THE EVALUATION AND MANAGEMENT OF NARCOLEPSY

Kiran Maski, MD MPH
Boston Children's Hospital
Harvard Medical School

18th Annual Sleep Medicine CME Course

Conflict of Interest Disclosures for Speakers

- Consulting Alkermes, Avadel, Harmony Biosciences, Jazz Pharmaceuticals, Takeda, Synchronicity Pharmaceuticals, Taysha Gene Therapies
- DSMB Chairperson Idorsia Pharmaceuticals
- Grant funding from Jazz Pharmaceuticals and Harmony Biosciences
- Collaborator on clinical trials sponsored by Takeda
- Royalties from UptoDate, Inc.

Case presentation

- Robert is a 21 year old in college who presents with ”always feeling tired”
  - He falls asleep inadvertently in class, in library when studying, and at work when doing computer tasks. Friends make fun of him for how much he sleeps and he finds it embarrassing.
    - Eye opener: Hit a stopped car when driving because he dozed off
  - He sleeps 7-8 hours a night but sleep is restless and wakes frequently
  - He complains of sleep paralysis when waking in the morning and sometimes when naps
  - He has very vivid dreams/nightmares and sleep talks
  - More recently feeling clumsy. “When I laugh, I have to sit down or my knees may buckle”

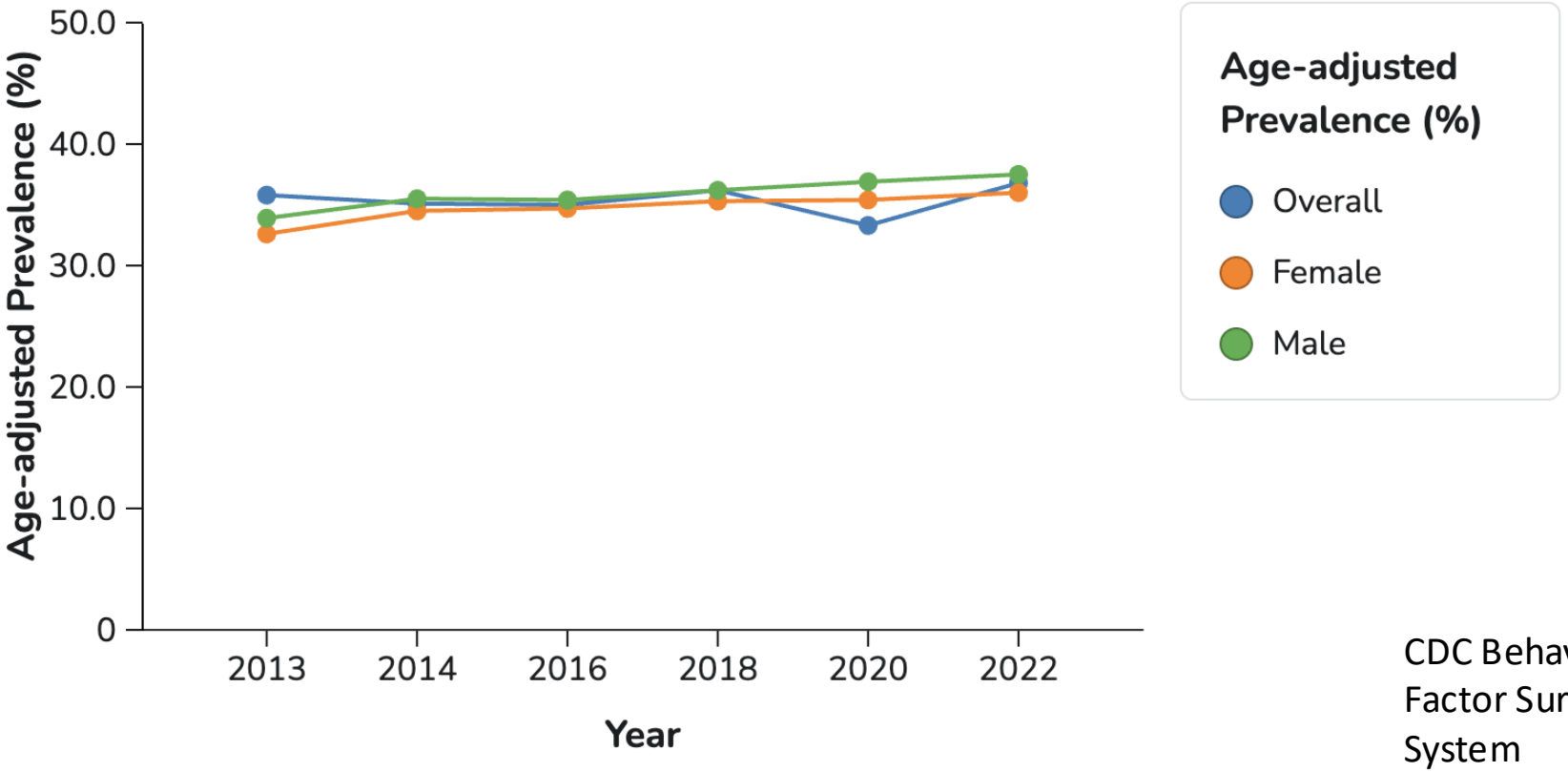
Common Causes of Daytime Sleepiness

1. Insufficient sleep
2. Circadian phase delays
3. Sleep disordered breathing (OSA)
4. Insomnia (complain more of fatigue)
5. Sedating medications
6. Somatic symptoms associated with medical or psychiatric conditions

Stable Trend of Insufficient Sleep in United States

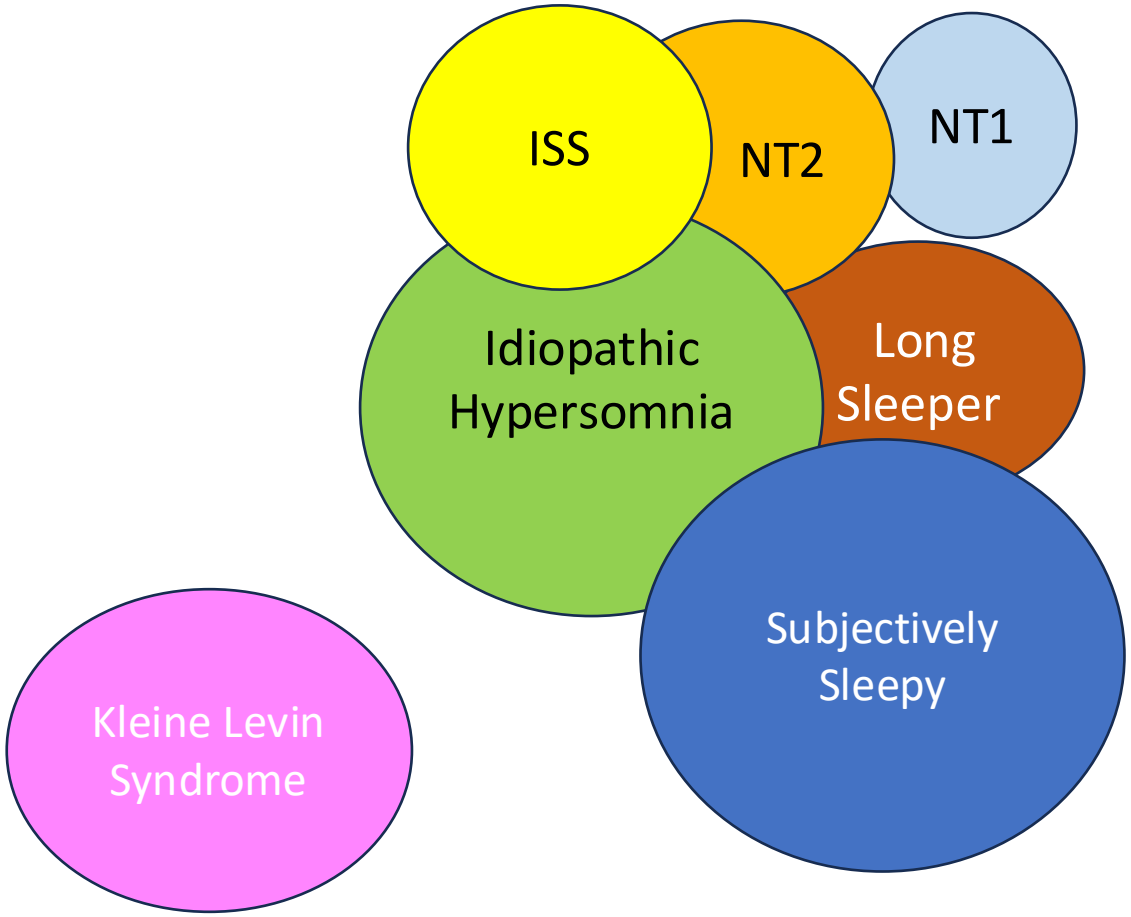
Trends in insufficient sleep, 2013–2022

The percentage of adults not getting enough sleep stayed the same from 2013 to 2022.



CDC Behavioral Risk Factor Surveillance System

CNS Disorders of Hypersomnolence



- ISS=Insufficient Sleep Syndrome
- Long Sleeper=needs >2 hours age specific normal
- IH=Idiopathic Hypersomnolence
- NT1=Narcolepsy with Cataplexy
- NT2=Narcolepsy without Cataplexy

International Classification of Sleep Disorders version 3 Text Revisions 2023

Narcolepsy Overview

- Narcolepsy Type 1 (NT1, narcolepsy with cataplexy)
- Narcolepsy Type 2 (NT2, narcolepsy without cataplexy)

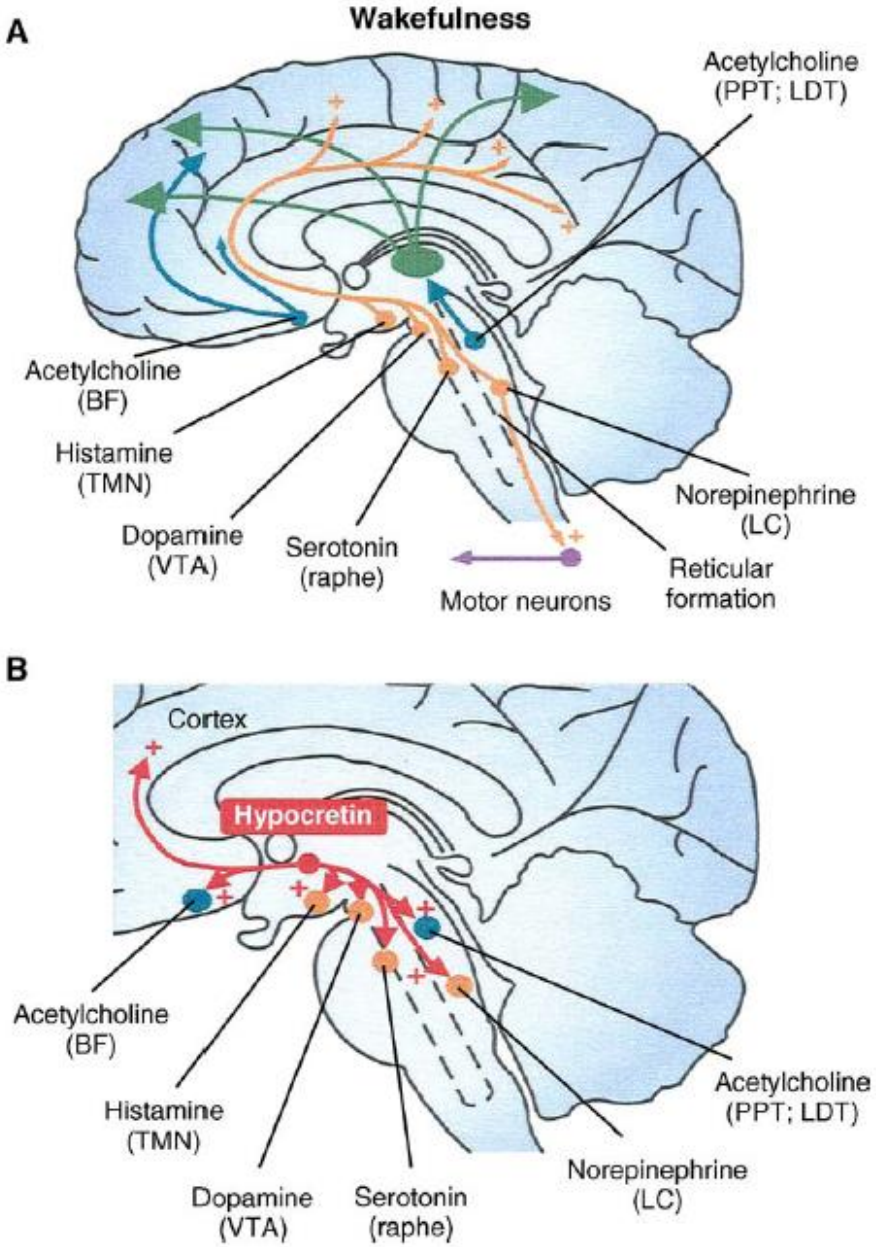
- NT1 is caused by loss of hypocretin/orexin neurons in lateral hypothalamus

- Characterized by the following:

  - Sleep and wake state imbalance
    - Excessive daytime sleepiness (100%)
    - Disrupted nighttime sleep (30-90%)

  - Cataplexy (sudden episodes of loss of muscle tone typically with emotion, 50-70%)
  - Sleep paralysis (20-30%)
  - Hypnogogic and hypnopompic hallucinations (20-30%)

International Classification of Sleep Disorders, version 3; Mitler M et al. 1990; Silber M et al., 2002;Pizza F et al. 2013; Kim LJ et al. 2015; Ohayon M et al. 2013



Espana R, Scammell TE. Sleep. 2004

Narcolepsy Core Symptoms

- Excessive daytime sleepiness (100%)
  - Worse when sedentary
    - May be more notable in school setting
  - +/- Irresistible sleep attacks lasting 15-30 minutes
- Hypnagogic and hypnopompic hallucinations (20-30%)
- Sleep paralysis (20-30%)

"Does not matter how much sleep I get, I am always tired"

"He will fall asleep within minutes in the car"

"I see someone, animals, shapes in the room when I fall asleep"

"I can't move my body for a few minutes when I wake up"

Mitler M et al. 1990; Silber M et al., 2002;Pizza F et al. 2013; Kim LJ et al. 2015; Ohayon M et al. 2013

"When he laughs, his head bobs up and down"

"When I get upset, my knees buckle "

"His face looks more droopy"

Typical Cataplexy (50-60%)

- Bilateral loss of muscle tone in the face, neck, or legs (e.g., buckling knees), with or without involvement of the arms
- Sudden and particularly positive emotions (e.g., laughing out loud); less frequently, anger may trigger an episode
- These episodes typically last for up to 1 minute but are usually less than 30 seconds
- Variable frequency (typical at least monthly)
- Consciousness is preserved, and there is an abrupt return of muscle tone after the attack
- Stereotypical for individuals but can have partial or full cataplexy

ICSD 3 TR, Van der Hoeven A SLEEP 2022

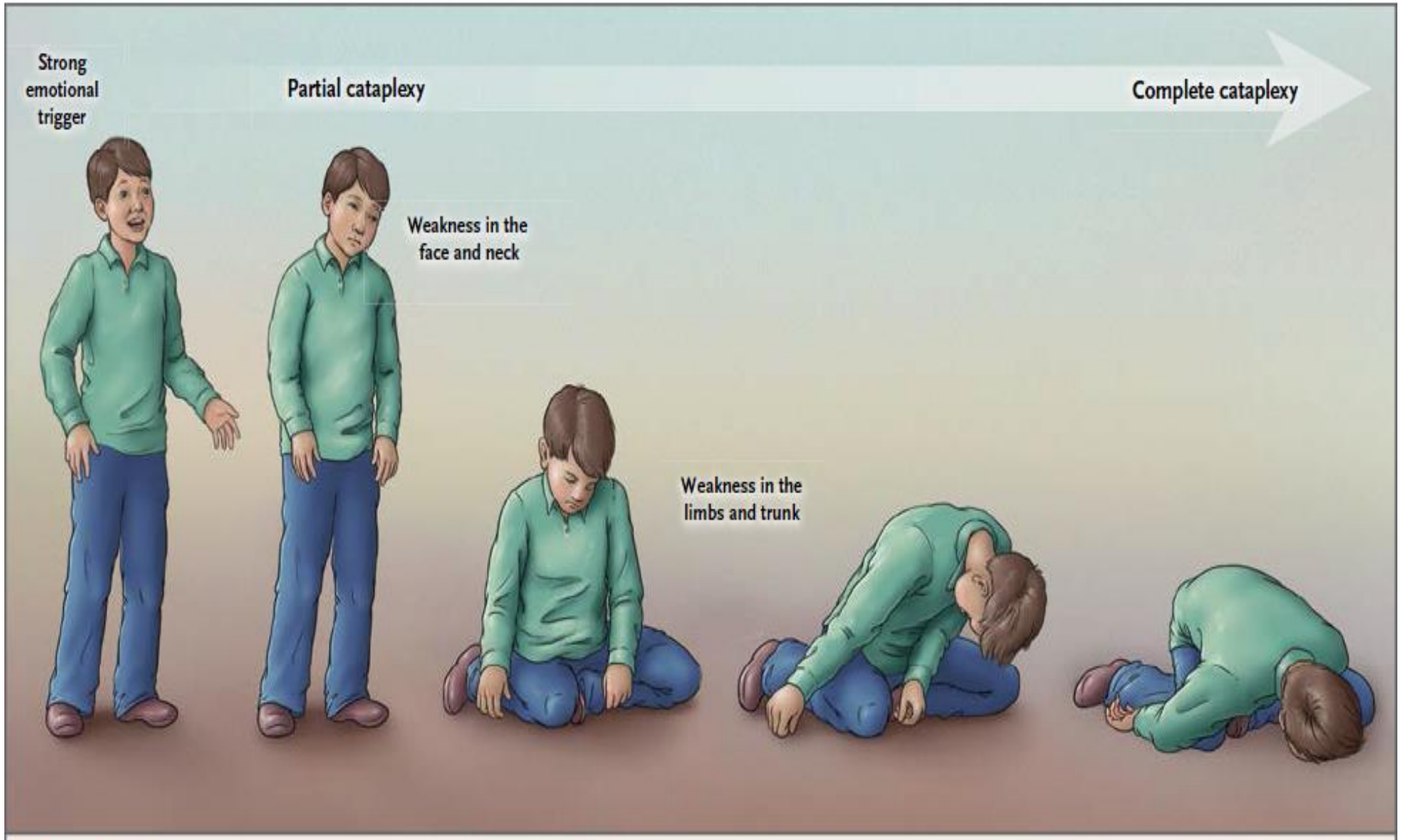


Figure 1. Cataplexy.

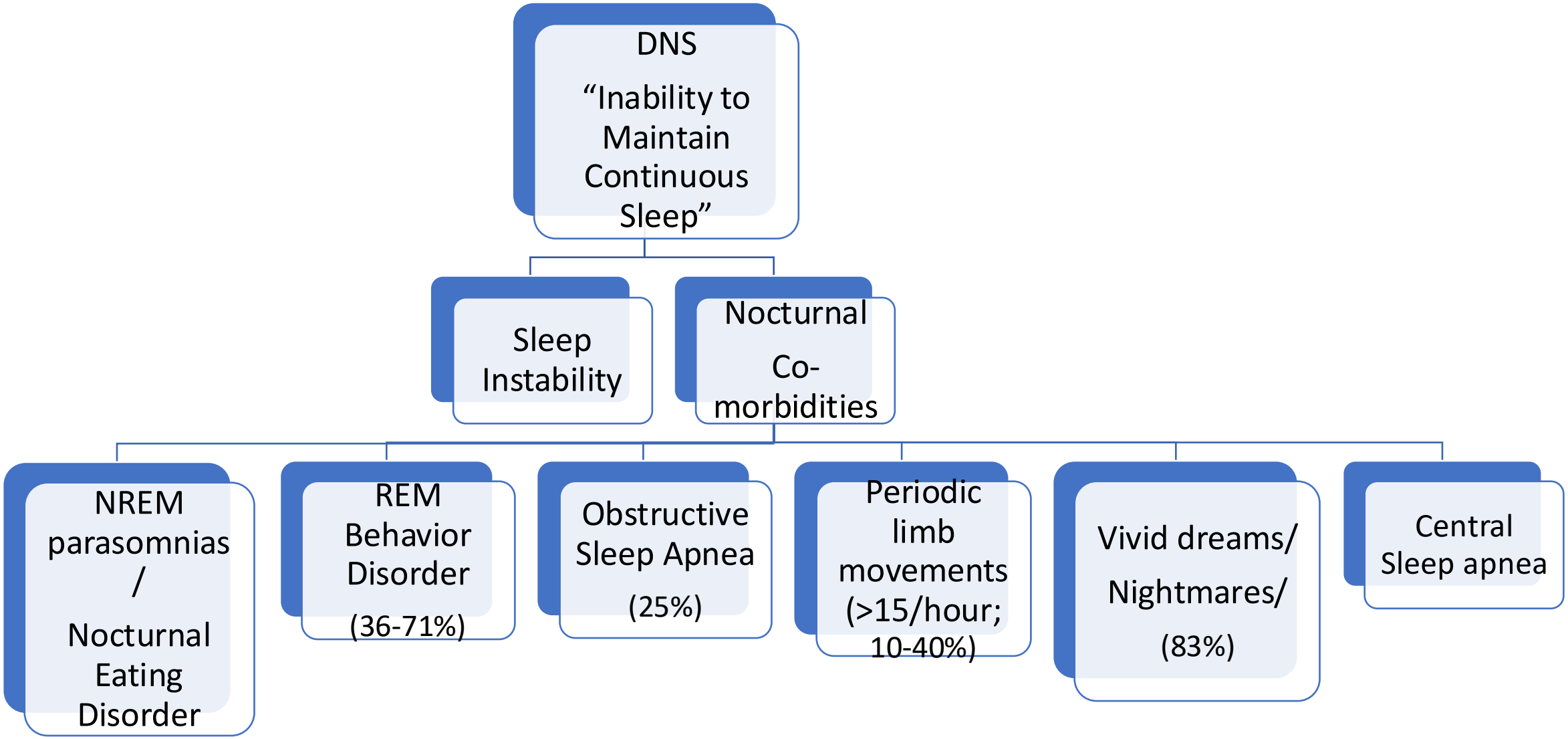
Cataplexy is characterized by sudden, emotionally triggered episodes of muscle weakness with preserved consciousness. These episodes typically begin with weakness of the muscles of the face and neck that then spreads to involve the muscles of the limbs and trunk.

Scammell, TE NEJM 2015

Cataplectic facies

Serra L et al., Movement Disorders. 2008

Disrupted Nighttime Sleep (DNS)



Roth T et al. JCSM 2013; Sazuki K PLoS One 2015; Sasai-Sakuma PLoS One 2015; Sansa G Sleep Med 2010, Pizza F et al Eur Neuro 2013, Wamsley E et al. SLEEP 2014, Maski K JCSM 2022

doi:10.1093/brain/awx096 BRAIN 2017: 140; 1669–1679 | 1669

BRAIN
A JOURNAL OF NEUROLOGY

The spectrum of REM sleep-related episodes in children with type 1 narcolepsy

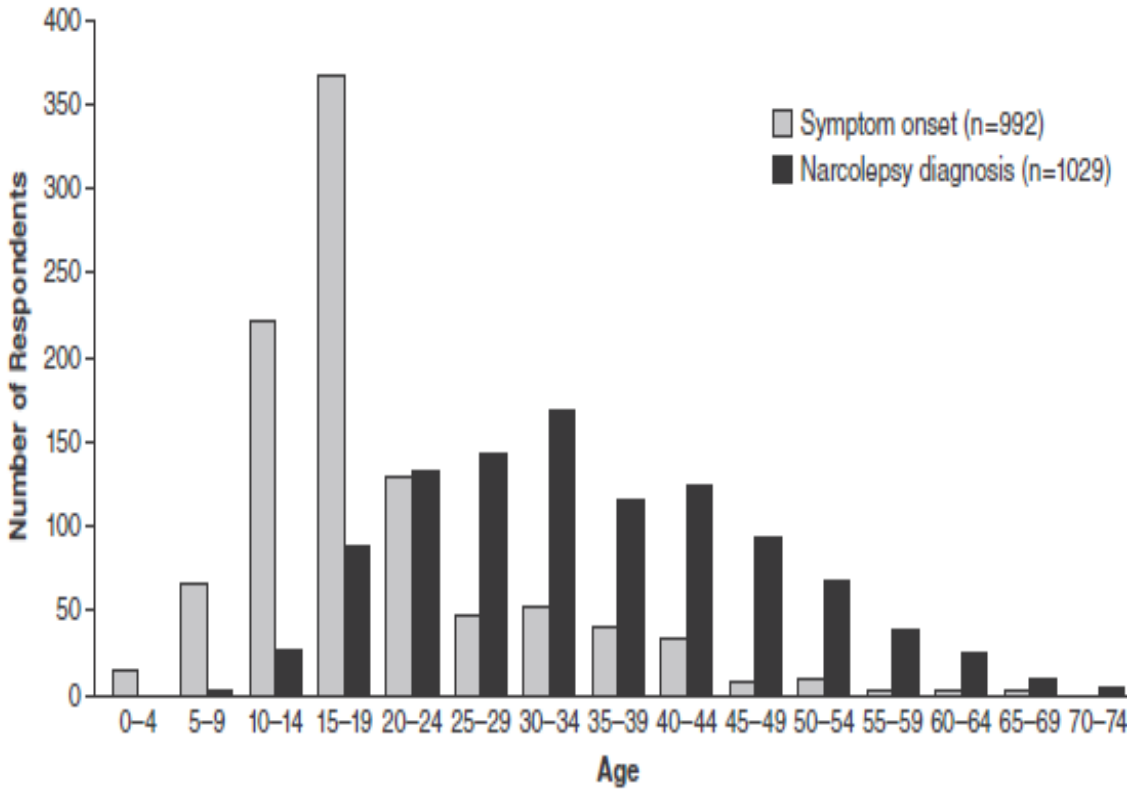
Elena Antelmi,[1,2] Fabio Pizza,[1,2] Stefano Vandi,[2] Giulia Neccia,[2] Raffaele Ferri,[3] Oliviero Bruni,[4] Marco Filardi,[1] Gaetano Cantalupo,[5] Rocco Liguori[1,2] and Giuseppe Plazzi[1,2]

Epidemiology

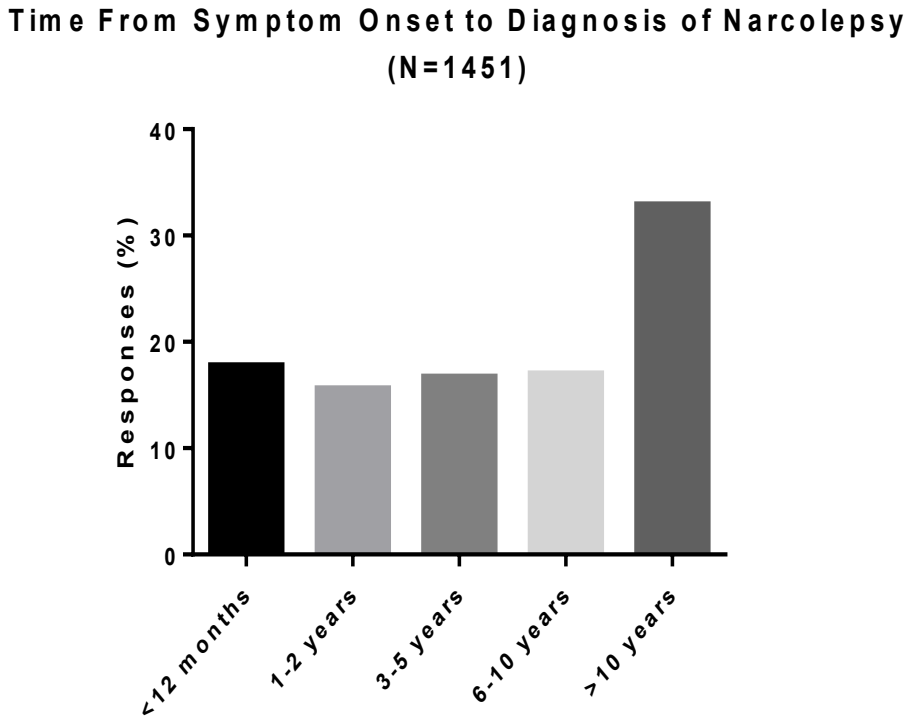
- Estimated prevalence is 0.03-0.16% of general population (incidence 1/2000)
- NT1 is more common in certain race/ethnic groups: Northern European, African-American, Asian
- Peak incidence is between 10-20 years of age

Longstreth WT et al. SLEEP, 2007

Delayed Diagnosis in Narcolepsy is a Clinical Problem



Thorpy MJ Neurology 1999; reprint Sleep Med, 2014



Factors that contribute to delay

- Pediatric onset of symptoms (OR=2.4)
- No cataplexy (OR=1.8)

Maski K et al. JCSM 2017

Medical Co-morbidities of Narcolepsy

- Obesity within months from onset (25-60%)
- Precocious puberty in children (16-40%)
- Obstructive sleep apnea (9-25%)
  - Can lead to misdiagnosis!
- Hypertension (41% of untreated patients and 58% on stimulants)
- Other: GI symptoms (dysmotility, constipation), headache, endocrinopathies

Poli F SLEEP 2013; Sansa Sleep Med 2010; Bosco A Neurology 2018,

Behavioral and Psychiatric Co-morbidities of Narcolepsy

- Attention Deficit Hyperactivity Disorder (33%)
- Cognitive Problems (Sustained Attention, Working Memory)
- Mood Disorders/Obsessive Compulsive Disorder (25%)

Lecendreux M SLEEP 2015, Cohen A Sleep Med 2018, Inocente CO Sleep Med 2014

Screening and Diagnosis

Tools to Assess Severity of Narcolepsy Symptoms

- **Epworth Sleepiness Scale/ Epworth Sleepiness Scale Children and Adolescent**
  - Daytime Sleepiness in passive and active situations (8 questions)
  - Reliable and valid Adults and 12-18 years (CHAD)
  - Normal <10; Value > 15 severe daytime sleepiness

- **Swiss Narcolepsy Scale**
  - Narcolepsy Type 1 only (5 questions)
  - Reliable and valid adults vs other sleep disorders
  - 77% sensitivity and 88.6% specificity

Narcolepsy Link

Janssen K Sleep Med 2017 ; Bargiotas P J Neurology 2019; Yang CM Psychiatry Clin Neurosci 2010; Maski K Neurology 2022

Tools to Assess Severity of Narcolepsy Symptoms

- **Ullanlinna Narcolepsy Scale (UNS)**
  - Daytime sleepiness and cataplexy (11 items)
  - Not developed or validated in pediatric narcolepsy cohort but used in clinical trials
- **Narcolepsy Severity Scale (NSS)/Pediatric Narcolepsy Severity Scale (P-NSS)**
  - Severity and function NT1; 14 to 15-items
  - Daytime sleepiness, disrupted sleep, cataplexy, sleep paralysis, HH
  - Validated and reliable adults and age 10 years and older
  - Languages: 1 (French) but translated in English
  - Discriminative validity between treated and untreated patients
- **Pediatric Hypersomnolence Survey**
  - Narcolepsy and IH (8-18 years), 14-item
  - Sensitivity and specificity of 81% vs controls and other sleep disorders

Hublin C J Sleep Res 1994; Barateau L Neurology 2021; Dauvilliers Y Neurology. 2017; Maski K Neurology 2022

	Often (3) (> 3/week)	Sometimes (2) (1-3/week)	Never (1) (Never noted)	DNK (0) (Do not know)
1. I fall asleep in class	☐	☐	☐	☐
2. I miss things in class because I am sleepy	☐	☐	☐	☐
3. My friends tell me I fall asleep easily	☐	☐	☐	☐
4. I fall asleep in the bus/car after school	☐	☐	☐	☐
5. I ask to go to the nurse's office or somewhere quiet to sleep during the school day	☐	☐	☐	☐
6. I feel weak in the knees when I laugh with my friends	☐	☐	☐	☐
7. My voice slurs when I laugh hard	☐	☐	☐	☐
8. My body feels weak briefly when I get excited or laugh	☐	☐	☐	☐
9. I dream when I sleep at night	☐	☐	☐	☐
10. My dreams seem very real	☐	☐	☐	☐
11. When I wake up, I can't move for a few minutes	☐	☐	☐	☐
12. I write silly things when taking notes in class because I am sleepy	☐	☐	☐	☐
13. It takes me a long time to do my homework because I am so tired	☐	☐	☐	☐
14. Doing homework makes me tired	☐	☐	☐	☐

Pediatric Hypersomnolence Survey

Sleep Logs

TWO WEEK SLEEP DIARY

AASM | SLEEP EDUCATION

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 "B" in the box to show when you go to bed. Put a "Z" in the box that shows when you think you fell asleep. **(4)** Put a "Z" in all the boxes that show when you are asleep at night or when you take a nap during the day. **(5)** Leave boxes empty 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 AM.

Date	Day of the week	Type of Day (Work, School, Day Off, Vacation)	Noon	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	Midnight	1 AM	2 AM	3 AM	4 AM	5 AM	6 AM	7 AM	8 AM	9 AM	10 AM	11 AM
sample	Mon.	Work		E					A	Z			B		Z	Z	Z	Z		Z	Z	C M				

week 1

week 2

Correct insufficient sleep prior to MSLT!

Retrospective study of Swiss sleep lab using actigraphy prior to PSG-MSLT, about 9% of chronic EDS patients had suspected behavioral insomnia based on actigraphy results

- Of 99 patients, only 37 successfully achieved improved sleep extension despite repeated attempts of clinical providers

	N=36 (baseline)	N=25 (after sleep extension)
Questionnaires and history		
Epworth sleepiness scale	**12.2**±4.6 (4-21)	**6.9**±3.7 (1-16)
Fatigue severity scale	**4.5**±1.4 (1.7-6.5)	**3.1**±1.8 (1.3-5.8)
Sleep attacks	**17** (47%)	**0** (0%)
Actigraphy		
'Time in bed': all nights	**6h48**±0h48 (5h17-8h25)	**8h12**±0h55 (6h35-9h53)
'Time in bed': working days	**6h19**±0h47 (4h55-7h57)	**7h38**±0h55 (5h37-9h05)
'Time in bed': weekends/holidays	**7h54**±1h18 (5h35-11h22)	**8h58**±1h11 (6h48-11h12)
Difference working days-weekends	**1h37**±1h05 (0h0-4h18)	**1h25**±1h19 (0h12-5h35)
Daytime naps	**9** (25%)	**1** (3%)
Multiple Sleep Latency Test	n=36	n=25
Mean sleep latency (minutes)	**4.0**±1.4 (1.5-7.0)	**12**.2±2.8 (10.0-20.0)
≥2 sleep onset REM periods (patients)	**15** (42%)	**0** (0%)
NREM 1→REM sequence (patients)	**7** (19%)	**0** (0%)
NREM 1→REM sequence (no. of naps)	**10/44** (23%)	**0/3** (0%)

Baumann-Vogel H J
Sleep Res 2021

ICSD 3 TR Diagnostic Criteria for Narcolepsy Type 1 (narcolepsy with cataplexy)

Criteria A-C must be met

A. Daily periods of irrepressible need to sleep or daytime lapses into drowsiness or sleep

- ~~The Excessive Daytime Sleepiness for at least 3 months~~

B. The presence of one or both of the following:

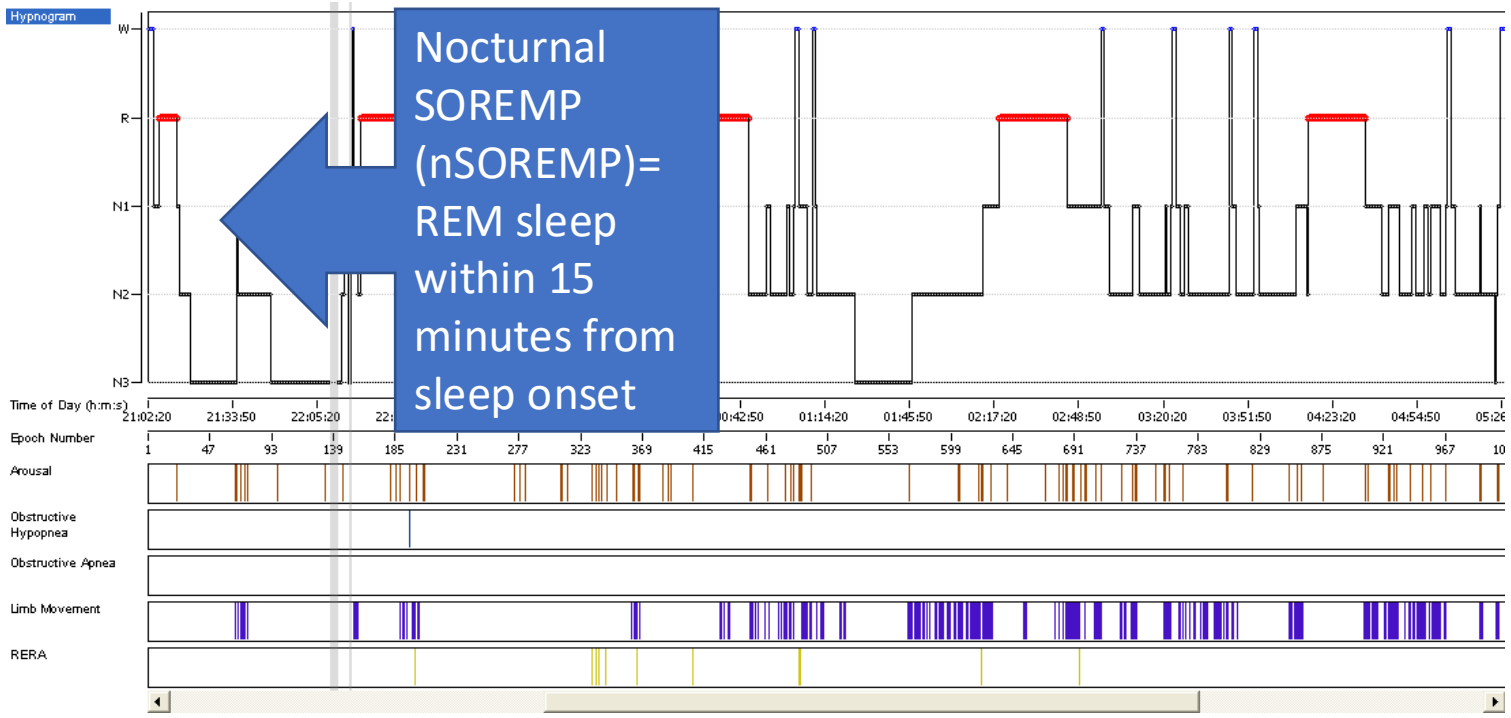
1. Typical Cataplexy and either:

   a. Mean sleep latency of ≤ 8 minutes and two or more sleep-onset REM periods (SOREMPs) on a Multiple Sleep Latency Test (MSLT) performed in accordance with current recommended protocols.

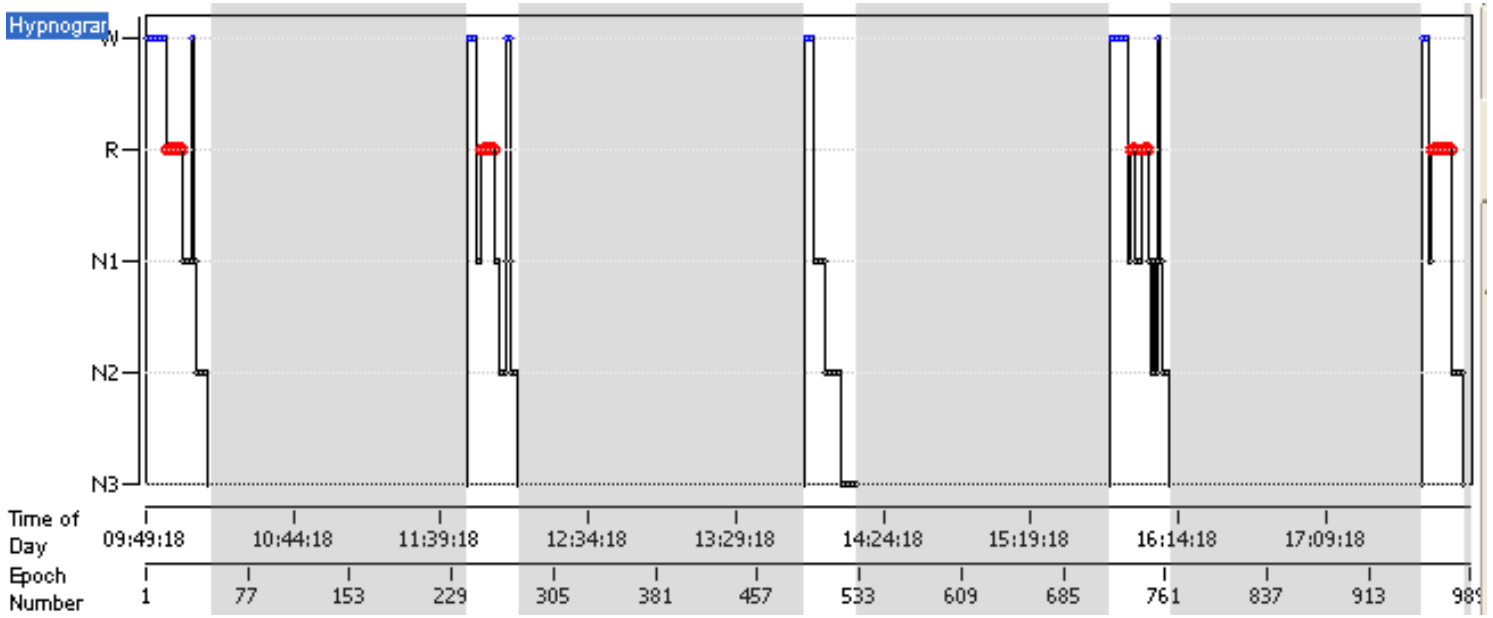
   b. A SOREMP (within 15 minutes of sleep onset) on nocturnal polysomnogram (nSOREMP).

2. CSF hypocretin-1 concentration, measured by radioimmunoassay, is ≤ 110 pg/mL (using a Stanford reference sample) or less than one-third of mean values obtained in normal subjects with the same standardized assay.

C. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, mental disorder, or medication/substance use or withdrawal.



Polysomnogram (PSG) of NT1 Patient



Multiple Sleep Latency Test (MSLT) of NT1 Patient

ICSD 3 TR Diagnostic Criteria for Narcolepsy Type 2 (narcolepsy without cataplexy)

<u>Criteria A-E must be met</u>

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into drowsiness or sleep occurring for at least three months.

B. A mean sleep latency of ≤ 8 minutes and two or more sleep-onset REM periods (SOREMPs) on an Multiple Sleep Latency Test (MSLT) performed in accordance with current recommended protocols. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

C. Cataplexy is absent.

D. If CSF hypocretin-1 concentration is measured by radioimmunoassay, it is either > 110 pg/mL (when using a Stanford reference sample) or more than one-third of mean values obtained in normal subjects with tl standardized assay.

E. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, mental disorder, or medication/substance use or withdrawal.

ICSD 3 TR Diagnostic Criteria for Idiopathic Hypersomnia

Criteria A-F must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into drowsiness or sleep occurring for at least three months.

B. Cataplexy is absent.

C. Polysomnography and Multiple Sleep Latency Test (MSLT) findings are not consistent with a diagnosis of narcolepsy type 1 or 2.

D. The presence of at least one of the following:

1. The MSLT, performed in accordance with current recommended protocols, shows a mean sleep latency of ≤ 8 minutes.

2. Total 24-hour sleep time is ≥ 660 minutes (typically 12–14 hours) on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation), *or* by wrist actigraphy in association with a sleep log (averaged over at least seven days with unrestricted sleep).

E. Insufficient sleep is ruled out (if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed, preferably confirmed by at least a week of wrist actigraphy).

F. The symptoms and signs are not better explained by a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, mental disorder, or medication/substance use or withdrawal.

Reliability of MSLT for NT2 and IH patients is poor

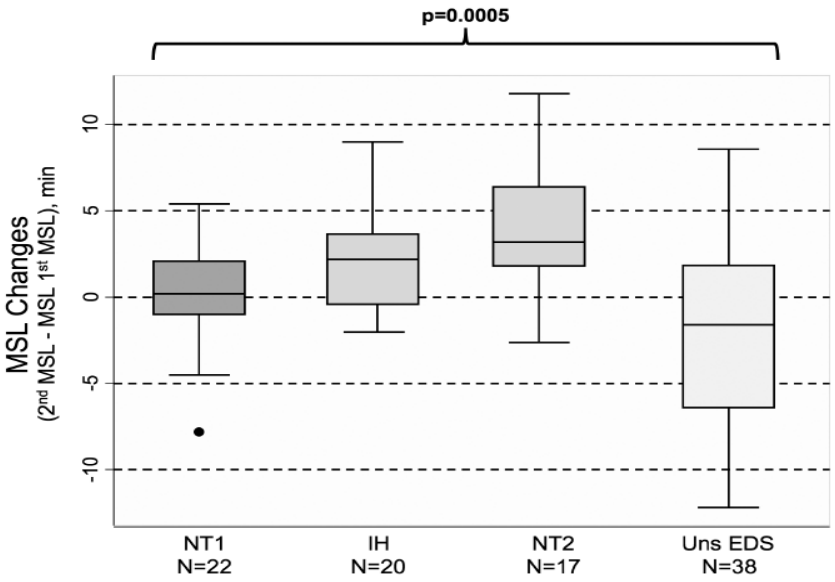


Figure 1—Changes in mean sleep latency (MSL) between the second and first MSLT in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), idiopathic hypersomnia (IH), and unspecified hypersomnolence (unspecified excessive daytime sleepiness [UnsEDS]).

- More variability between tests for NT2, IH and subjective sleepy patients than NT1 patients
- Classification consistency on MSLT retesting was only 25% IH and 47% for NT2.

Lopez R et al. SLEEP 2017

Highlights from AASM 2021 and 2024 recommended protocols for the Multiple Sleep Latency Test

- Preparation: Ensure adequate sleep duration for age (sleep log, validated sleep tracking device/actigraphy)
- Procedural:
  - Set-up of PSG at least 30 min before habitual sleep time to allow for nSOREMP
  - Electronic devices shut off 30 minutes before lights out for PSG <u>and</u> MSLT naps
  - Ideally 7 hours sleep on PSG prior to MSLT (minimum 6)
  - Shared decision making with parents/caregivers to stay in MSLT room with pediatric patient to alleviate anxiety if needed
  - Specifies clinical information that should be in report (habitual sleep times, medications, surveys, protocol deviations)

Krahn L JCSM 2021; Maski K, Carter J, Amos L, Rosen C, AASM staff et al. JCSM 2024

Recommendation: Wean REM suppressing medications for minimum 2 weeks prior to testing

- SSRI/SNRI/TCA/anti-psychotics are known to suppress REM sleep amount and prolong REM sleep onset latency
- Among 164 pediatric patients having MSLTs (mean age 11.9 years), 17% on REM-AD at time of testing
  - No significant difference on MSL between those on (mean 11.47, SD 0.5) or off REM-ADs (10.36, SD 1.1)
  - Significant difference on number of SOREMPs between those on REM-Ads (0.18, SD 0.19) or off REM-ADs (0.62, SD 0.09)

- *Takeaway: May be ok to keep patients on REM-ADs if evaluating for idiopathic hypersomnia but not narcolepsy*

Mansukhani M et al JCSM 2021

Treatment and Management

What are most impactful symptoms in daily life for people with narcolepsy?

Narcolepsy Type 1, n=943

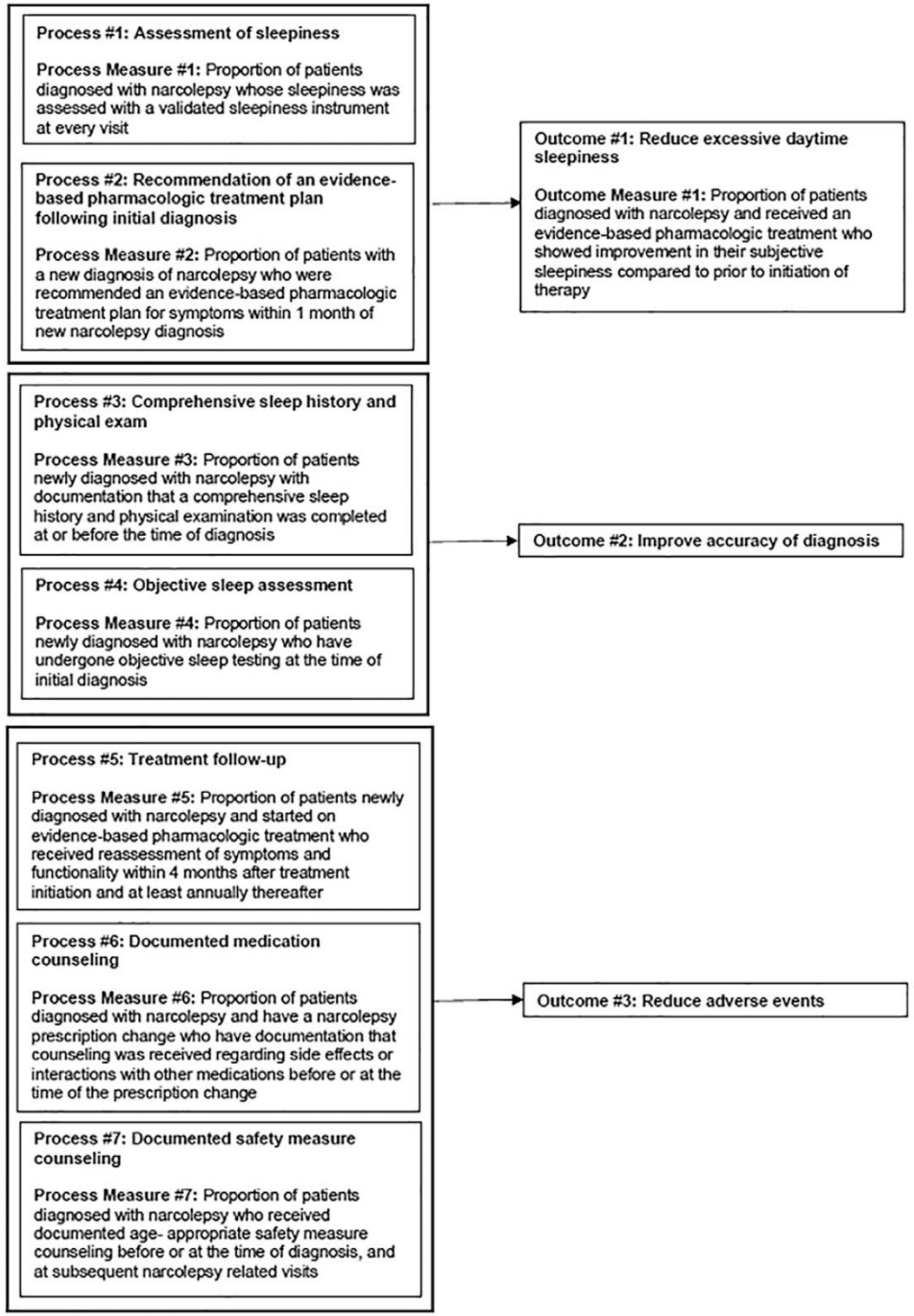
1. Excessive Daytime Sleepiness (75.3%)
2. Difficulty thinking, remembering, concentrating, or paying attention (46.9%)
3. Cataplexy (43.5%)
4. Disrupted Nighttime Sleep (34.4%)
5. Irritability, mood instability, and less positive mood (25%)

Narcolepsy Type 2, n=313

1. Excessive Daytime Sleepiness (87.5%)
2. General fatigue/never rested feeling (54%)
3. Difficulty thinking, remembering, concentrating, or paying attention (53%)
4. Waking Unrefreshed in AM (39%)
5. Irritability, mood instability, and less positive mood (34.8%)

Maski K et al Listening to the Patient Voice JCSM 2017

Figure 2—Revised narcolepsy quality measures driver diagram.



JCSM | Journal of Clinical Sleep Medicine

SPECIAL ARTICLES

Quality measure for care of patients with narcolepsy: 2025 update after measure maintenance

Robin M. Lloyd, MD[1]; T'Auna Crawford, BS[2]; Ryan Donald, MD[3]; Diedra D. Gray, MPH[2]; William J. Healy, MD[4]; Mithri R. Junna, MD[1]; Daniel Lewin, PhD[5]; Amee Revana, DO, FAASM[6]; Sharon Schutte-Rodin, MD[7]

1. Use same validated instrument before and after treatment initiation
2. Note update on language: patients on *escalating* sedating medications regimen

administered for comorbid conditions (eg, opioids for pain, benzodiazepines for seizures)

3. Note need to document

contraindications to the recommended evidence-based pharmacologic
treatment.

Lloyd R et al JCSM Nov 2025

Treatment of excessive sleepiness: Traditional Stimulants

	Dose	Mechanisms of Action	Side Effects
Methylphenidate IR, ER (e.g. Ritalin, Focalin, Concerta) Schedule II	-10-60 mg/day IR Divided dosing BID, TID -ER (18-54 mg) -Appx 1 mg/kg/day	• DAT inhibitor (inhibits DA reuptake) • Duration of action: 3-5 hours (IR); 6-12 hours (ER); 2-8 hours (SR)	irritability, headaches, insomnia, GI upset, hypertension, arrhythmias, anxiety, psychosis
Mixed amphetamine salts (Adderall) Schedule II	5-40 mg/day BID-TID or ER -Appx 0.5 mg/kg/day	• DAT inhibitor (inhibits DA reuptake); increases DA from presynaptic cleft • Duration of action: 4-6 hours (IR); 8-12 hours (XR)	same, reduced appetite, weight loss, psychosis (2x higher than MP)*
Lisdexamphetamine (Vyvanse) Schedule II	20-70 mg/day About 1/3 potency of mixed amphetamine	• Duration of action: 8-12 hours	Same, Hyperhidrosis, skin rash, dry mouth

FDA approved to treat EDS in pediatric narcolepsy

*Moran LV NEJM 2019

Treatment of excessive sleepiness

	Dose	Mechanism of Action	Side Effects
Modafinil (Provigil)	50-200 mg BID (morning and afternoon)	R,S, enantiomer Weak DAT Inhibitor, inhibit DA reuptake Tmax: 2-4 hours; T1/2: 15 hours	Headache, nausea, nervousness, insomnia, rash, psychosis**, SJS**, dyspepsia, backpain, hypertension, OCP interaction
Armodafinil (Nuvigil)	50-250 mg qA	Longer acting R-enantiomer, Weak DAT Inhibitor, inhibit DA reuptake Tmax: 2 hours; T1/2: 15 hours. Higher [plasma] in afternoon*	Same
Solriamfetol (Sunosi)	75-150 mg q AM	DAT and NET Inhibitor, Inhibit DA and NE reuptake Tmax 2-3 hours; T1/2: 7 hours	HA (21%), Increased HR, BP, Nausea/diarrhea (11%), anxiety (5%)
Atomoxetine (Strattera)	10-50 mg qAM	Inhibits NE reuptake Tmax 1-2 hours; T1/2: 5-8 hours	Similar to stimulants but lower frequencies

Treatment of daytime sleepiness and cataplexy

	Dose	Mechanism of Action	Side Effects/Notes
Sodium Oxybate (Xyrem, generic) Once nightly (Lumryz)	2.25-4.5 g twice nightly 4.5-9 grams bedtime	?; GABA-B agonist	REMS: OSA/hypoventilation, depression, SI, psychosis, driving safety Nausea, hallucinations, dizziness, OSA, weight loss/gain
Low-salt Oxybate (Xywav)	2.25-4.5 g twice nightly	?; GABA-B agonist	Same *FDA approved for adult IH Consider if HTN/high blood pressure/renal disease
Pitolisant (Wakix) FDA approved EDS and cataplexy	4.45 to 35.6 mg qAM	H3-receptor antagonist/inverse agonist (increase HA synthesis and release) Tmax: 3 hours; T1/2: 20 hours	HAs, insomnia, irritability, anxiety, nausea (all <10%); potential for QTc prolongation with SSRI/SNRIs

Other treatments of cataplexy

	Typical dose		Side effects
Venlafaxine (Effexor)	37.5-325 mg XR qAM (IR formulation BID)	Inhibits 5-HT and NE reuptake	Serotonin syndrome, SI risks, Weight gain, nausea
Fluoxetine (Prozac)	20-60 mg qAM	Inhibits 5HT reuptake	Same, dry mouth, sexual dysfunction
Protriptyline (Vivactyl)	2.5-5 mg TID (max 60 mg/day)	Monoamine Reuptake Inhibitor (5HT, NE, DA)	Anticholinergic effects, Cardiac arrhythmia, abnormal LFTs
Clomipramine	25-75 mg qday	Monoamine Reuptake Inhibitor (5HT, NE, DA)	Anticholinergic effects (>10% constipation, dry mouth). Cardiac arrhythmia,

Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline

Kiran Maski, MD, MPH[1]; Lynn Marie Trotti, MD, MSc[2]; Suresh Kotagal, MD[3]; R. Robert Auger, MD[4]; James A. Rowley, MD[5]; Sarah D. Hashmi, MBBS, MSc, MPH[6]; Nathaniel F. Watson, MD, MSc[7]

Adult patients with narcolepsy

1. We recommend that clinicians use modafinil for the treatment of narcolepsy in adults. (STRONG)
2. We recommend that clinicians use pitolisant for the treatment of narcolepsy in adults. (STRONG)
3. We recommend that clinicians use sodium oxybate for the treatment of narcolepsy in adults. (STRONG)
4. We recommend that clinicians use solriamfetol for the treatment of narcolepsy in adults. (STRONG)
5. We suggest that clinicians use armodafinil for the treatment of narcolepsy in adults. (CONDITIONAL)
6. We suggest that clinicians use dextroamphetamine for the treatment of narcolepsy in adults. (CONDITIONAL)
7. We suggest that clinicians use methylphenidate for the treatment of narcolepsy in adults. (CONDITIONAL)

Pediatric patients with narcolepsy

21. We suggest that clinicians use modafinil for the treatment of narcolepsy in pediatric patients. (CONDITIONAL)
22. We suggest that clinicians use sodium oxybate for the treatment of narcolepsy in pediatric patients. (CONDITIONAL)

JCSM 2021

European guideline and expert statements on the management of narcolepsy in adults and children

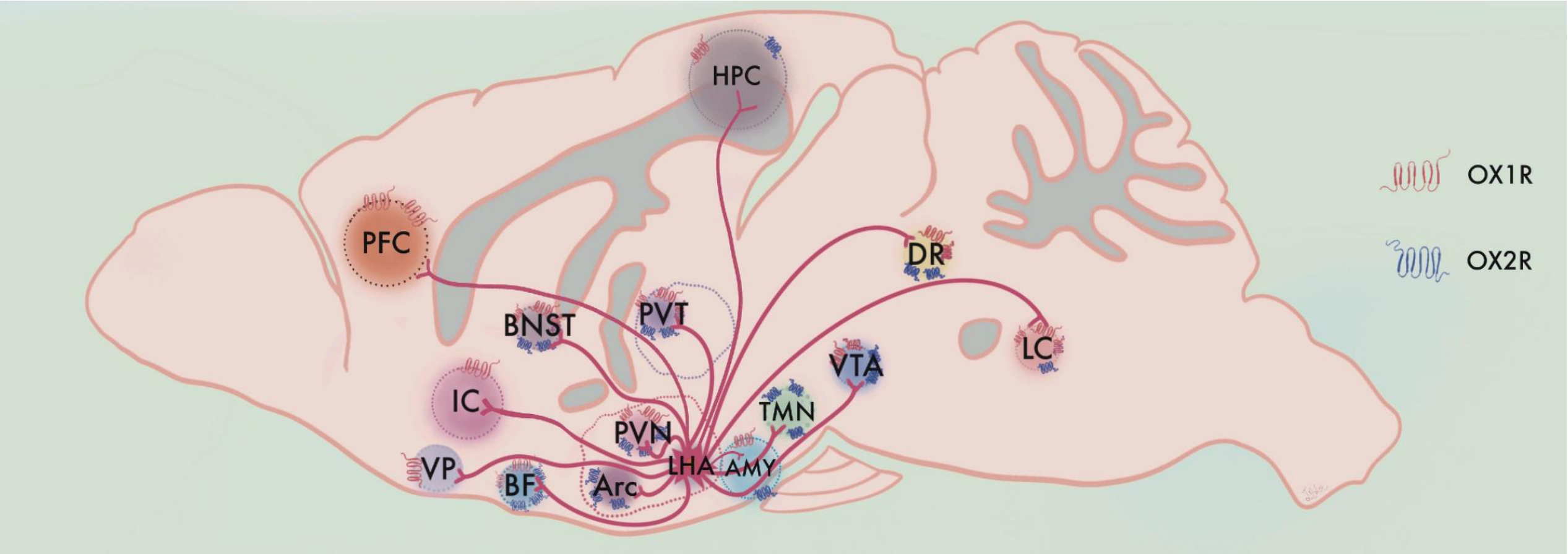
Pharmacological management

	EDS unique/ main symptom	EDS and Cataplexy	EDS, Cataplexy and DNS
1st LINE	**Monotherapy** (alphabetical order): ➤ MODAFINIL *or* ➤ PITOLISANT *or* ➤ SOLRIAMFETOL* *Consider optimal dosage and titration* *If not or only partially effective after 4-6 weeks: change to another monotherapy, if not successfull, change to second line options*	**Monotherapy:** ➤ ➤ OXYBATES OR PITOLISANT (mild/mod cataplexy) **Combination therapies:** ➤ VEN/CLO, *and* 1.line WPA *or* ➤ SXB # *and* 1.line WPA *Consider optimal dosage and titration* *If not or only partially effective after 4-6 weeks: change to second line options*	**Monotherapy:** ➤ OXYBATES **Combination therapies:** ➤ SXB # and/or VEN/CLO, *and* 1. line WPA *or* ➤ Any WPA, VEN/CLO and (only exceptionally and only short-term) Sleep aid: trazodone
2nd LINE	***Change to combination therapy:*** ➤ PIT *and* MOD *or* SOL ➤ SXB # *and* any WPA or ***Change to monotherapy:*** ➤SXB # *or* ➤MPH *or* ➤AMPH	***Change to combination therapy:*** ➤ Exchange SXB # to VEN/CLO (and vice versa) or ➤ SXB #, VEN/CLO *and* 1.line WPA or ➤Exchange VEN/CLO to another AD	

DNS = Disturbed nocturnal sleep
WPA = wake-promoting agents (MOD, SOL, PIT, MPH, AMPH)
MOD = Modafinil; SOL = Solriamfetol;
PIT = Pitolisant; SXB = Sodium Oxybate;
VEN = Venlafaxine; CLO = Clomipramine (low-dose); MPH = Methylphenidate;
AMPH = Amphetamines; AD = Antidepressant
*Suggested from trials, few clinical experience;
Consider sleep apnea before starting with SXB

Modified from Bassetti C and Kallweit U et al. Euro J Neurol 2021

Orexin Receptor 2 Clinical Trial Developments for NT1 (adults)



Orexin 1 and 2 receptors=Basal forebrain, hippocampus, dorsal raphe, ventral tegmentum, amygdala

Orexin 1 > 2 receptors=Locus coeruleus, insula, ventral pallidum/basal ganglia), PFC

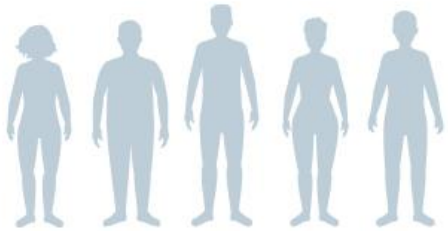
Orexin 2 > 1 receptors=Tuberomammillary Nucleus (wake/sleep), PVN of hypothalamus (arousal)

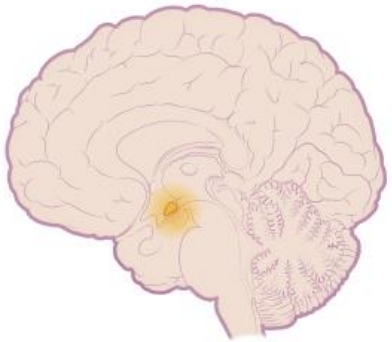
Mieda M et al Frontiers Endocrin 2013

Oveporexton: Orexin 2 rec agonist Phase 2 TAK 860 for NT1

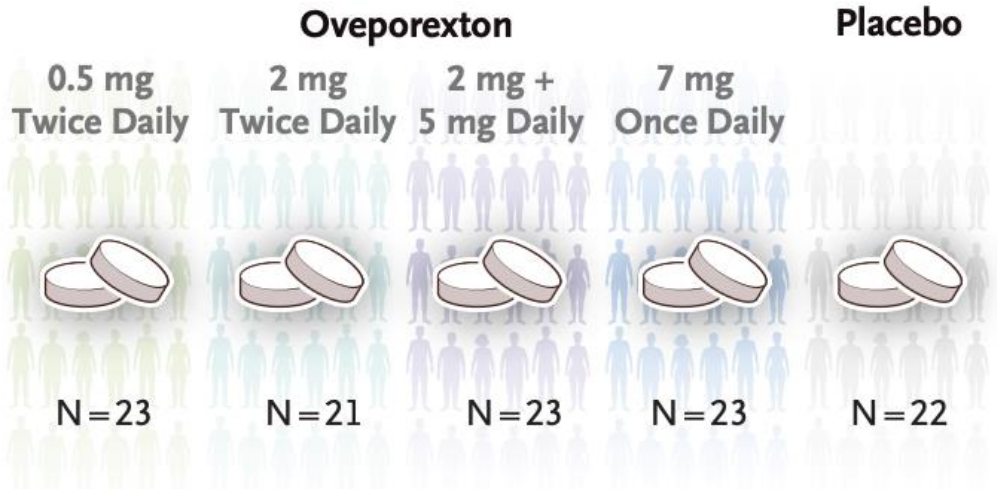
Participants

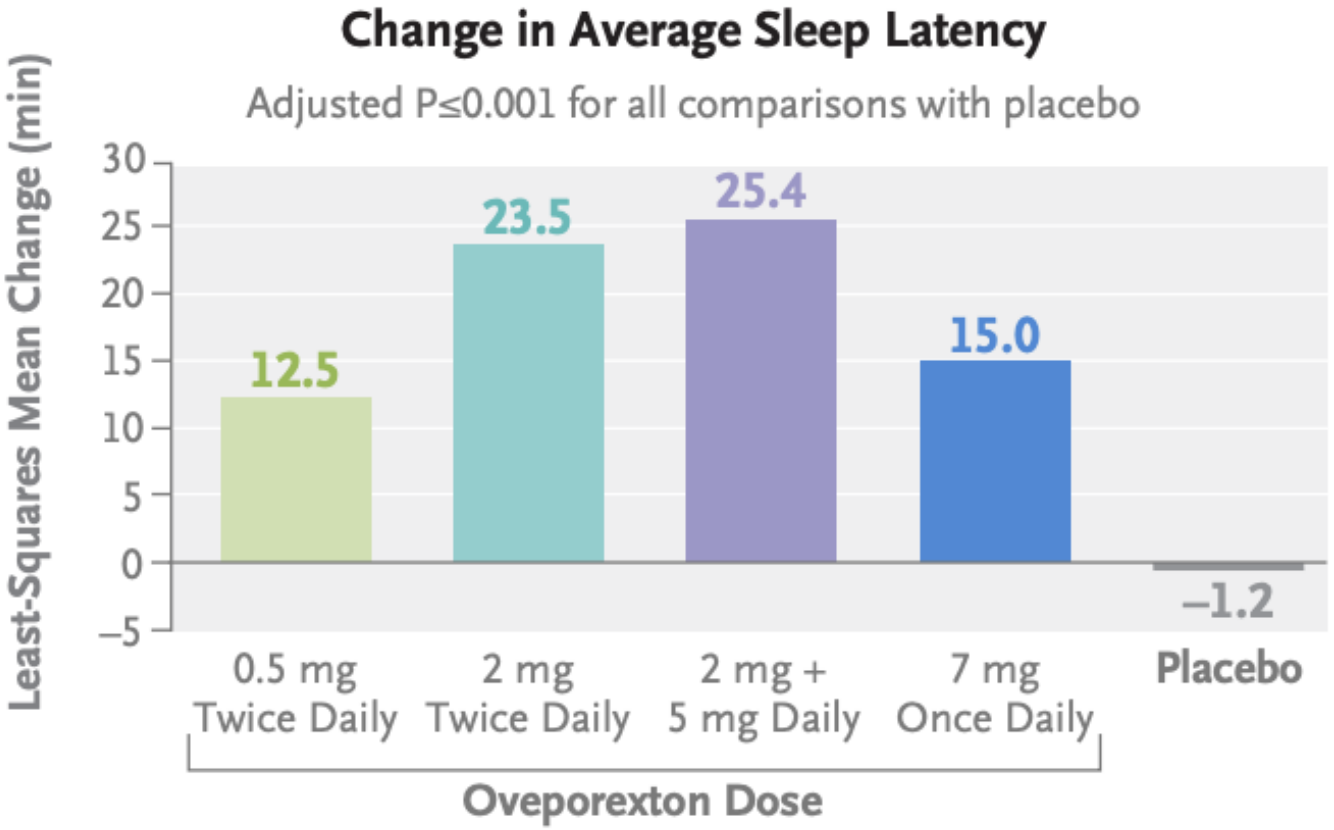
- 112 adults
- Mean age, 34 years
- Women: 52%; Men: 48%





Loss of hypothalamic orexin-producing neurons



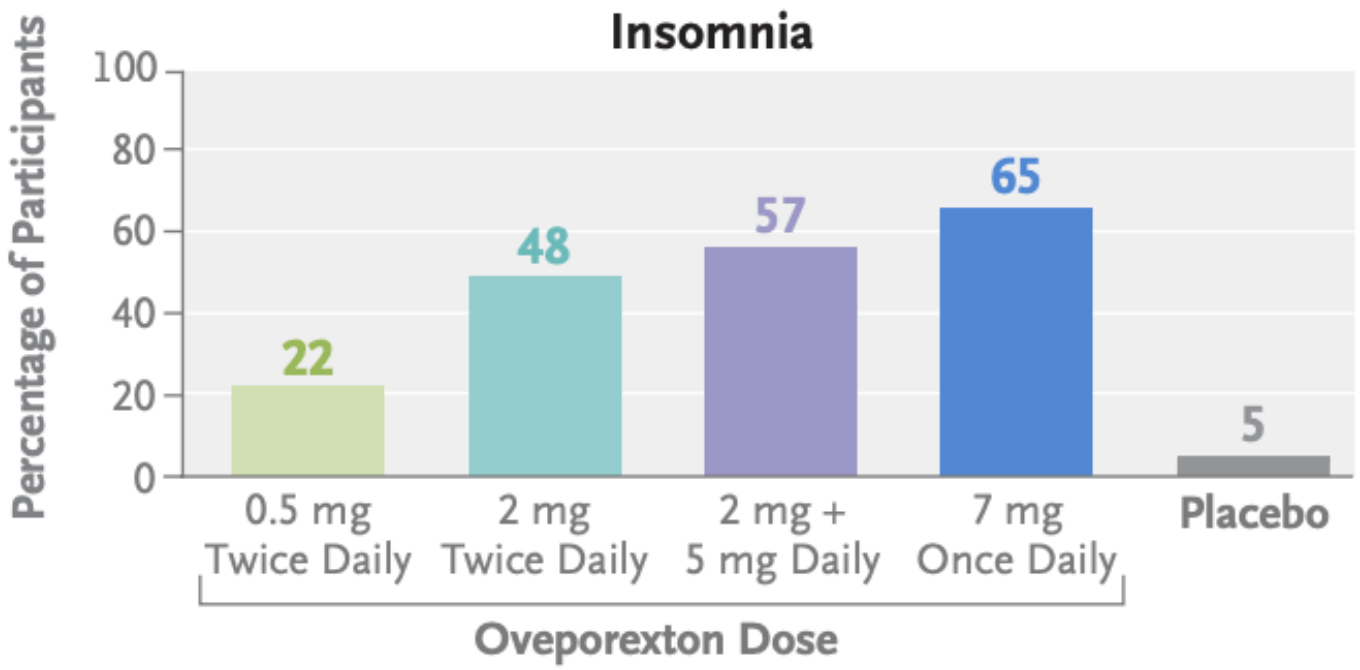


Dauvilliers Y NEJM 2025

Randomized for 8 weeks

Oveporexton: Orexin 2 rec agonist Phase 2 Adverse Outcomes

- 32-91% Adverse Events (most mild to moderate)
  - 4-14% Serious AE attributed to study drug
    - Cataplexy, insomnia, headache and insomnia



- AE frequency 22-65%
- Dose dependent
- Most insomnia improved over first week

Other AE:

- Increase urinary frequency and urge (13-52%)
- Hypersalivation (9-26%)
- Headache (4-14%)
- Nasopharyngitis (9-10%)

- No drop outs due to adverse events
- No significant differences in liver enzymes from placebo

Dauvilliers Y NEJM 2025

JAMA Neurology

RCT: Effects of Oveporexton, an Orexin Receptor 2-Selective Agonist, on Cognition in Narcolepsy Type 1

POPULATION

54 Men, 58 Women

Adults (18-70 y) with a confirmed diagnosis of narcolepsy type 1

Mean (SD) age, 34.0 (11.5) y

SETTINGS / LOCATIONS

33 Clinical centers in the US, Europe, Japan, and Australia

INTERVENTION

112 Participants randomized

23 Oveporexton, 0.5 mg/0.5 mg
Twice-daily oral oveporexton, 0.5 mg, then 0.5-mg doses 3 hours apart for 8 wk

21 Oveporexton, 2 mg/2 mg
Twice-daily oral oveporexton, 2 mg, then 2-mg doses 3 hours apart for 8 wk

23 Oveporexton, 2 mg/5 mg
Twice-daily oral oveporexton, 2 mg, then 5-mg doses 3 hours apart for 8 wk

23 Oveporexton, 7 mg/placebo
Twice-daily oral oveporexton, 7 mg, then placebo doses 3 hours apart for 8 wk

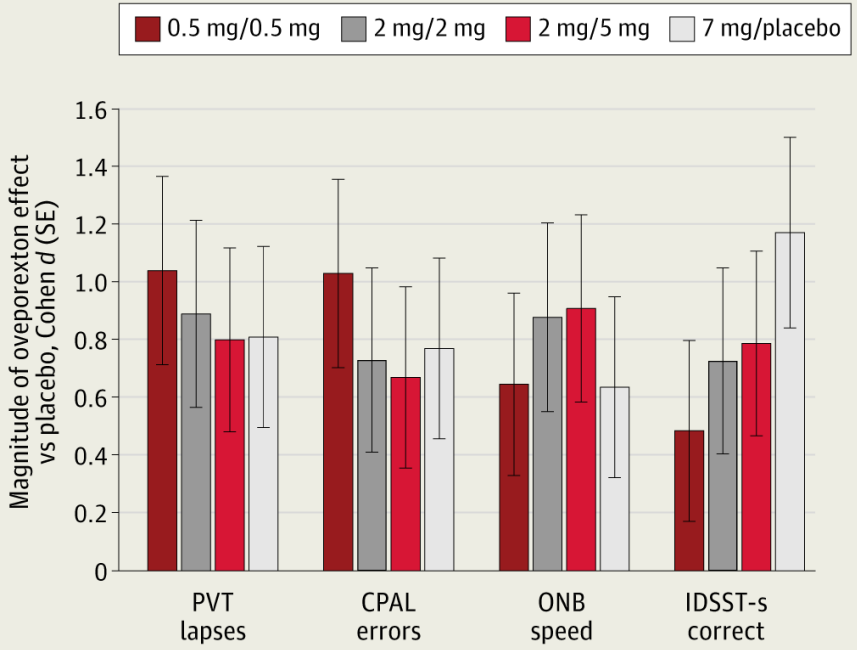
22 Placebo/placebo
Twice-daily placebo, 3 hours apart for 8 wk

PRIMARY OUTCOME

Cognition as measured by the Psychomotor Vigilance Task (PVT) for attention, Continuous Paired Associate Learning (CPAL) for memory, and One Back (ONB) and International Digit Symbol Substitution Test-symbols (IDSST-s) for executive function

FINDINGS

Treatment with oral oveporexton improved measures of attention, memory, and executive function



Lammers GJ, Plazzi G, Mignot E, et al. Effects of oveporexton, an orexin receptor 2-selective agonist, on cognition in narcolepsy type 1: a secondary analysis of a randomized clinical trial. *JAMA Neurol*. Published online December 8, 2025. doi:10.1001/jamaneurol.2025.4825

© AMA

Phase 3 Trials Oveporexton (TAK-861) in Narcolepsy Type 1

Study Design

- Phase 3 RCT, placebo controlled, double blind, multi-national
- Oveporextan 1-2 mg BID vs placebo
- 12-week treatment period

Endpoint	Measure	Key Week-12 Outcome
Primary	Maintenance of Wakefulness Test (MWT)	Sleep latency normalized (~21–25 min) vs ~3–4 min placebo
Daytime Sleepiness	Epworth Sleepiness Scale	~85% achieved ESS ≤10
Cataplexy	Weekly Cataplexy Rate	≈66–79% reduction from baseline
Disease Severity	Narcolepsy Severity Scale	>70% reached lowest severity category
Safety	Adverse events	Generally well tolerated; insomnia & urinary urgency most common

FirstLight (NCT06470828) and RadiantLight (NCT06505031)

Mignot E. CHEST, Volume 168, Issue 4, A7316 - A7317 2025

Other Future Treatments:

- Orexin 2 receptor agonists (ALKS 2680, ORX 750)

  Phase 2 for IH and NT2
- Serdexmethylphenidate (pro-drug methylphenidate; KP 1077)
- Reformulated pitolisant for IH
- Reboxetine

Non-pharmacological Management for Narcolepsy and IH

- Naps may not be helpful for IH but generally helpful for narcolepsy
- Later start time for classes or first period study hall/work (IH)
- If sleepy during day
  - Extra time on timed test/stop clock
  - Extra time on projects
  - Ability to drink water, take movement breaks, chew gum, fidget toys
  - Stand desks
- Activity encouraged/maintain a schedule
- CBT-H (hypersomnia) for psychosocial support, coping, stigma self-advocacy
- Social supports: Hypersomnia Foundation, Narcolepsy Network, Project Sleep, Wake Up Narcolepsy, etc.

Ong J et al. JCSM 2020

Conclusion

- Daytime sleepiness is epidemic issue most commonly due to insufficient sleep
- When severe sleepiness persists despite normal sleep, consider CNS disorders of hypersomnolence
  - Diagnostic delays common and refer to neurologist/sleep medicine specialist
- Diagnosis of narcolepsy requires orexin CSF testing (NT1) or diagnostic sleep studies (PSG-MSLT)
- Treatments are available that improve symptoms
  - Must be customized to patient needs
  - Novel treatments on the horizon