

CMEO



BriefCase

Differential Diagnosis for Narcolepsy

*This program is supported by an independent
medical education grant from Jazz Pharmaceuticals*

Richard K. Bogan, MD, FCCP, FAASM

Associate Clinical Professor

University of South Carolina Medical School,
Columbia, SC

Medical University of South Carolina, Charleston, SC

Principal, Bogan Sleep Consultants, LLC

Columbia, SC

Michael J. Thorpy, MD

Professor of Neurology

Albert Einstein College of Medicine

Director, Sleep-Wake Disorders Center,
Department of Neurology

Montefiore Medical Center, Bronx, NY

President, New York State Society of Sleep Medicine

Past President, Sleep Section of the Academy of Neurology

Learning Objective

Use appropriate diagnostic tools to differentiate narcolepsy from EDS associated with other medical and psychiatric disorders.

Patient Case: Andrea



- 30-year-old Hispanic woman presents to PCP for sleepiness
- Chief complaint: very sleepy during the day; believes it is due to getting poor sleep; reports “drifting in and out of sleep” at night; symptoms impacting work performance
- Works as a financial advisor (hybrid home/in-office schedule); struggles to focus at work due to sleepiness; works extra hours on evenings to catch up and occasionally stays up late only getting 5-6 hours of sleep/night
- Puts off everything else (family visits, laundry, dishes, social activities, etc.) to stay caught up on work; feels too exhausted to catch up with non-work stuff on the weekends and just wants to rest
- Reports transient loss of leg strength during a recent work presentation when she struggled with answering a question; similar episodes have happened in the past
- Past medical history: generalized anxiety disorder, obesity (BMI 30 kg/m²)
- Current findings: BP = 130/82 mmHg, HR = 78 BPM, PHQ-9 = 12, ESS = 17/24
- Current medications: escitalopram 20 mg once daily (for generalized anxiety)

BMI = body mass index; BP = blood pressure; BPM = beats per minute; ESS = Epworth Sleepiness Scale; HR = heart rate; PCP = primary care professional; PHQ = Patient Health Questionnaire

Patient Case: Andrea (continued)



- **PCP recommendations:** sleep minimum 7-8 hours/night, limit caffeine in evenings, and start with moderate exercise 2-3x/week for weight loss and to help with sleep
- **One-month follow-up:**
 - No significant improvement in symptoms (ESS = 16/24); worsened stress due to symptoms impacting work performance
 - Additional questioning reveals symptoms have been going on since high school and steadily worsening
- **PCP refers to sleep specialist for additional evaluation**

Narcolepsy: Patient Presentation

Narcolepsy prevalence:

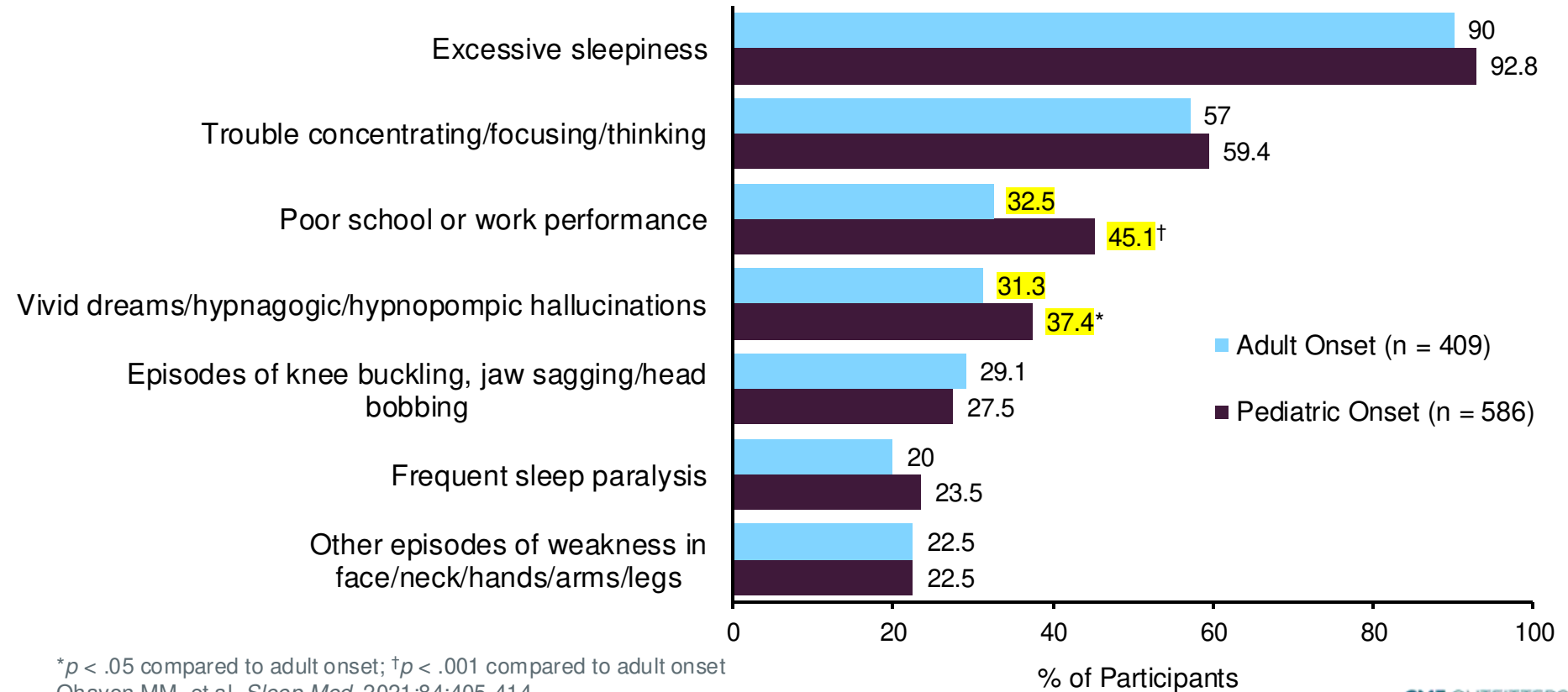
Also seen with:

C	ataplexy	65%-75%	→	Hypotension, seizure
H	allucinations	33%-80%	→	Schizophrenia, nightmares, depression
E	xcessive daytime sleepiness (EDS)	100%	→	Periodic limb movements, OSA, IH, depression, insomnia, sleep deprivation
S	leep paralysis	25%-50%	→	Depression, nightmares, schizophrenia, psychiatric disorders
S	leep disruption	30%-95%	→	OSA, insomnia, sleep deprivation, periodic limb movements

IH = idiopathic hypersomnia; OSA = obstructive sleep apnea

Cheung J, Ruoff CM. Central nervous system hypersomnias. In: *Sleep and Neurologic Disease*. 2017. Roth T, et al. *J Clin Sleep Med*. 2013;9(9):955-965. Thorpy MJ, Dauvilliers Y. *Sleep Med*. 2015;16(1):9-18. Moturi S. *Psychiatry (Edgmont)*. 2009;6(6):38-44.

Symptoms Leading to First Consultation



* $p < .05$ compared to adult onset; [†] $p < .001$ compared to adult onset
Ohayon MM, et al. *Sleep Med.* 2021;84:405-414.

Misdiagnosis of Narcolepsy and Common Comorbidities

% of Participants Reporting	Participants Reporting:					
	Misdiagnosed Conditions			Correctly Diagnosed Comorbid Conditions		
	Pediatric Symptom Onset (n = 541)	Adult Symptom Onset (n = 374)	P Value*	Pediatric Symptom Onset (n = 541)	Adult Symptom Onset (n = 374)	P Value*
Depression	34.2	29.1	.108	32.0	35.3	.296
ADHD	19.2	12.3	.005	8.9	11.0	.294
Anxiety disorder	17.6	15.2	.354	27.5	25.7	.529
Insomnia	15.7	13.4	.326	7.0	5.9	.493
Bipolar disorder	14.2	9.1	.019	3.0	3.7	.512
Hypersomnia	14.0	14.4	.868	8.7	11.0	.251
OSA	10.9	14.2	.138	9.6	14.2	.033
Epilepsy	7.8	3.7	.013	1.3	0.5	.253
Schizophrenia	5.4	2.1	.015	0.2	0.0	.405
Dementia	2.2	2.4	.852	0.0	0.0	—

59.3% reported receiving at least one misdiagnosis before being diagnosed with narcolepsy

*Pediatric onset vs. adult onset

ADHD = attention-deficit/hyperactivity disorder

Ohayon MM, et al. *Sleep Med.* 2021;84:405-414.

Audience Response

Which of the following should be considered when developing a differential diagnosis in patients with EDS?

- A. Narcolepsy, obstructive sleep apnea, periodic limb movement disorder
- B. Narcolepsy, idiopathic hypersomnia, anemia
- C. Narcolepsy, depression, hypothyroidism
- D. Narcolepsy, circadian rhythm abnormalities, hypotension
- E. I don't know

Audience Response

Which of the following should be considered when developing a differential diagnosis in patients with EDS?

- A. Narcolepsy, obstructive sleep apnea, periodic limb movement disorder
- B. Narcolepsy, idiopathic hypersomnia, anemia
- C. Narcolepsy, depression, hypothyroidism
- D. Narcolepsy, circadian rhythm abnormalities, hypotension
- E. I don't know

Differential Diagnosis

EDS

- Obstructive sleep apnea syndrome
- Sleep deprivation/poor sleep hygiene
- Depression
- Substance/drug intake
- Idiopathic hypersomnia, KLS
- Periodic limb movement disorder
- Circadian rhythm abnormality
- Behavioral symptoms of EDS
 - Irritability, poor attentiveness, aggression, hallucinations



Cataplexy

- Seizure
- Hypotension
- Psychogenic origin



Hallucinations

- Schizophrenia
- Nightmares
- Panic attacks



KLS = Kleine-Levin syndrome

Nevsimalova S. *Curr Neurol Neurosci Rep.* 2014;14(8):469. Warman J, et al. *Neurology.* 2013;80(7 Suppl):S43.003.

Dauvilliers Y, et al. *Neurol Neurosurg Psychiatry.* 2003;74(12):1667-1673. Zhou J, et al. *Shanghai Arch Psychiatry.* 2014;26(4):232-235.

Screening Tools: Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

- 0 = would **never** doze
- 1 = **slight chance** of dozing
- 2 = **moderate chance** of dozing
- 3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading _____	—
Watching TV _____	—
Sitting, inactive in a public place (e.g. a theatre or a meeting) _____	—
As a passenger in a car for an hour without a break _____	—
Lying down to rest in the afternoon when circumstances permit _____	—
Sitting and talking to someone _____	—
Sitting quietly after a lunch without alcohol _____	—
In a car, while stopped for a few minutes in the traffic _____	—

0-5: Lower normal daytime sleepiness

6-10: Higher normal daytime sleepiness

11-12: Mild excessive daytime sleepiness

13-15: Moderate excessive daytime sleepiness

16-24: Severe excessive daytime sleepiness

Patient Case: Andrea



- 30-year-old Hispanic woman presents to sleep specialist after referral from PCP
- Sleep specialist findings during clinical interview:
 - She dreams all night between periods of awakening
 - Reports that occasionally during these periods of awakening she cannot move her body and occasionally sees a black figure at the end of her bed that disappears once she fully awakes and can move
 - She reports that as she is falling into sleep she occasionally experiences very vivid hallucinations, sees rapidly moving colors and shapes like looking into a kaleidoscope; also feels at these times like she is floating in water
- Sleep specialist recognizes the symptom of cataplexy and phase delay consistent from PCP visit report, the hypnagogic hallucinations, and sleep paralysis
- ESS: 16/24
- Sleep study is ordered for the patient



Audience Response

Which of the following would indicate a diagnosis of narcolepsy type 1 per the ICSD-3 diagnostic criteria?

- A. EDS for at least 3 months, cataplexy OR a mean sleep latency of ≤ 8 minutes and 2 or more SOREMPs on a daytime MSLT
- B. EDS for at least 3 months, cataplexy AND a SOREMP on the nocturnal PSG
- C. EDS for at least 3 months, OR a mean sleep latency of ≤ 8 minutes and 2 or more SOREMPs on a daytime MSLT
- D. EDS for at least 3 months, AND a SOREMP on the nocturnal PSG
- E. I don't know

Audience Response

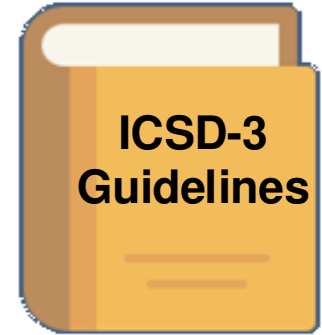
Which of the following would indicate a diagnosis of narcolepsy type 1 per the ICSD-3 diagnostic criteria?

- A. EDS for at least 3 months, cataplexy OR a mean sleep latency of ≤ 8 minutes and 2 or more SOREMPs on a daytime MSLT
- B. EDS for at least 3 months, cataplexy AND a SOREMP on the nocturnal PSG
- C. EDS for at least 3 months, OR a mean sleep latency of ≤ 8 minutes and 2 or more SOREMPs on a daytime MSLT
- D. EDS for at least 3 months, AND a SOREMP on the nocturnal PSG
- E. I don't know

ICSD-3 Diagnostic Criteria for Narcolepsy Type 1 (NT1)

Criteria A and B must be met:

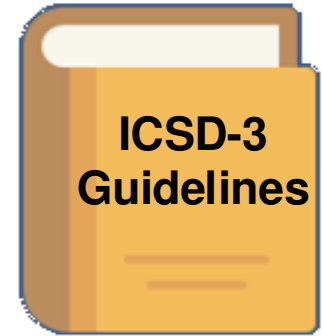
- A. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
- B. The presence of one or both of the following:
 1. Cataplexy **and** a mean sleep latency of ≤ 8 minutes and 2 or more sleep-onset REM periods (SOREMPs) on a daytime Multiple Sleep Latency Test (MSLT) **or** cataplexy and a SOREMP on the nocturnal PSG
 2. CSF hypocretin-1 concentration ≤ 110 pg/mL (or $< 1/3$ of values in normals)



ICSD-3 Diagnostic Criteria for Narcolepsy Type 2 (NT2)

Criteria A-E must all be met:

- A. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
- B. A mean sleep latency of ≤ 8 minutes and 2 or more sleep-onset REM periods (SOREMPs) on a daytime MSLT
- C. Cataplexy is *absent*
- D. CSF hypocretin-1 concentration not measured or > 110 pg/mL
- E. Hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, OSA, delayed sleep phase, medications/drugs or their withdrawal



Diagnostic Tools



- Clinical interview
 - Important to determine differential diagnosis
- Sleep study
 - Polysomnography
 - Daytime Multiple Sleep Latency Testing (MSLT)
- Cerebrospinal fluid hypocretin levels
 - NT1 vs. NT2

Polysomnography (PSG)

Short sleep latency

Short REM latency

SOREMP (<15 minutes)

Reduced sleep efficiency

Frequent awakenings

Increased number of arousals

REM sleep fragmentation

Increased stage 1 sleep

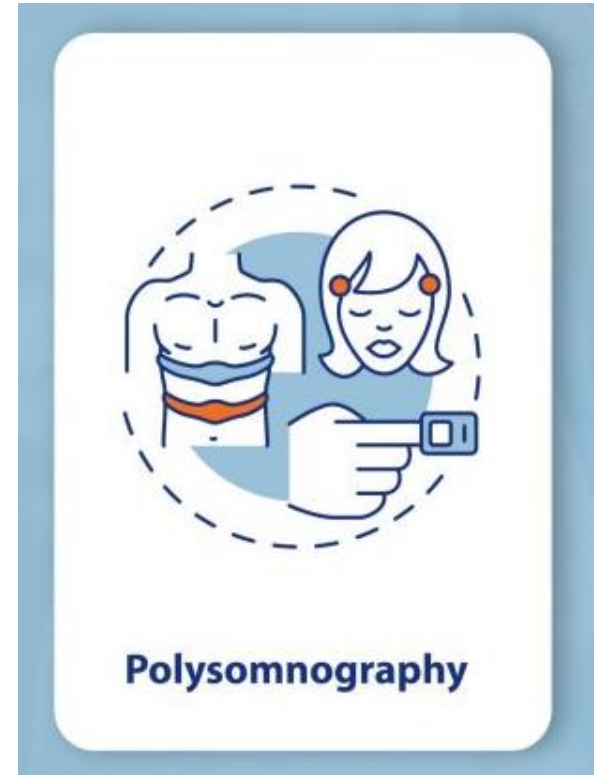
Reduced slow-wave sleep

Reduced total sleep time

Increased REM-NREM cycle (120 minutes)

NREM = non-REM

Dietmann A, et al. *Sleep Med.* 2021;79:6-10. Andlauer O, et al. *JAMA Neurol.* 2013;70(7):891-902.
Image adapted from AAIRS Website. <https://aairsonline.com/sleep-tests/>.



Limitations in PSG in Narcolepsy

Insufficient nocturnal sleep (< 6 hours)

Delayed sleep onset due to environmental factors

Delayed sleep phase

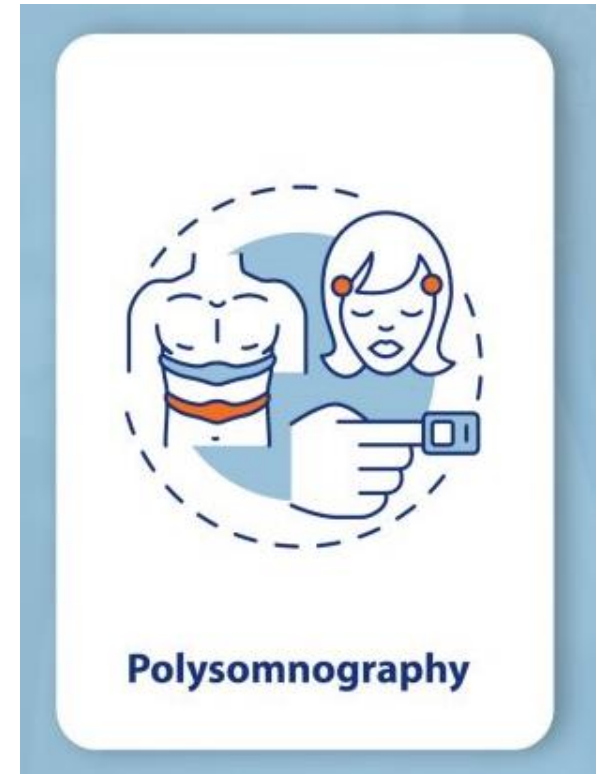
Rem suppressant medications

Alcohol or illicit drug use

Sleep comorbidities: OSA, insomnia

MSLT must follow PSG

Home test inadequate



Limitations of the MSLT in Narcolepsy

False-positive MSLT

- ≥ 2 SOREMS occur in 13% of men and 6% of women
- ≥ 2 SOREMS and MSLT latency < 8 minutes occurs in 6% of men and 1% of women
- Can be caused by shift work, OSA, insufficient sleep, etc.

False-negative MSLT (~ 20%)

- Anxiety, psychotropic medications, noise in lab, etc.

MSLT often not performed per guidelines

- Actigraphy and sleep logs not done routinely
- Patients not routinely sleep satiated
- PSG sleep time of 6-7 hours may not be enough

Poor test/re-test reproducibility in NT2 and IH

- Diagnosis changes in ~ 50%



**Multiple sleep
latency test**

Differentiation Between Narcolepsy and IH

NT1

NT2

IDIOPATHIC HYPERSOMNIA

Cataplexy

CSF hypocretin-1 concentration ≤ 110 pg/mL

≥ 2 SOREMPs on MSLT (may substitute 1 from PSG if nocturnal REM latency ≤ 15 min)

- Refreshing naps
- Disrupted sleep
- Sleep paralysis
- Sleep-related hallucinations

EDS (e.g., ESS > 10)

MSLT Sleep latency ≤ 8 minutes

No cataplexy

Normal CSF hypocretin-1 concentration

Sleep inertia

< 2 SOREMPs on PSG/MSLT or none if nocturnal REM latency ≤ 15 min

May have long sleep (≥ 11 hours in a 24-hour period)

Unrefreshing naps

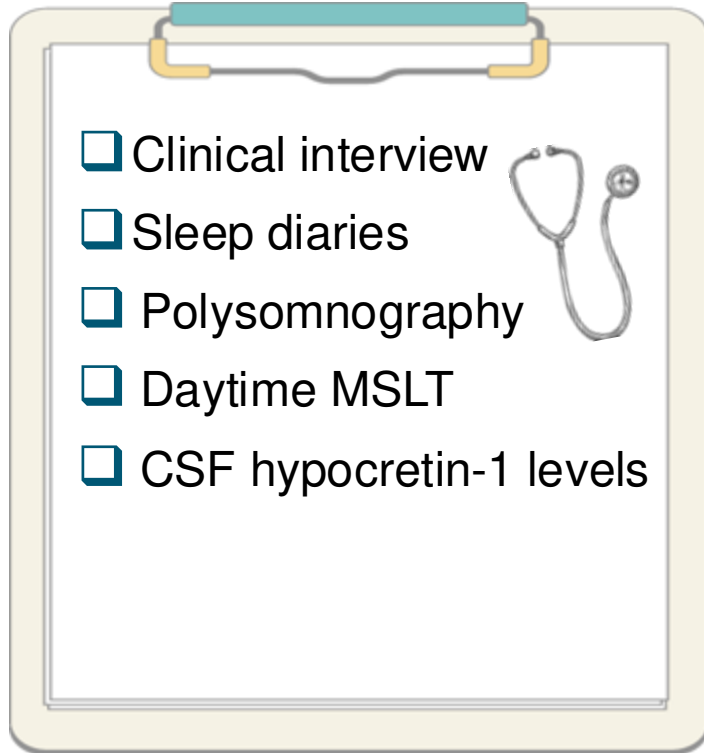
Circadian dysrhythmia

May have spontaneous remission

MORE COMMON IN NT1

MORE COMMON IN IDIOPATHIC HYPERSOMNIA

Narcolepsy Diagnosis Pitfalls



- Subtleties of diagnosis
- Interpreting diagnostic tests
- Timing of diagnostic tests
- Identifying partial cataplexy
- Comorbidity with other sleep disorders is common:
 - ~ 25% of patients with narcolepsy also have OSA
- 82% of patients with narcolepsy receive a diagnosis \geq 1 year from symptom onset; one-third $>$ 10 years

Patient Case: Andrea



- Findings from an overnight sleep study

PSG

Sleep Latency: 12 minutes
REM latency: 14.5 minutes

MSLT

Mean sleep latency: 4 minutes
SOREMPS per MSLT: 4

What do these findings indicate?

Discussion Questions

What are some things we can implement in our screening practices to better identify narcolepsy?



What can help us more effectively develop differential diagnosis for complex patients presenting with EDS?



How can we ensure our sleep study/MSLT provides the most reliable and accurate information?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Screen all patients with complaints of sleep dysfunction and EDS for symptoms associated with narcolepsy.
- Consider comorbidities with similar presentations when evaluating any patient with EDS and considering a potential narcolepsy diagnosis.
- Utilize ICSD-3 criteria when assessing any patient with symptoms of EDS for potential narcolepsy diagnosis.

CMEO 
BriefCase

1

Recognition of Narcolepsy
in Your Patients

CMEO 
BriefCase

3

Choosing and Optimizing
Therapy in Narcolepsy

www.cmeoutfitters.com/sleep-disorders-hub/

Sleep Disorders Hub

Free resources and education to educate health care professionals and patients on sleep disorders

<https://www.cmeoutfitters.com/sleep-disorders-hub/>

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.