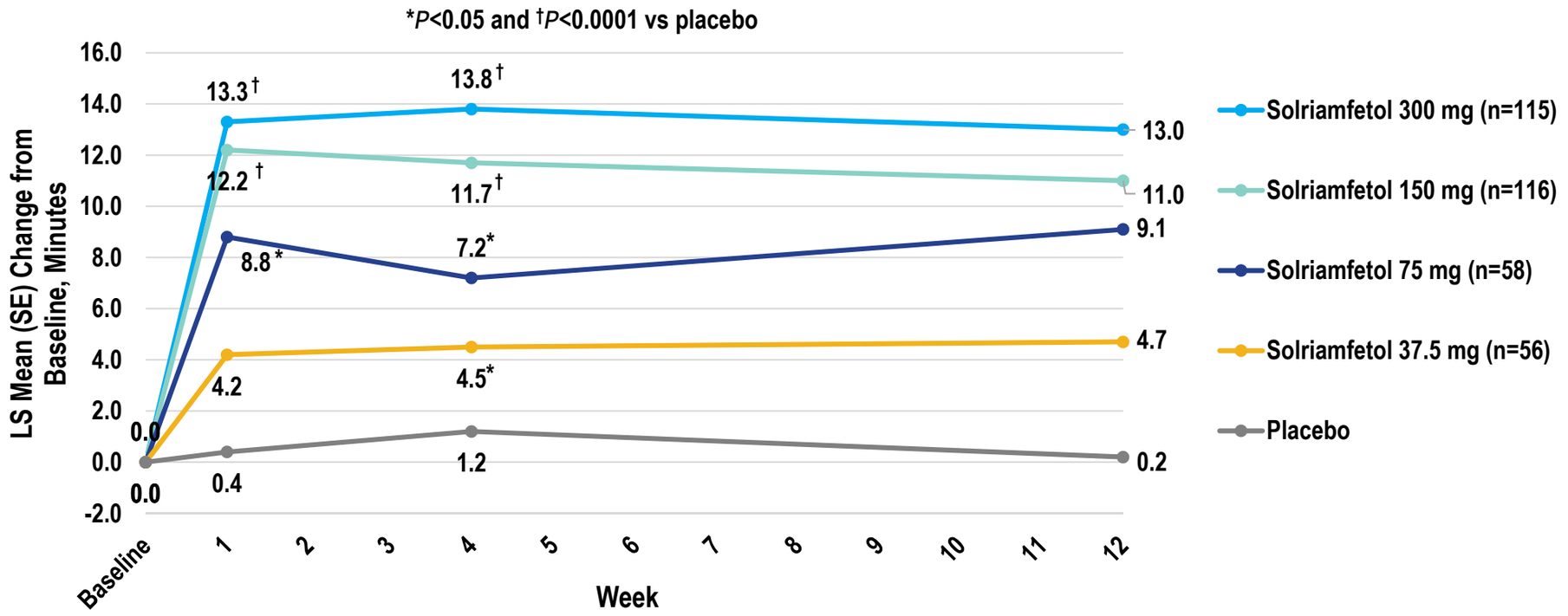


Schweitzer PK, Strohl KP, Malhotra A, et al. *Sleep. 2018;* 41(S1):A231.

Solriamfetol: Consistent Increased Sleep Latency

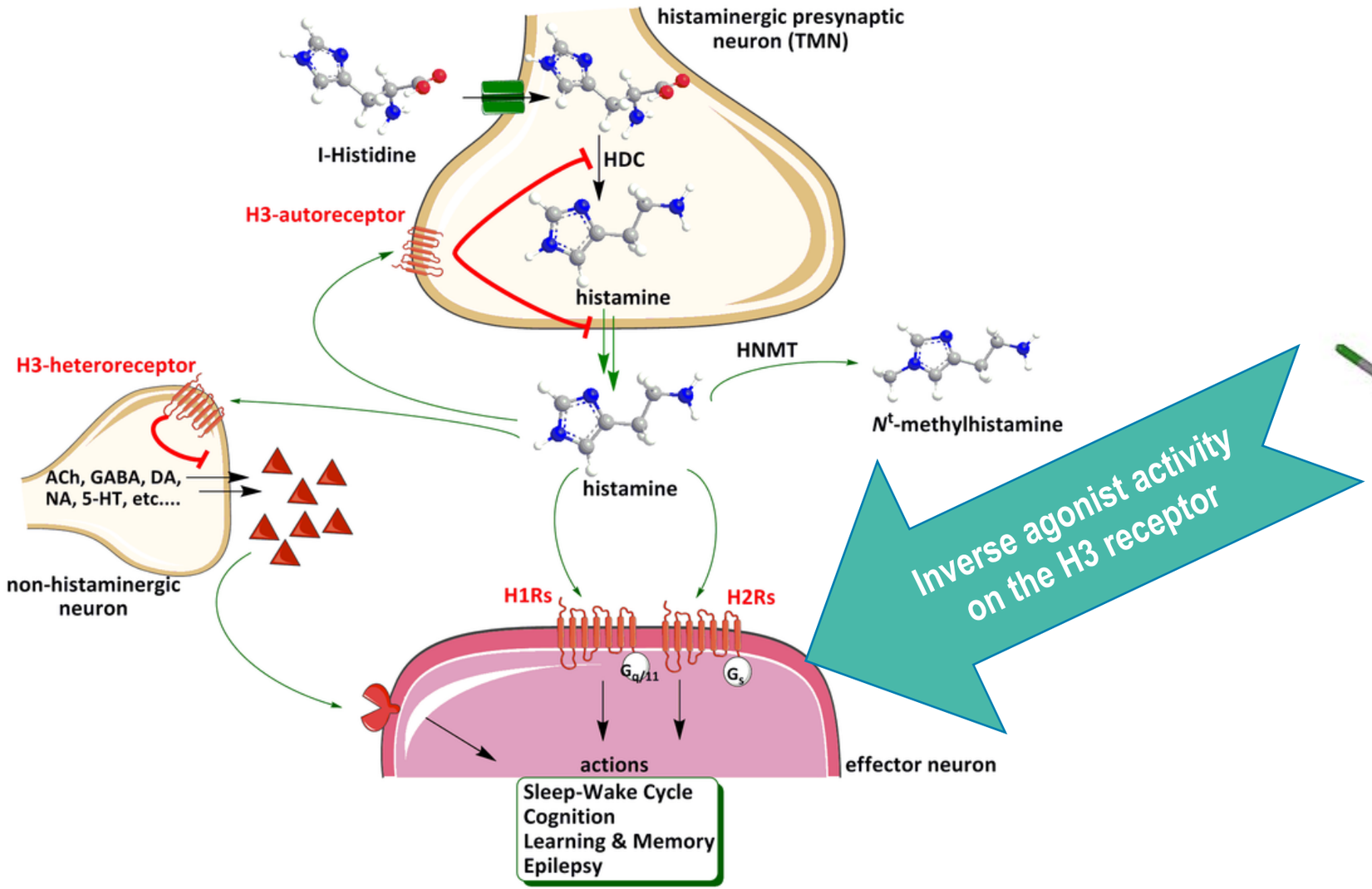
Solriamfetol provided consistent, significant increase in sleep latency over 12 weeks.

Increase in Sleep Latency Over 12 Weeks: Solriamfetol vs. Placebo

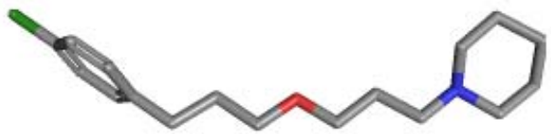


Schweitzer PK, Rosenberg R, Zammit G.K., et al. *Sleep Medicine*. December 2017;40(S1):e298.

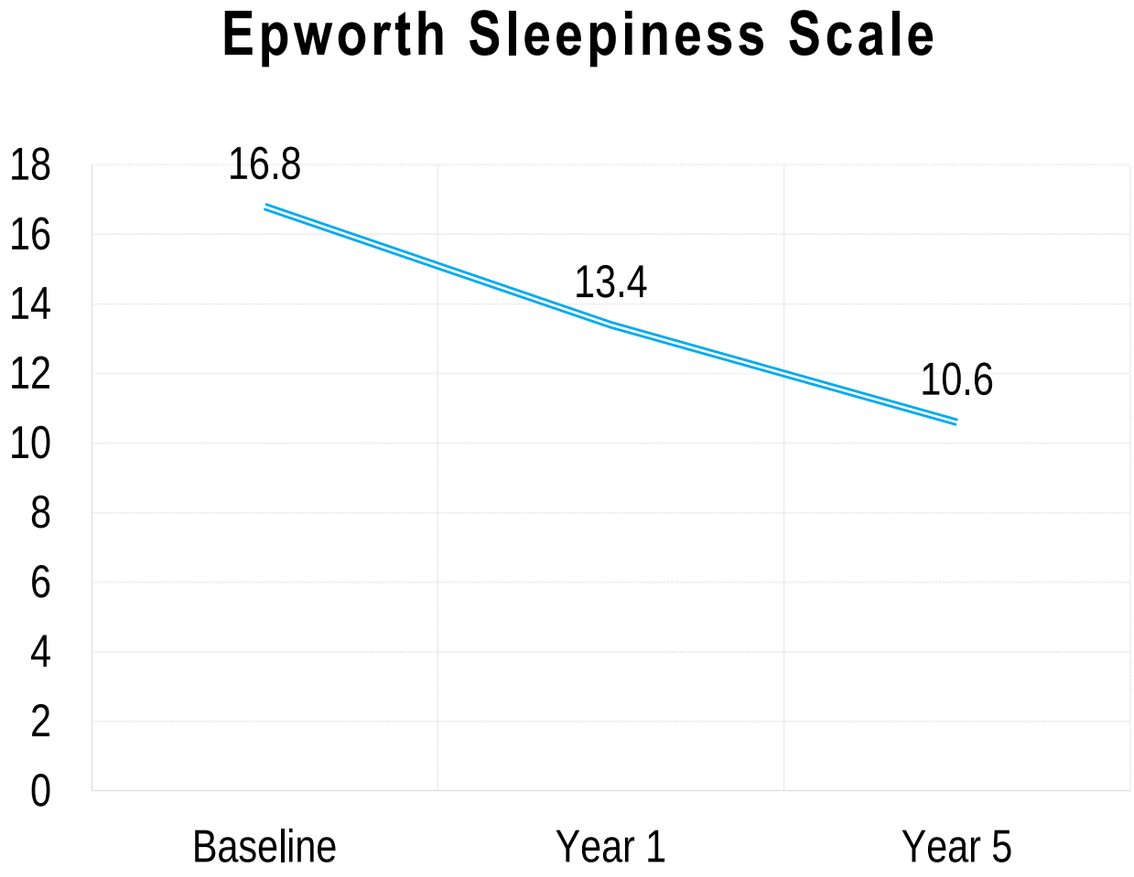
Pitolisant Mechanism of Action



Pitolisant



HARMONY III Trial: Pitolisant



Pitolisant reduced excessive daytime sleepiness more than 3 points at one year and about 6 points at five years.

Dayno JM. An Open-Label, Naturalistic Study to Assess the Long-Term Safety of Pitolisant in Adult Patients with Narcolepsy With or Without Cataplexy: Results from the Harmony III Study Five Year Extension. Oral Presentation at 7th International Symposium on Narcolepsy. Beverly, MA: September 11, 2018.

Summary

CPAP	EDS	Approved Therapies	Investigational Therapies
Benefits patients with most severe OSA the most.	Excessive Daytime Sleepiness affects many patients despite CPAP use.	Modafinil and Armodafinil are FDA-approved and AASM-recommended for EDS in treated OSA. As CNS stimulants, both have significant risks.	A number of new therapies are in development. Solriamfetol is in phase 3 clinical trials for EDS in OSA. Pitolisant in phase 3 trials for hypersomnia.

OSA Benefit Design and Care Coordination Strategies for Optimal Outcomes

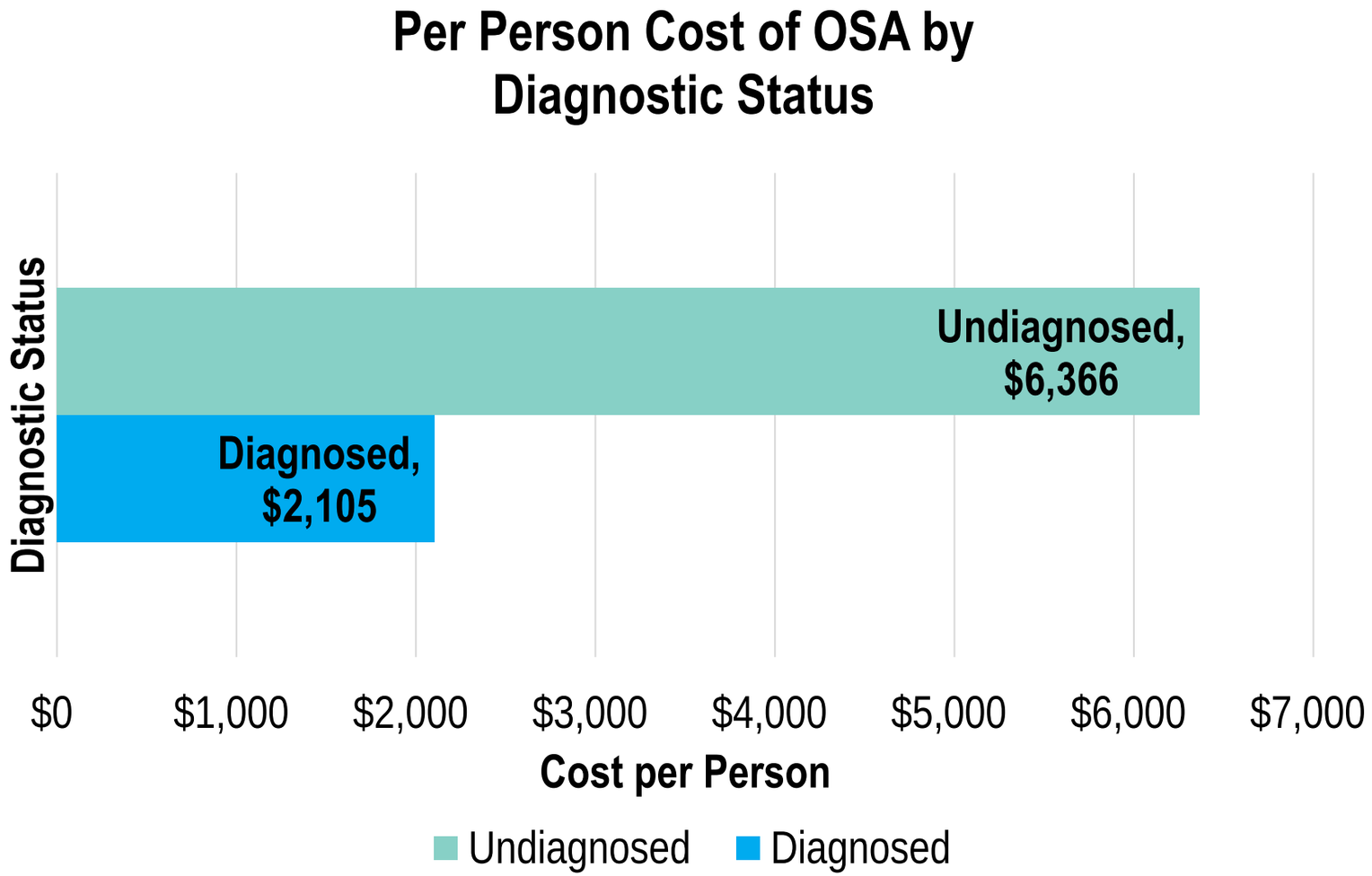
Jeffrey D. Dunn, PharmD, MBA

Vice President, Clinical Strategy and Programs and Industry Relations
Magellan Rx Management

The Cost of Undiagnosed OSA by Member

3x

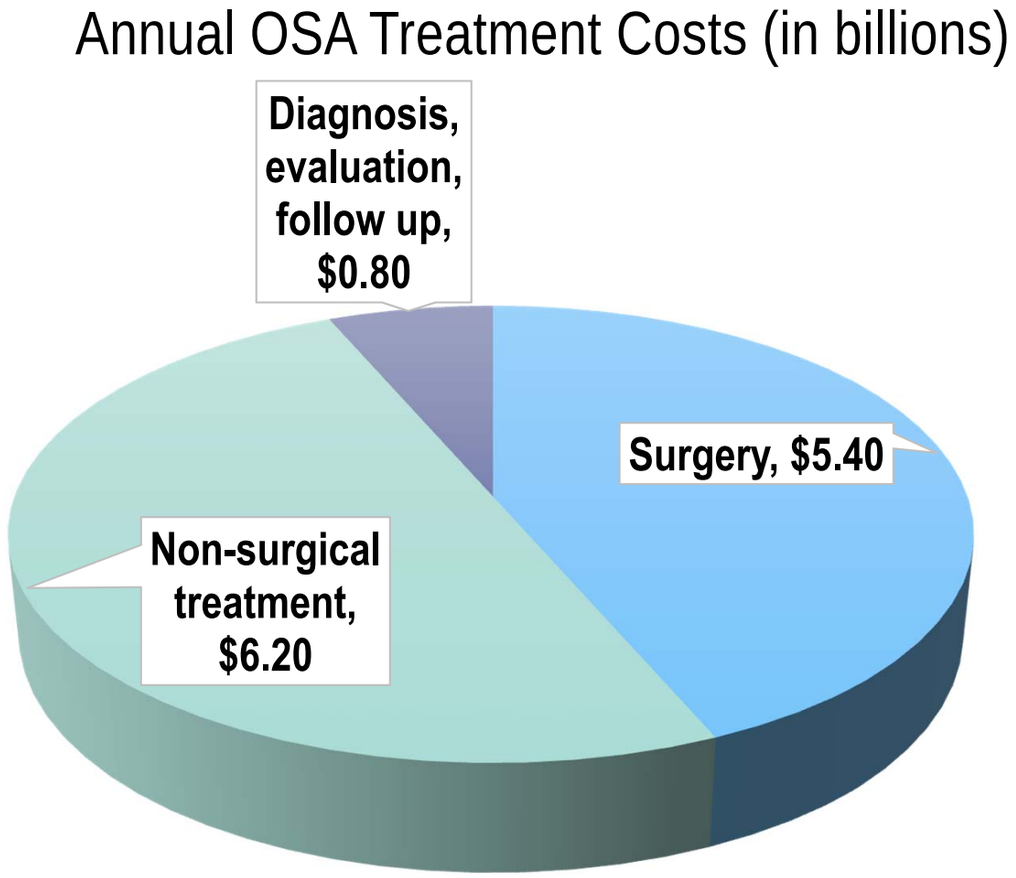
Members with undiagnosed OSA have triple the medical costs of those who have received diagnoses.



Frost & Sullivan. Hidden health crisis costing America billions. Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system. Darien, IL: American Academy of Sleep Medicine; 2016. Available at: https://aasm.org/resources/pdf/sleep-apnea-economic-crisis.pdf. Accessed December 2018.

The Cost of Care

- Diagnosis, evaluation and follow up account for just 6% of total OSA treatment costs.
- Total treatment costs are approximately $12.4 billion annually.



Frost & Sullivan. Hidden health crisis costing America billions. Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system. Darien, IL: American Academy of Sleep Medicine; 2016. Available at: https://aasm.org/resources/pdf/sleep-apnea-economic-crisis.pdf. Accessed December 2018.

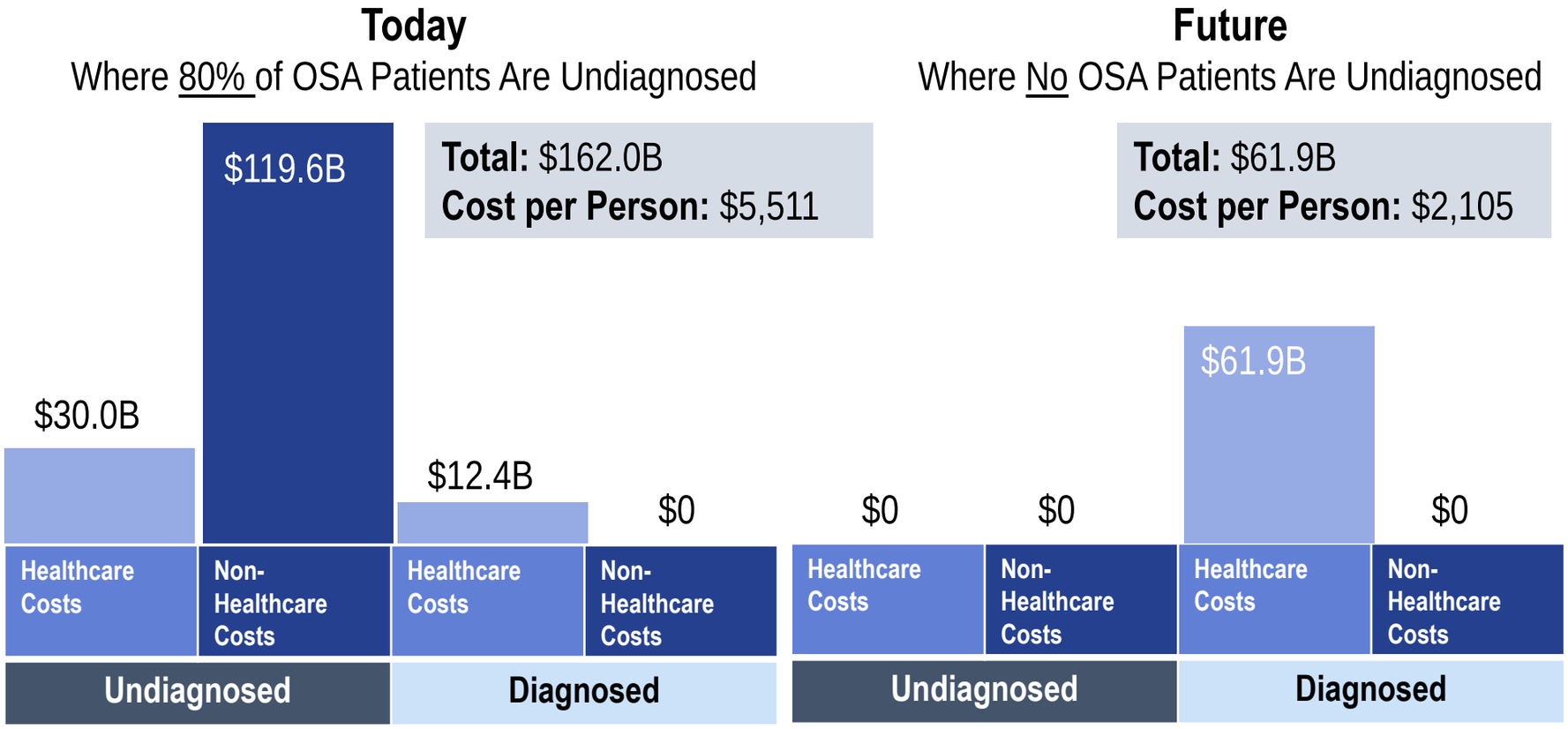
Savings Associated With OSA Treatment

$100.1 billion

- Annual savings for payers and purchasers if every American with OSA were diagnosed and treated.
- Treatment costs would be more than offset by reduced healthcare utilization, management of comorbidities, increased productivity, and reduced accident-related costs.

Frost & Sullivan. Hidden health crisis costing America billions. Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system. Darien, IL: American Academy of Sleep Medicine; 2016. Available at: https://aasm.org/resources/pdf/sleep-apnea-economic-crisis.pdf. Accessed December 2018.

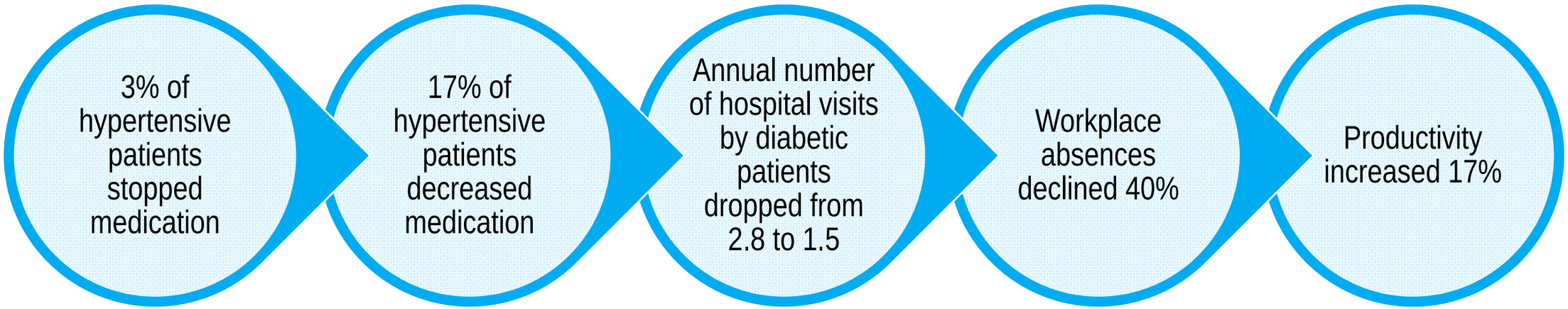
How Treatment Reduces Costs



Exploring the Economic Benefits of OSA Diagnosis and Treatment. American Academy of Sleep Medicine. https://aasm.org/advocacy/initiatives/economic-impact-obstructive-sleep-apnea/. Published August 2016. Accessed December 2018.

OSA Treatment Improves Comorbidities

- OSA treatment can reduce burden of hypertension and T2DM.
- Among 506 US patients actively receiving treatment for OSA:



Frost & Sullivan. Hidden health crisis costing America billions. Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system. Darien, IL: American Academy of Sleep Medicine; 2016. Available at: https://aasm.org/resources/pdf/sleep-apnea-economic-crisis.pdf. Accessed December 2018.

Employers Invest in OSA

Alphabet

Schneider Electric

HUFFPOST

UPREHS
Union Pacific Railroad Employes Health Systems

aetna

Humana.

Frost & Sullivan. Hidden health crisis costing America billions. Underdiagnosing and undertreating obstructive sleep apnea draining healthcare system. Darien, IL: American Academy of Sleep Medicine; 2016. Available at: https://aasm.org/resources/pdf/sleep-apnea-economic-crisis.pdf. Accessed December 2018.

Path from Initial Visit to Treatment

Office visit

PCP reviews physical, clinical signs and symptoms

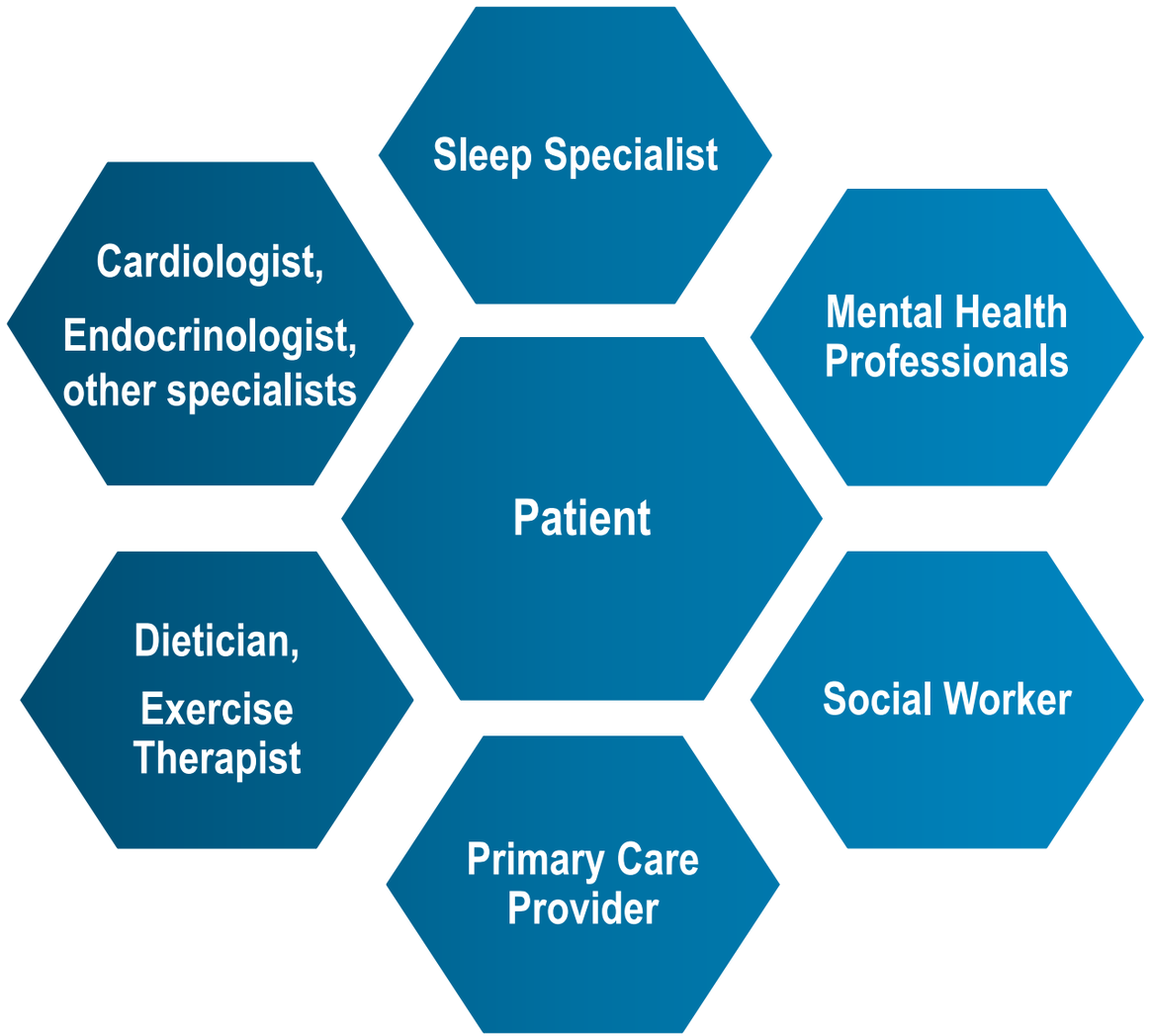
PCP uses STOP Sleep Apnea Questionnaire

PCP refers to patient to sleep specialist

Sleep specialist recommends home sleep test or performs PSG and evaluates results

Health Plan Case Management Services

Case management services may coordinate referral process and ensure patients go to the appropriate specialists.



Pharmacy Benefit Design

- OSA typically managed under the medical benefit with CPAP and surgery being the most common therapeutic interventions.
- Benefit design and coverage criteria should reflect recommendations of evidence-based guidelines:

Formulary Positioning

Utilization management interventions

Benefit design arrangements

- Provide inclusive coverage with reasonable cost-sharing based on formulary tiering to avoid adversely impacting therapeutic adherence.
- Plans should recognize complexity of OSA treatment and its benefits.

Sample OSA Pharmacy Benefit Design

Current treatment guidelines advocating modafinil and armodafinil for EDS in OSA

Evaluate available and investigational therapies for EDS based on safety, efficacy and cost

✓Benefit design and coverage criteria:

✓- Inclusive coverage

✓- Promote access to agents with different MOAs to optimize outcomes in diverse populations

✓- Tiering/cost-sharing

✓- Utilization management

Potential Factors in OSA Formulary Decisions

HEDIS = Healthcare Effectiveness Data and Information Set; JCAHO = Commission on Accreditation of Healthcare Organizations; NCQA = National Committee for Quality Assurance; PBM = pharmacy benefit manager.

Academy of Managed Care Pharmacy. Format for formulary submissions. Version 2.0.

Summary

Patients with undiagnosed OSA have three times the healthcare costs of patients with OSA who receive treatment.

Diagnosing and treating all patients with OSA would save more than $100 billion per year.

Employers increasingly value and invest in OSA diagnosis and treatment programs.

Pharmacy benefit design should balance:

- Treatment guidelines
- Safety, cost, and efficacy of investigational agents for EDS
- Inclusive coverage
- Access to multiple mechanisms of action for diverse populations
- Implementation of utilization management interventions