Front-Line Management of Excessive Daytime Sleepiness due to Obstructive Sleep Apnea:

A Partnership with Providers, Patients, and Their Care Partners

sleep360

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Faculty Disclosure

- **Dr. Greg Mattingly:** Consultant- AbbVie, Acadia, Alkermes, Axsome, Eisai, Ironshore, Intracellular, Janssen, Lundbeck, Neos, Neurocrine, Otsuka, Redax, Roche, Rhodes, Sage, Sunovion, Supernus, Takeda, Teva, and Trispharma; Research- AbbVie, Acadia, Alkermes, Avanir, Axsome, Boehringer Ingelheim, Emalex, Janssen, Medgenics, NLS-1 Pharma AG, Redax, Roche, Sage, Sunovion, Supernus, Takeda, and Teva; Speakers Bureau- AbbVie, Alkermes, Eisai, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Supernus, Takeda, and Tris Pharma.

- **Dr. David Neubauer:** Advisory Board—Eisai Inc., Idorsia Pharmaceuticals; Consultant—Eisai Inc., Idorsia Pharmaceuticals.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Describe the prevalence of and potential factors contributing to EDS due to OSA
- Identify EDS due to OSA in patients through the implementation of appropriate clinical and diagnostic strategies
- Assess the limitations of traditional approaches in the management of EDS due to OSA and evaluate the safety and efficacy of novel pharmacologic agents
- Optimize the management of EDS due to OSA through shared decision-making discussions with patients and their care partners which incorporate novel pharmacologic agents into clinical practice where appropriate

Excessive Daytime Sleepiness

Clinician's Challenge: Is it sleepiness?

Patients tell us:

I'm so....	tired	"I have no energy at all."
	exhausted	"I just don't feel like doing anything."
	fatigued	"I can't keep my eyes open."
	run down	"I feel like I could fall asleep anytime."
	worn out	
	sluggish	
	sleepy	

Differentiating “sleepiness” from “tiredness”

- Assess tendency for daytime sleep episodes
  - Napping
  - Inadvertent sleep (e.g., “nodding off”)
    - During a meeting
    - Sitting at a computer
    - Reading
    - Watching television
  - Drowsy driving
- Consider possible influences
  - Somatic conditions (e.g., anemia, hypothyroidism, deconditioning)
  - Psychiatric disorders (e.g., depressive episode, substance use disorders)
  - Sedating medications and subtances
  - Lifestyle factors
    - Daily routines
    - Activity level

Chervin RD. Approach to the patient with excessive daytime sleepiness. In: *UpToDate*, Scammell TE Eichler, (Eds), UpToDate, Waltham, MA (Accessed September 2022).

What is Excessive Daytime Sleepiness (EDS)?

Daytime sleepiness:

> "… the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep.
>
> Sleepiness may vary in severity and is more likely to occur in sedentary, boring, or monotonous situations that require little active participation."

American Academy of Sleep Medicine. *International classification of sleep disorders, 3rd edition.* Darien, IL: American Academy of Sleep Medicine; 2014.

Assessing EDS

- History from patient and when possible from family and significant others
  - Nighttime and daytime sleep episodes
  - Daytime impairment
- Sleep diary
- Sleepiness scales
  - Stanford Sleepiness Scale – current feeling
  - Epworth Sleepiness Scale – recent life experience
- Sleep laboratory testing
  - Multiple Sleep Latency Test (MSLT)
  - Maintenance of wakefulness Test (MWT)

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NATIONAL SLEEP FOUNDATION

Sleep Diary: Morning

Complete in Morning

Start date: __/__/__ Day of week:	Day 1 ____	Day 2 ____	Day 3 ____	Day 4 ____	Day 5 ____	Day 6 ____	Day 7 ____
I went to bed last night at:	PM / AM	PM / AM	PM / AM	PM / AM	PM / AM	PM / AM	PM / AM
I got out of bed this morning at:	AM / PM	AM / PM	AM / PM	AM / PM	AM / PM	AM / PM	AM / PM
Last night I fell asleep:							
Easily	☐	☐	☐	☐	☐	☐	☐
After some time	☐	☐	☐	☐	☐	☐	☐
With difficulty	☐	☐	☐	☐	☐	☐	☐
I woke up during the night:							
# of times							
# of minutes							
Last night I slept a total of:	Hours	Hours	Hours	Hours	Hours	Hours	Hours
My sleep was disturbed by: List mental or physical factors including noise, lights, pets, allergies, temperature, discomfort, stress, etc.							
When I woke up for the day, I felt:							
Refreshed	☐	☐	☐	☐	☐	☐	☐
Somewhat refreshed	☐	☐	☐	☐	☐	☐	☐
Fatigued	☐	☐	☐	☐	☐	☐	☐
Notes: Record any other factors that may affect your sleep (i.e. hours of work shift, or monthly cycle for women).							

Sleep Diary: End of Day

Complete at the End of Day

Day of week: ____	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
I consumed caffeinated drinks in the: (M)orning, (A)fternoon, (E)vening, (N/A)							
M / A / E / NA How many?	____	____	____	____	____	____	____
I exercised at least 20 minutes in the: (M)orning, (A)fternoon, (E)vening, (N/A)							
Medications I took today:							
Took a nap? (circle one)	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
If Yes, for how long?							
During the day, how likely was I to doze off while performing daily activities: No chance, Slight chance, Moderate chance, High chance							
Throughout the day, my mood was… Very pleasant, Pleasant, Unpleasant, Very unpleasant							
Approximately 2-3 hours before going to bed, I consumed:							
Alcohol	☐	☐	☐	☐	☐	☐	☐
A heavy meal	☐	☐	☐	☐	☐	☐	☐
Caffeine	☐	☐	☐	☐	☐	☐	☐
Not applicable	☐	☐	☐	☐	☐	☐	☐
In the hour before going to sleep, my bedtime routine included: List activities including reading a book, using electronics, taking a bath, doing relaxation exercises, etc.							

TWO WEEK SLEEP DIARY

INSTRUCTIONS:

1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line (I) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't got back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7:00 in the morning.

Today's Date	Day of the week	Type of Day Work, School, Off, Vacation	NOON	1PM	2	3	4	5	6PM	7	8	9	10	11PM	Midnight	1AM	2	3	4	5	6AM	7	8	9	10	11AM
sample	Mon.	Work		E					A	■			I		■	■	■	■		■	■	C M				
week 1																										
week 2																										

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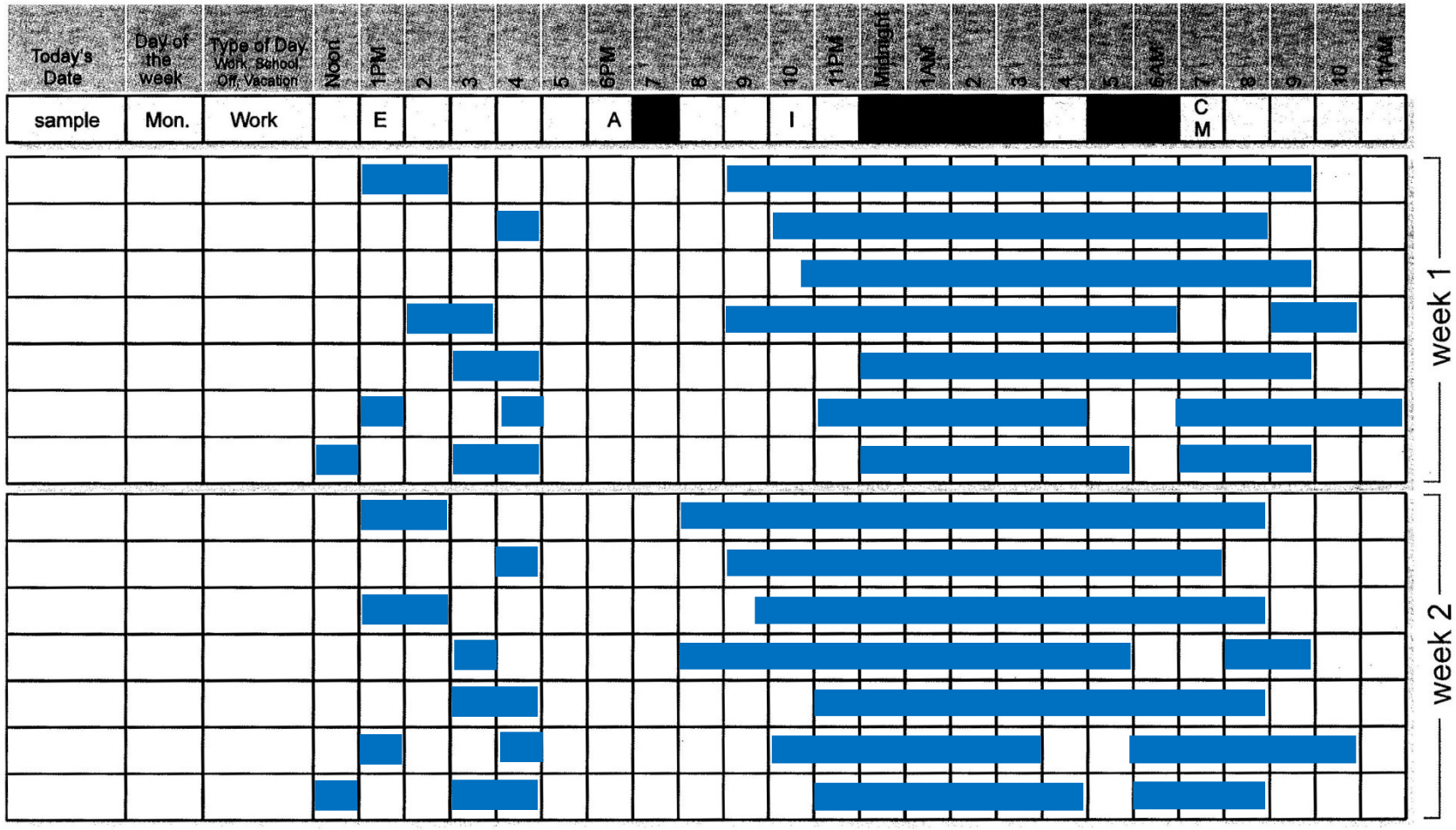


Epworth Sleepiness Scale

Use the following scale, *circle the most appropriate number for each situation*

0 = would *less than once a month doze*
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing

Situation	Chance of Dozing			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place (eg, a theater or a meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after a lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3

Normal < 8

EDS> 10

Johns MW. *Sleep*. 1991;14(6):540-545.

Common Causes of EDS

- Insufficient sleep
- Comorbid conditions
- Medications/substances
- Sleep disorders
  - Obstructive sleep apnea
  - Circadian rhythm sleep-wake disorders
  - Central disorders of hypersomnolence
    - Narcolepsy (types 1 and 2)
    - Idiopathic hypersomnia
    - Kleine-Levin syndrome

Chervin RD. Approach to the patient with excessive daytime sleepiness. In: *UpToDate*, Scammell TE Eichler, (Eds), UpToDate, Waltham, MA (Accessed September 2022)

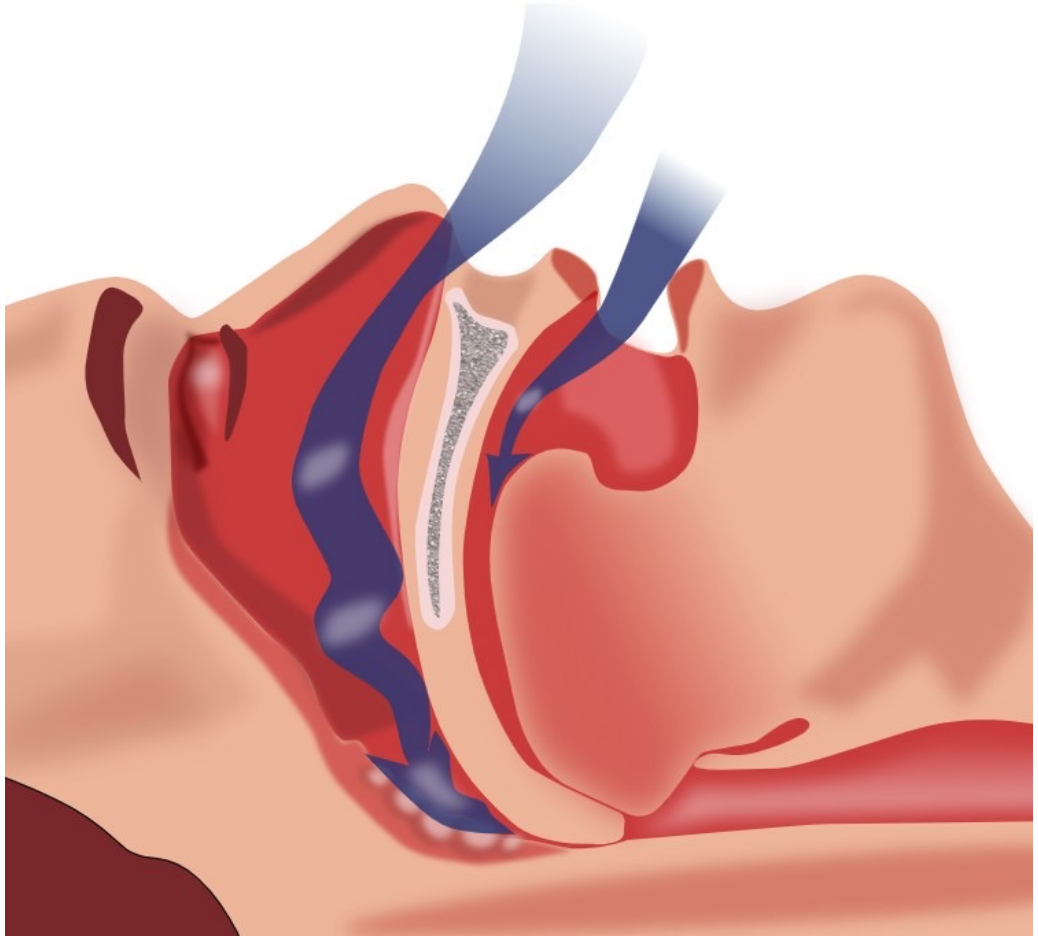
Recognition and Accurate Diagnosis

What is Obstructive Sleep Apnea (OSA)

- OSA essential features
  - Repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstructive during sleep that last at least 10 seconds
  - Often result in reduction in blood oxygen saturation, especially during REM sleep
  - Usually terminated by brief arousals from sleep
  - Events often more pronounced when sleeping in the supine position
- Sleep study diagnostic criteria: Apnea Hypopnea Index (AHI) ≥ 5/hour
- Severity
  - Frequency of events
    - Mild: AHI ≥ 5 to < 15
    - Moderate: AHI ≥ 15 to < 30
    - Severe: AHI ≥ 30
  - Degree of oxyhemoglobin desaturation

American Academy of Sleep Medicine. *International classification of sleep disorders, 3rd edition.* Darien, IL: American Academy of Sleep Medicine; 2014.

Obstructive Sleep Apnea



Clinical presentation

- Daytime sleepiness
- Loud snoring
- Witnessed breathing interruptions
- Awakenings with gasping or choking

Common comorbidities

- Obesity
- Hypertension – often treatment resistant
- Diabetes mellitus
- Dyslipidemia
- Depressed mood

American Academy of Sleep Medicine. *International classification of sleep disorders, 3rd edition.* Darien, IL: American Academy of Sleep Medicine; 2014.
Illustration credit: Habib M'henni / Wikimedia Commons

OSA and Mental Health

Possible OSA symptoms

- Disrupted nighttime sleep
- Excessive daytime sleepiness
- Fatigue
- Poor concentration
- Irritability
- Inability to enjoy usual activities
- Discouragement

Depression and OSA

- Higher prevalence of depression among people with OSA
- Depression correlated with severity of excessive daytime sleepiness
- Does treating OSA help depression?

BaHammam AS, Kendzerska T, Gupta R, et al. Comorbid depression in obstructive sleep apnea: An under-recognized association. *Sleep Breath*. 2016;20(2):447-456.

OSA Screening: STOP-Bang

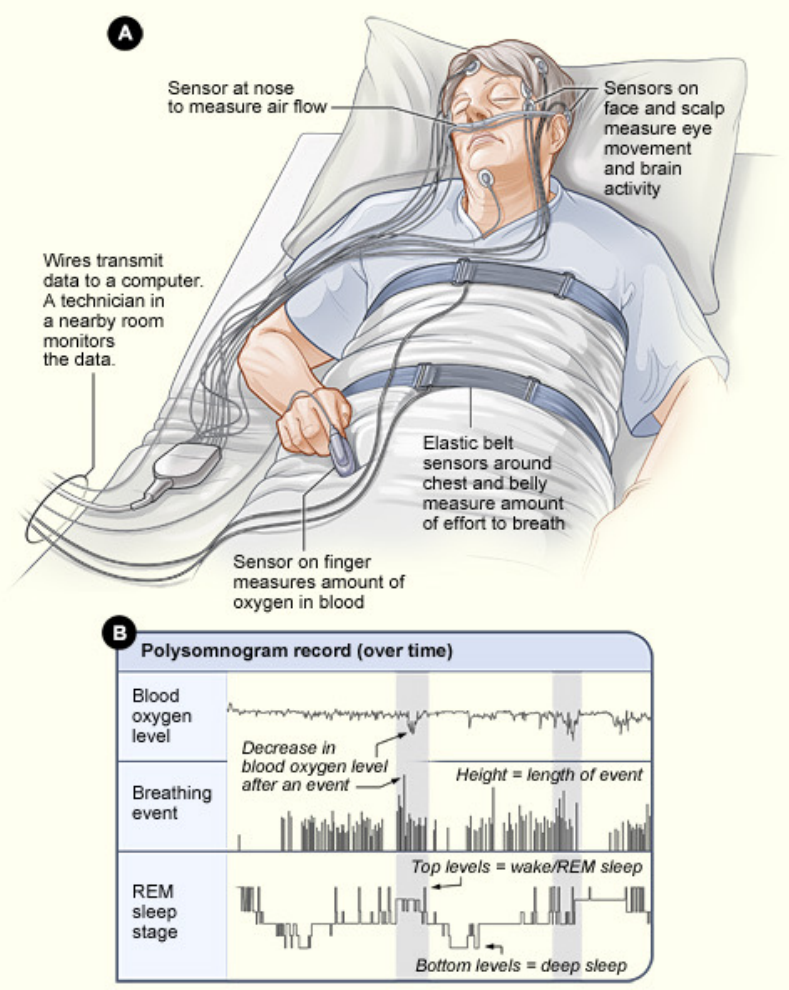
- Risk factors of OSA
  - **S**: Snoring?
  - **T**: Tired? (daytime fatigue, sleepiness)
  - **O**: Observed? (stopping breathing, choking, gasping)
  - **P**: Pressure? (high blood pressure)

  - **B**: BMI > 35?
  - **A**: Age > 50?
  - **N**: Neck size large? (Men > 16 inches, Women > 15 inches)
  - **G**: Gender = male?
- Scoring: Risk for OSA
  - **Low**: 0-2; **Intermediate**: 3-4; **High**: 5-8

BMI = body mass index

Chung F, et al. *Anesthesiology*. 2008;108(5):812-821. Nagappa M, et al. *PLoS One*. 2015;10(12):e0143697.

Polysomnographic Study

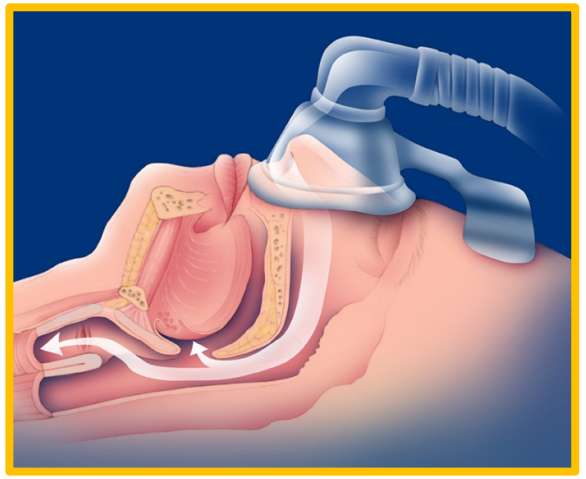


U.S. Department of Health & Human Services

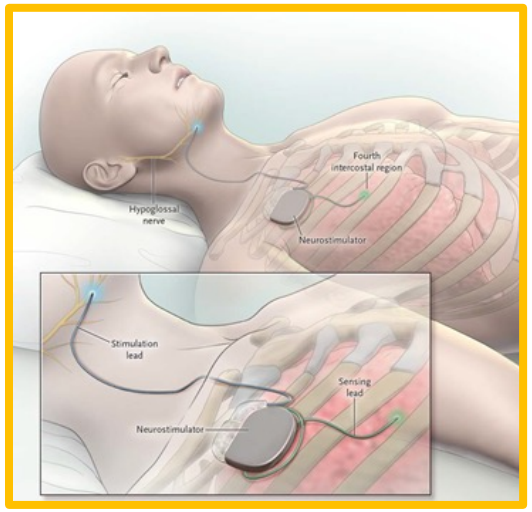
National Institutes of Health – National Heart, Lung, and Blood Institute

Treatments for OSA

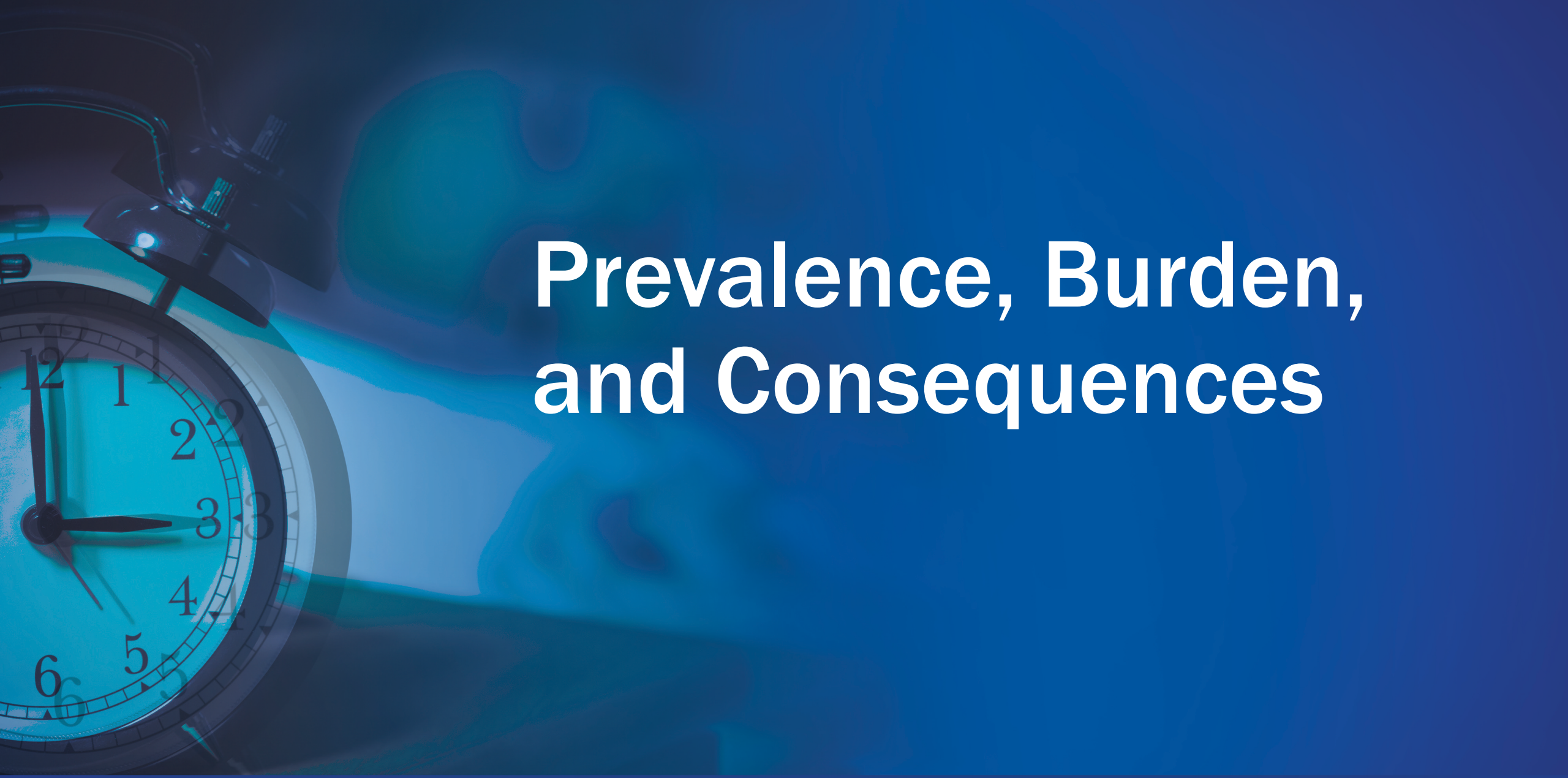
- Lifestyle modifications
  - Avoid sedating substances
  - Weight loss when appropriate
- Positive Airway Pressure (PAP)
  - CPAP: continuous at one pressure
  - APAP: auto-adjusting throughout the night within prescribed range
  - Nasal interface optimal for most patients
- Mandibular advancement device (oral appliance)
- Hypoglossal nerve stimulation (pacemaker implant)



- Surgery
  - Bariatric
  - Nasal procedures
  - Upper and lower pharyngeal procedures
  - Maxillomandibular advancement



Kryger M et al. *Principles and Practice of Sleep Medicine*. Seventh Edition. Elsevier; 2022. Andrade RGS, Viana FM, Nascimento JA, et al. Chest 2018; 153: 665–674.



Prevalence, Burden, and Consequences

EDS in OSA

- Prevalence: Approximately 60% of patients report EDS
- Significant quality of life impairment in all domains
- EDS in OSA patients is an independent risk factor for:
  - Overall morbidity and mortality
  - Workplace accidents and motor vehicle crashes
  - Cardiovascular events
  - Hypertension
  - Heart failure
  - Stroke
  - Insulin resistance
- Effective PAP therapy beneficial for EDS in most OSA patients

Kryger M et al. *Principles and Practice of Sleep Medicine*. Seventh Edition. Elsevier; 2022. Craig S, Pépin JL, Randerath W, Caussé C, Verbraecken J, Asin J, Barbé F, Bonsignore MR. Eur Respir Rev. 2022 May 25;31(164):210230.

Residual Excessive Daytime Sleepiness in OSA

- Persistent subjective complaints of EDS despite adequate OSA therapy that normalizes breathing and oxygenation parameters
- Prevalence: studies show 6% to 55% following PAP therapy
- Primary risk factors:
  - Higher baseline Epworth Sleepiness Scale score
  - Lower PAP treatment adherence (nights used, average duration)
  - Male, younger age, higher BMI
- Cause likely multifactorial, possibly including:
  - Sleep fragmentation from arousals from pharyngeal collapse
  - Sympathetic nervous system activation
  - Intermittent hypoxia with cellular injury
  - Chronic inflammation
  - Cytokine production
  - Sleep disruption related to PAP use

Li Z, Cai S, Wang J, Chen R. Front Neurol. 2022 Jun 27;13:911996. Craig S, Pépin JL, Randerath W, Caussé C, Verbraecken J, Asin J, Barbé F, Bonsignore MR. Eur Respir Rev. 2022 May 25;31(164):210230.

Current and Emerging Treatment Options

Management of Residual EDS in OSA

Optimize PAP adherence

- Minimum adherence generally regarded as PAP use ≥ 4 hours/night for ≥ 70% of days over a 30-day period
  - Greater adherence rates are related to lower residual EDS
- Review device data for nights used, duration, pressure delivered, leakage, and estimated residual AHI

Consider treatment alternatives for OSA

Ensure proper adherence to healthy sleep habits

Optimize treatment of comorbid causes of EDS

For residual sleepiness despite above consider wake-promoting medication

- Modafinil/armodafinil
- Solriamfetol

Coordinate care with patient, family, significant others, clinicians, and respiratory team

PAP = positive airway pressure.

Kribbs NB, et al. *Am Rev Respir Dis*. 1993;147(4):887-895. Gasa M, et al. *J Sleep Res*. 2013;22(4):389-397. Ballard RD. *J Fam Pract*. 2008;57(8 Suppl):S24-S30. Garnock-Jones KP, et al. *CNS Drugs*. 2009;23(9):793-803. Black JE, et al. *J Clin Sleep Med*. 2010;6(5):458-466.

Wake-Promoting Medications for Residual EDS

- Patient selection
  - EDS severity: drowsy driving, impaired work performance, marked fatigue
  - Typically ESS ≥ 10
- FDA-approved for residual EDS in treated OSA
  - Modafinil/armodafinil
  - Solriamfetol
- Non-evidence-based use
  - Amphetamines
  - Caffeine
- Investigational for OSA residual EDS
  - Pitolisant
  - Orexin receptor agonists

Kryger M et al. *Principles and Practice of Sleep Medicine*. Seventh Edition. Elsevier; 2022. Pepin JL. Evaluation and management of residual excessive daytime sleepiness in adults with obstructive sleep apnea. In: *UpToDate*, Collop N, Finlay G, (Eds), UpToDate, Waltham, MA (Accessed September 2022)

Modafinil

Indication	To improve wakefulness in adults with EDS associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder
Mechanism of action	Unknown (appears to increase dopaminergic signaling)
Typical doses	OSA: 200 mg daily in the morning (Decrease dose with severe hepatic impairment)
Warnings	Serious rash (Stevens-Johnson Syndrome), angioedema/anaphylaxis, multi-organ hypersensitivity, psychiatric symptoms, cardiovascular disease
Contraindications	Known hypersensitivity
Adverse effects	Headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, dyspepsia
Key potential interactions	CYP3A4/5 inducer (cyclosporine, midazolam, triazolam) Steroidal contraceptives: Use alternate or concomitant method during use and one month after discontinuation CYP2C19 inhibitor (phenytoin, diazepam, propranolol, clomipramine)
Special considerations	Concerns regarding use during pregnancy

See Prescribing Information for full details; https://www.accessdata.fda.gov/scripts/cder/daf/

Armodafinil

Indication	To improve wakefulness in adults with EDS associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder
Mechanism of action	Unknown (appears to increase dopaminergic signaling)
Typical doses	OSA: 150 to 250 mg once daily in the morning (Decrease dose with severe hepatic impairment)
Warnings	Serious rash (Stevens-Johnson Syndrome), angioedema/anaphylaxis, multi-organ hypersensitivity, psychiatric symptoms, cardiovascular disease
Contraindications	Known hypersensitivity
Adverse effects	Headache, nausea, dizziness, insomnia
Key potential interactions	CYP3A4/5 inducer (cyclosporine, midazolam, triazolam) Steroidal contraceptives: Use alternate or concomitant method during use and one month after discontinuation CYP2C19 inhibitor (phenytoin, diazepam, propranolol, clomipramine)
Special considerations	Concerns regarding use during pregnancy

See Prescribing Information for full details; https://www.accessdata.fda.gov/scripts/cder/daf/

Solriamfetol

Indication	To improve wakefulness in adults with EDS associated with narcolepsy or obstructive sleep apnea
Mechanism of action	Dopamine and norepinephrine reuptake inhibitor
Typical doses	OSA: starting dose 37.5 mg, maximum dose 150 mg daily (Reduce dose with renal impairment; avoid with end-stage disease)
Warnings	Blood pressure/heart rate increases Use caution in patients with history of psychosis or bipolar disorders
Contraindications	Concurrent or recent MAOI use
Adverse effects	Headache, nausea, decreased appetite, insomnia, anxiety
Key potential interactions	Use caution with drugs that increase blood pressure and/or heart rate, and with dopaminergic drugs
Special considerations	Avoid with unstable cardiovascular and serious heart arrhythmias

See Prescribing Information for full details; https://www.accessdata.fda.gov/scripts/cder/daf/

Practical Take-Aways

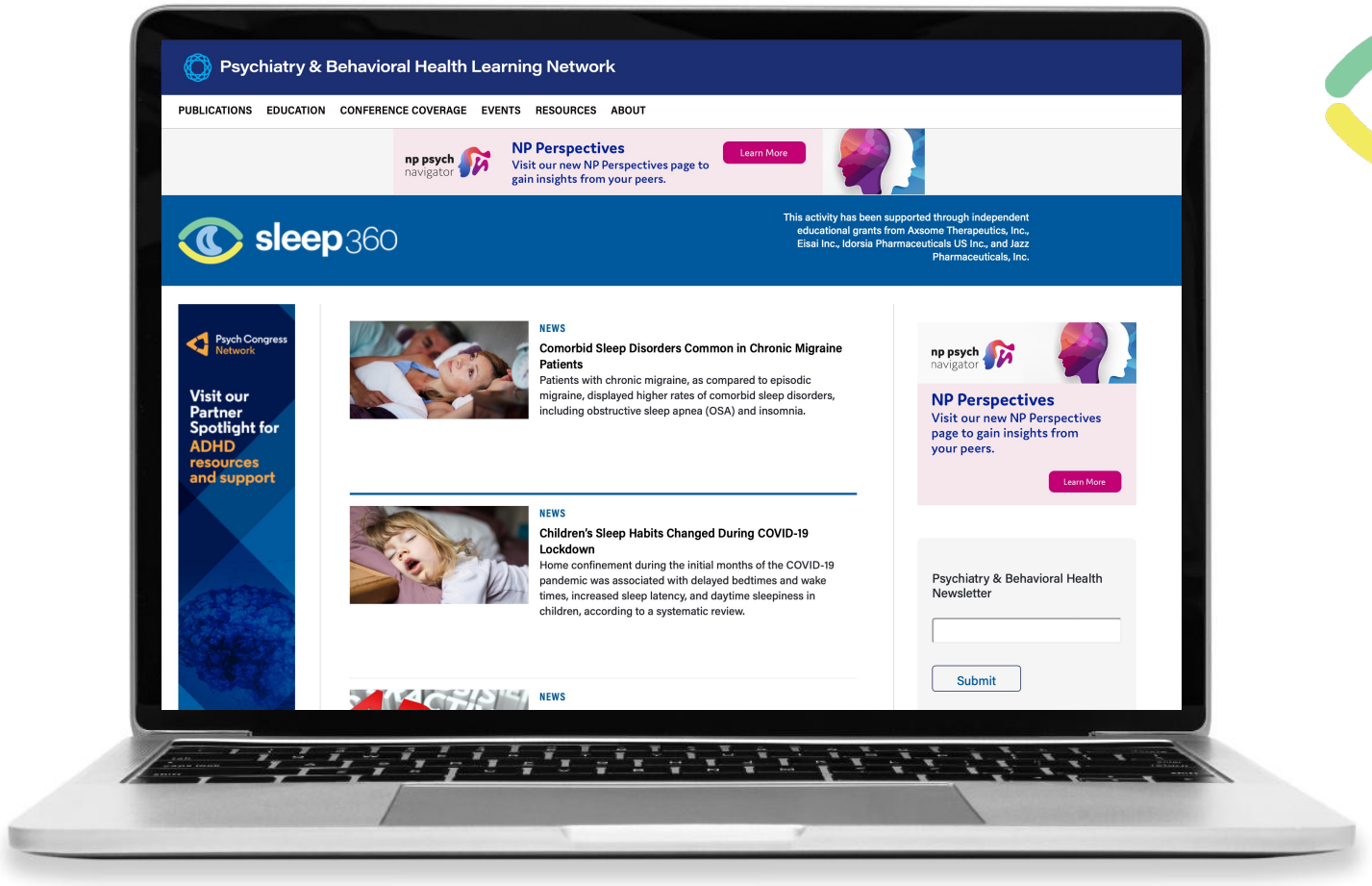
Practical Take-Aways

Routinely ask patients and their families about daytime sleepiness and how it affects all of their lives. Screen patients with the Epworth Sleepiness Scale (ESS).

Obstructive sleep apnea (OSA) is a common disorder with serious consequences, especially when untreated. Screen patients with the STOP-Bang scale.

Explore reasons why OSA patients might remain excessively sleepy during the daytime despite treatment for the disorder. Consider the use of a waking promoting medication for appropriate patients.

Visit the Resource Center



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