HITTING REFRESH ON EXCESSIVE DAYTIME SLEEPINESS

Managing Patients with Narcolepsy and Idiopathic Hypersomnia

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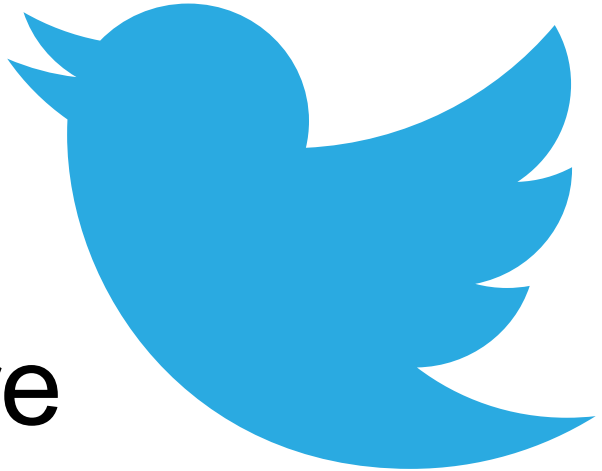

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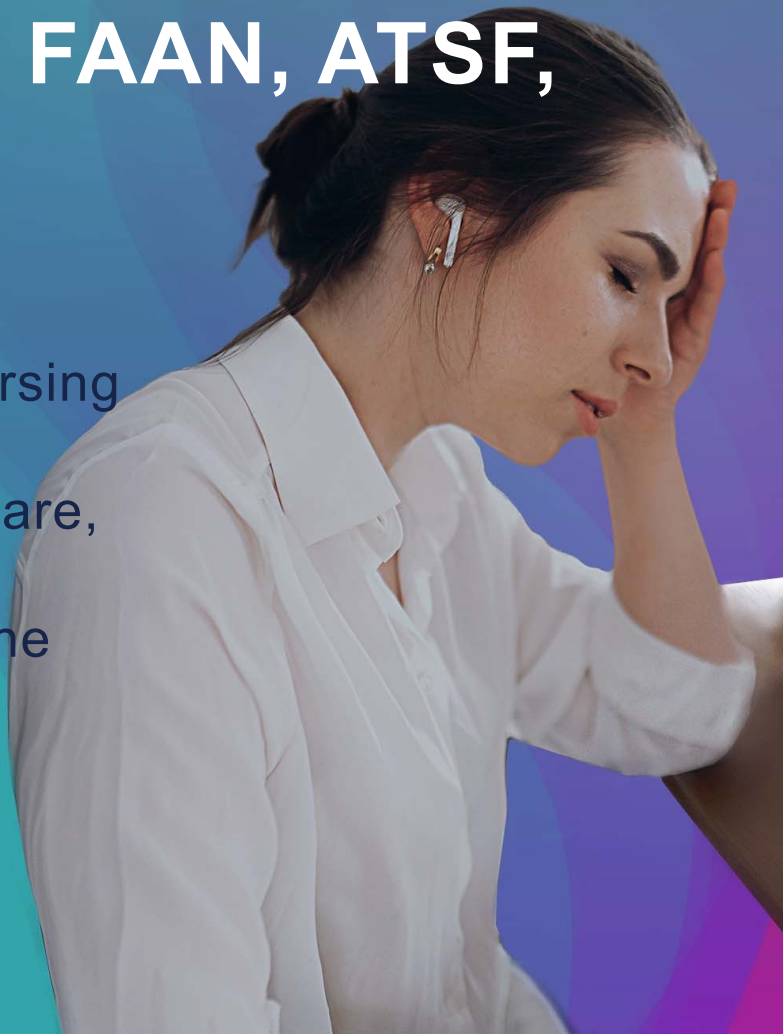


LEARNING OBJECTIVE 1

Differentiate the spectrum of EDS across the subtypes of narcolepsy (type 1, type 2).

LEARNING OBJECTIVE 2

Apply data from recent clinical trials to treatment decision-making in patients with narcolepsy.

LEARNING OBJECTIVE 3

Evaluate the impact of emerging agents for the management of EDS in patients with idiopathic hypersomnia.

Case 1: Savannah

PRESENTATION

- 26-year-old black female graduate student
- Constantly feels the need to take a nap
- 3-4 awakenings during the night but does not have trouble going back to sleep
- Vivid dreams, colorful, seem real, sometimes disturbing
- Often awakened with sensation of inability to move and impending doom and panic

PAST MEDICAL HISTORY

- No major problems except a history of anxiety
- Diagnosed as having attention deficit disorder some years ago
- Previous psychiatric evaluation due to:
  - Panic attacks at night
  - Poor concentration
  - Irritability
  - Mood changes with fatigue

SYMPTOM REVIEW

- Symptoms began in her mid-teenage years
- Slowly progressed
- History of vivid dreams and dream enactment characterised by talking in her sleep or frequent movements, which upon awakening were usually during a dream
- No history of:
  - Snoring
  - Restless leg symptoms, periodic leg movements
  - Muscle weakness or “melting” with emotion

MEDICATION

- Escitalopram, 10 mg daily
  - Slightly reduced the anxiety
- Methylphenidate, titrated over the years to 20 mg twice daily
  - Improved memory and helped with academic performance
  - Caused tremor in hands, clenching of teeth in the day, mild anxiety, increase in heart rate
- Oral hormonal contraceptives

SLEEPINESS SCALES SCORES

ESS (Epworth Sleepiness Scale)	19/24
ISI (Insomnia Severity Index)	19/28
FOSQ (Functional Outcome of Sleep Questionnaire)	9.5/20

EXAMINATION

Results of detailed medical examination

Heart rate	95 beats/minute (respirations normal)
BMI (body mass index)	31 (obese)
Mild hand tremor	
Metabolic studies ruled out • Hypothyroidism • Anaemia • Diabetes	

Sleep diary

Bedtime	22:00-22:30
Sleep latency	< 5 minutes Multiple awakenings during the night
Awakened	08:00-08:30 Occasionally slept later at the weekends by ~1 hour
Daily naps	Accurately recorded and confirmed by actigraphy

Polysomnography

Polysomnography with multiple sleep latency test was performed

- Upon consultation with patient and her primary care physician:
- Escitalopram discontinued 2 weeks prior
- Methylphenidate discontinued 1 week prior

Sleep latency	5 minutes
TST (Total Sleep Time)	420 minutes
WASO (Wake After Sleep Onset)	42 minutes
Sleep stages N1 N2 N3 REM REM latency	 5% 55% 15% 25% 8.5 minutes

- Video recording demonstrated paroxysmal extremity movements and talking episodically during the night, especially in the last third of the night
- No snoring noted

REM = rapid eye movement

Polysomnography (cont.)

AHI	4/hour Phasic REM hypoventilation
Minimum O_2 saturation	88%
ODI	4/hour
Saturation index below 90%	1 minute
PLMS	15/hour
PLMS arousal index	4.2/hour
MSLT	Mean 3.5 minutes 3 SOREM during 4 naps

AHI = Apnoea Hypopnea Index; MSLT = multiple sleep latency testing; ODI = Oxygen Desaturation Index; PLMS = periodic limb movements of sleep; SOREM = sleep onset rapid eye movement

Audience Response

What diagnosis would you give Savannah?

A. Idiopathic hypersomnia
B. Narcolepsy type 1
C. Narcolepsy type 2
D. None of the above
E. I am not sure

Case 2: Janet

PAST MEDICAL HISTORY

- Janet is a 23-year-old white female
- Weight: 159 lbs
- Height: 5’7
- BMI: 24.9
- No notable personal or familial medical history
- No history of depression

SYMPTOM REVIEW

- EDS since at least 10 years of age (difficult to remember age of onset)
- Very long sleep times: 12 – 15 hours/day
  - Weekends/vacation will sleep from 11pm to 1-2pm next day
  - Extremely difficult to wake-up in the morning: requires ~ 5 alarm clocks
- Rarely naps, but when she does, always > 1 hour, usually 2-3; naps without dreams
- Sleep inertia after awakening in the morning and after naps: > 1-2 hours daily
- Daytime and night-time sleep are never refreshing
- Problems at school and work, including arriving late and fighting sleepiness
- No cataplexy or sleep paralysis
- Some hallucinations
- Rare non-rapid eye movement (NREM) parasomnias

MEDICATION

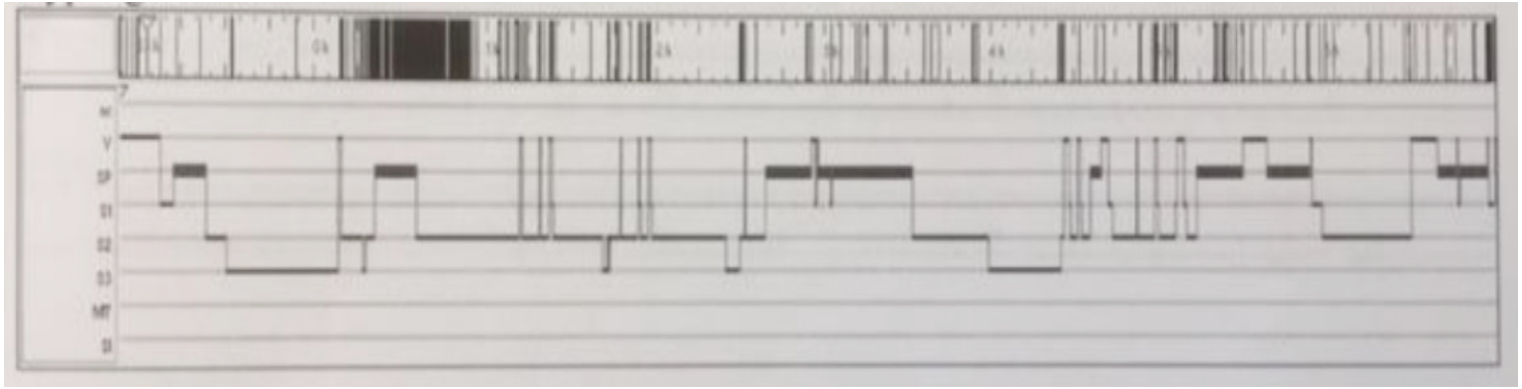
- None

SLEEPINESS SCALES SCORES

ESS	12/24
Beck Depression Inventory (BDI)	13/63

Polysomnography

Polysomnography with MSLT was performed: Primary Evaluation



- Normal: Short REM sleep (but slept before the recording)
- Good sleep efficiency, AHI, PLMS < 5/h
- Sleep latency: 8-10-10-12-14; mean at 10.8 min
- 0 SOREMPs

Polysomnography

Secondary Evaluation: PSG – mMSLT then 32-hour controlled bed-rest condition protocol

- Total sleep time: 20.5/32h
- No “real” nap
- Normal sleep the second night… Protocol stopped after 32h

Audience Response

What diagnosis would you give Janet?

A. Idiopathic hypersomnia
B. Narcolepsy type 1
C. Narcolepsy type 2
D. None of the above
E. I am not sure

Up to 200,000 People in the US Have Narcolepsy[1]

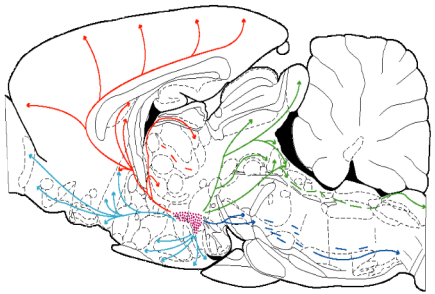
- On average, 5% of patients seen in US sleep centers have a primary diagnosis of narcolepsy[2*]
  - After OSA, narcolepsy is the most common cause of EDS seen in US sleep center[2,5*]
- Comorbid occurrence with other primary sleep disorders is common[3,4]
  - 25% of patients with narcolepsy have OSA[3†]

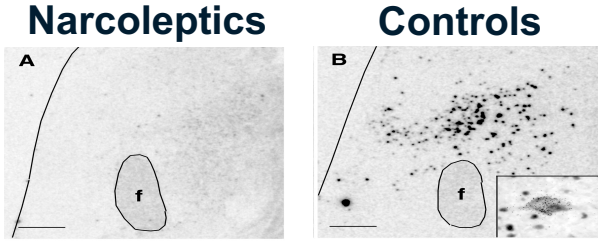
Yet… 82% of patients with narcolepsy receive a diagnosis ≥ 1 year from symptom onset; one-third > 10 years![6]

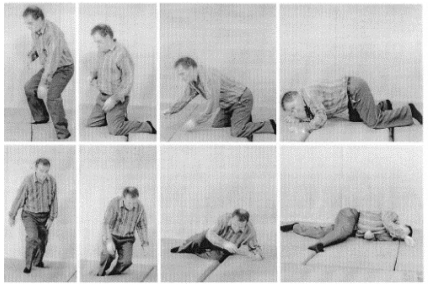
*Based on a two-month, prospective, point-prevalence survey of 3,970 patients evaluated at 19 accredited regional sleep centers in the US.[2]
†Based on a study of 133 patients with a diagnosis of narcolepsy who were evaluated for OSA features (i.e., AHI ≥ 10).[4]
EDS = excessive daytime sleepiness; OSA = obstructive sleep apnea

1. National Institutes of Health (NIH). Narcolepsy. U.S. Department of Health and Health Services. 2017. https://catalog.ninds.nih.gov/pubstatic/17-1637/17-1637.pdf. Accessed June 10, 2021.; 2. Punjabi NM, et al. *Sleep*. 2000;23(4):471-480. 3. Sansa G, et al. *Sleep Med*. 2010;11(1):93-95.; 4. Black J, et al. *Sleep Med*. 2017;33:13-18.; 5. Ahmed IM, Thorpy MJ. *Sleepiness: Causes, Consequences and Treatment*. 2011.; 6. Maski K, et al. *J Clin Sleep Med*. 2017;13(3):419-425.

Neurobiology of NT1: Loss of Orexin/Hypocretin Neurons







Destruction of hypocretin (Hcrt) neurons

Absence of CSF hypocretin

EDS | **SOREMP** | **Cataplexy**

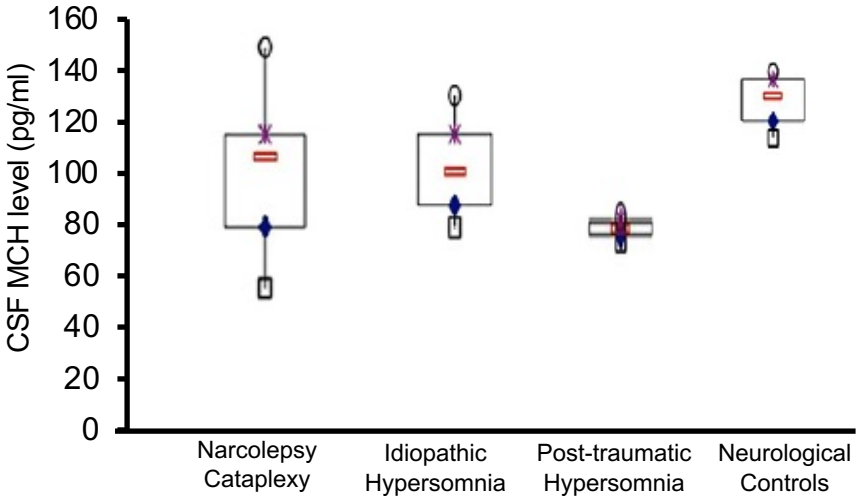
NARCOLEPSY TYPE 1 (NT1)

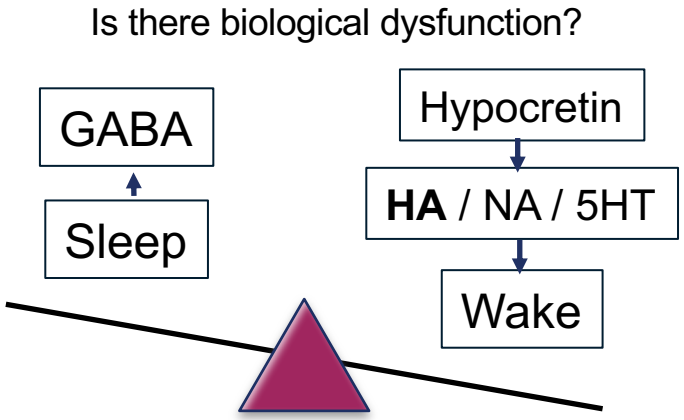
CSF = cerebrospinal fluid; SOREMP = sleep onset REM periods

Sakuri T, et al. Orexin (hypocretin) and narcolepsy. In: *The Genetic Basis of Sleep and Sleep Disorders.* 2013.

Neurobiology of NT2: Pathology of Lateral Hypothalamus?

- Sleep-wake instability with high REM sleep propensity
  - Partial lesion of Hcrt neurons? Increased activity of MCH neurons
- Circadian disturbances to explain the high REM sleep propensity





No association between MCH, histamine, and hypocretin levels, EDS, SOREMPs, cataplexy

NT2: Problem with phenotyping and stability of NT2. Unclear pathophysiology? No identified specific biomarker.

GABA = gamma-aminobutyric acid; MCH = melanin concentrating hormone

Peyron C, et al. *Sleep Med*. 2011;12(8):768-772.; Barateau L, et al. *Sleep*. 2021;zsab012.

The Two Variants of Narcolepsy: ICSD-3 Criteria

Narcolepsy Type 1 (NT1)
(Narcolepsy with Cataplexy)
A and B must be met.

A. EDS for at least 3 months
   - Use validated questionnaires such as ESS

B. At least one of the following:
   - Cataplexy and a positive MSLT*
     - Low mean sleep latency < 8 mins
     - ≥ 2 SOREMPs on MSLT-PSG
   - Low CSF hypocretin-1 concentrations (≤ 110pg/ml or < 1/3 of normal)

Narcolepsy Type 2 (NT2)
(Narcolepsy without Cataplexy)
A and B must be met.

A. EDS for at least 3 months

B. Positive MSLT*
   - Low mean sleep latency < 8 mins
   - ≥ 2 SOREMPs on MSLT-PSG

C. Cataplexy is absent

D. CSF hypocretin-1 concentrations > 110pg/ml if measured

E. Hypersomnolence and MSLT findings not better explained by other causes:
   - Insufficient sleep, OSAS, delayed sleep phase, drug intake/withdrawal

*Positive MSLT: mean sleep latency of < 8 minutes and ≥ 2 SOREMPs

Sateia MJ. *Chest.* 2014;146(5):1387-1394.

Differential Diagnosis

- EDS
  - OSAS
  - Sleep deprivation/poor sleep hygiene
  - Depression
  - Substance/drug intake
  - Idiopathic hypersomnia
  - Kleine-Levin syndrome
  - Poor sleep hygiene
  - Periodic Limb Movement Disorder
  - Circadian rhythm abnormality
  - Behavioral symptoms of EDS (irritability, poor attentiveness, aggression, hallucinations)
- Cataplexy
  - Typical cataplexy
    - To be videoed if possible
  - Atypical cataplexy
    - Long (> 2 min), unilateral, rare episodes (1/yr), altered consciousness, no triggers or negative emotions only
    - HLA DQB1*06:02 negative, normal orexin levels
  - Differential diagnosis
    - Seizure, hypotension, psychogenic
- Hallucinations
  - Schizophrenia
  - Night terrors
  - Panic attacks

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.

Comorbidities Contribute to Underdiagnosis

- 60% of narcolepsy is misdiagnosed with other conditions
  - Daytime sleepiness is a frequent symptom
  - Narcolepsy is a rare disease
- Comorbid disturbed nighttime sleep, OSA, PLMS, RBD, etc. may confound narcolepsy presentation
- Insufficient sleep, ADHD, and other hypersomnolence disorders (idiopathic hypersomnia, medications, substances, medical disorders) require healthcare provider expertise in differentiating
- Epilepsy and syncope may be confused with cataplexy

ADHD = attention deficit hyperactivity disorder; RBD = REM sleep behavior disorder

Carter LP. *Sleep*. 2013;36(Suppl.):A254.; Thorpy MJ, Krieger AC. *Sleep Med*. 2014;15(5):502-507.

Self-Report Measures Can Be Used in Clinical Practice

Epworth Sleepiness Scale (ESS)

- The ESS is the most frequently used, validated self-report assessment of a patient's sleepiness[1]
- On a 4-point scale, patients rate their likelihood of falling asleep during 8 different situations (reading, driving, etc.)[2]
- The ESS can also be used to monitor the progression of or improvement in sleepiness over time[3]

Functional Outcomes of Sleep Questionnaire (FOSQ)

- The FOSQ (or shorter FOSQ-10) assesses the effect of sleepiness on daily functioning[4,5]
- Evaluates 5 domains[4,5]
  - General productivity
  - Activity level
  - Vigilance
  - Social outcomes
  - Intimate/sexual relationships

Subjective measures rely on patients to accurately report their own sleepiness; however, they are[4]:

- Practical for monitoring progression or improvement in EDS
- Simple to administer

1. Miglis MG, Kushida CA. *Sleep Med Clin*. 2014;9(4):491-498. 2. Johns MW. *Sleep*. 1991;14(6):540-545.
3. Ahmed IM, Thorpy MJ. *Sleepiness: Causes, Consequences and Treatment*. 2011.
4. Chapman JL, et al. *Sleep Med Clin*. 2016;11(3):353-363. 5. Chasens ER, Ratcliffe SJ, et al. *Sleep*. 2009;32(7):915-919.

Patients With Narcolepsy Can Have a Wide Range of Medical Comorbidities Contributing to the Burden of Disease[1]

- In a sample of patients with narcolepsy (n = 9,132) vs. matched controls without narcolepsy (n = 46,559),[2] an excess prevalence (%) of comorbidities in patients with narcolepsy observed:[2]

Sleep apnea (45.6%)	Obesity (8.8%)
Mood disorders (24.1%)	Restless leg syndrome (4.9%)
Headache/migraine (20%)	Periodic limb movement disorders (3.7%)
Anxiety disorders (13.2%)	REM behavior disorder (0.5%)
Diabetes (9.3%)	

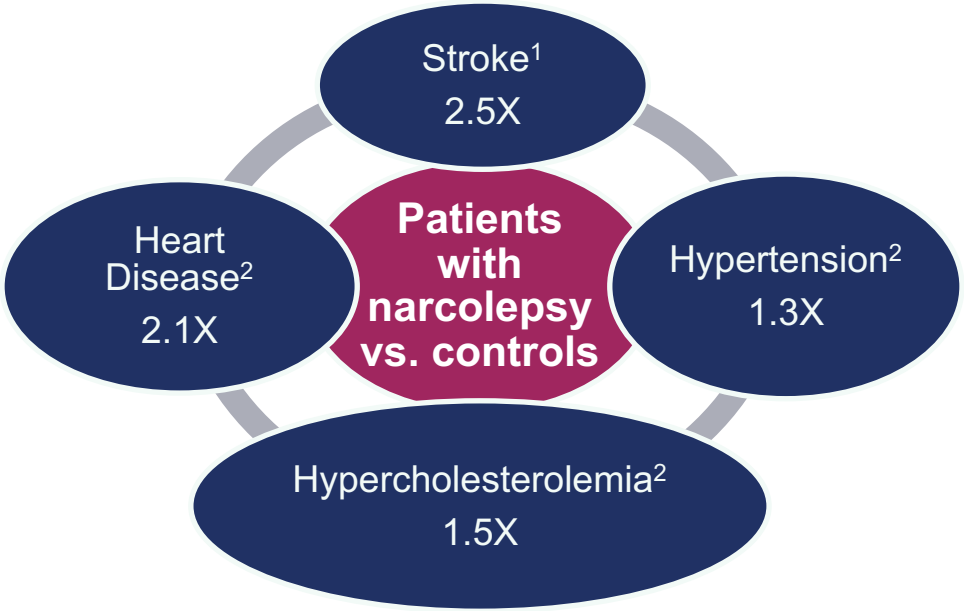
- A higher prevalence of objectively identified conditions was also observed among patients with narcolepsy than in controls[1]
- Consider concomitant medications for comorbid conditions when determining a narcolepsy treatment[1]

CVD = cardiovascular disease; MACE = major adverse cardiac event

1. Thorpy MJ, Dauvilliers Y. *Sleep Med*. 2015;16(1):9-18.; 2. Black J, et al. *Sleep Med*. 2017;33:13-18.

Cardiovascular Impact of Narcolepsy

RISKS



INCIDENCE:*

in patients with narcolepsy (n = 12,816) vs. controls (n = 38,441):[3]

- CVD without hypertension **(13.29/7.99)**
- MACE **(11.75/6.86)**
- Heart failure **(5.72/3.41)**
- Stroke **(4.28/2.17)**
- Ischemic stroke **(3.69/1.91)**
- Edema **(9.84/4.22)**
- A composite of stroke, atrial fibrillation, and edema **(17.73/8.88)**

*per 1,000 person-years. CVD = cardiovascular disease; MACE = major adverse cardiac event

1. Black J, et al. *Sleep Med.* 2017;33:13-18.; 2. Ohayon MM. *Sleep Med.* 2013;14(6):488-492.;
3. Ben-Joseph R, et al. *Sleep*. 2021;44(Suppl 2):A198.

The Vast Impact of IH

On the Individual:[1,2]

35%	Do not feel they receive support from friends or family
26%	Dismissed from their jobs or forced to relocate due to their symptoms
21%	Do not feel they have autonomy over their work schedule
13%	Divorced or broke up with a partner because of their condition

Beyond the Individual:[2,3,4]

- Inability to wake up, maintain energy for chores/responsibilities alone creates sense of dependence
- Responsibilities requiring unscheduled waking (i.e., caring for infants at night), can be extremely difficult
- Sleep inertia can affect family routines (i.e., waking/ dressing children for school)
- Risk of falling asleep at the wheel may make driving uncomfortable

1. Trotti LM. *Sleep Med Clin*. 2017;12(3):331-344.; 2. Arnulf I, et al. *Sleep Med Clin*. 2019;14(3):333-350.;
3. Trotti LM, et al. *Sleep Med Clin*. 2020;75:343-349.; 4. Billiard M, Sonka K. *Sleep Med Rev*. 2016;29:23-33.;
4. Pizza F, et al. *PLoS One*. 2015;10(6):e0129386.

Coping Strategies for IH

Napping:[1,2]

- Often > 60 mins

Maintain hyperactive states:[1]

- Increased motor activity
- Speaking continuously to maintain alertness
- Performing multiple activities at once (i.e., writing while listening to music)

Nonpharmacologic strategies:[3]

- Caffeine
- Nicotine
- Exercise
- Chewing gum
- Temperature manipulations

1. Arnulf I, et al. *Sleep Med Clin*. 2019;14(3):333-350.; 2. Trotti LM, et al. *Sleep Med Clin*. 2020;75: 343-349.;
3. Neikrug AB, et al. *Behave Sleep Med.* 2017;15(2):158-171.

IH Diagnosis: ICSD-3 Criteria/Limitations

Current Approach

A. **Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 months**

B. Fewer than two SOREMPs on MSLT (or fewer than one if nocturnal REM latency was ≤ 15 min)

C. No cataplexy

D. At least one of the following:
   1. Mean sleep latency ≤ 8 min on MSLT
   2. **Total 24-h sleep time ≥ 660 min on 24-h PSG or wrist actigraphy (averaged over ≥ 7 d)**

E. Insufficient sleep syndrome is ruled out

F. The hypersomnolence and/or MSLT findings are not better explained by other causes

What Should Be Discussed

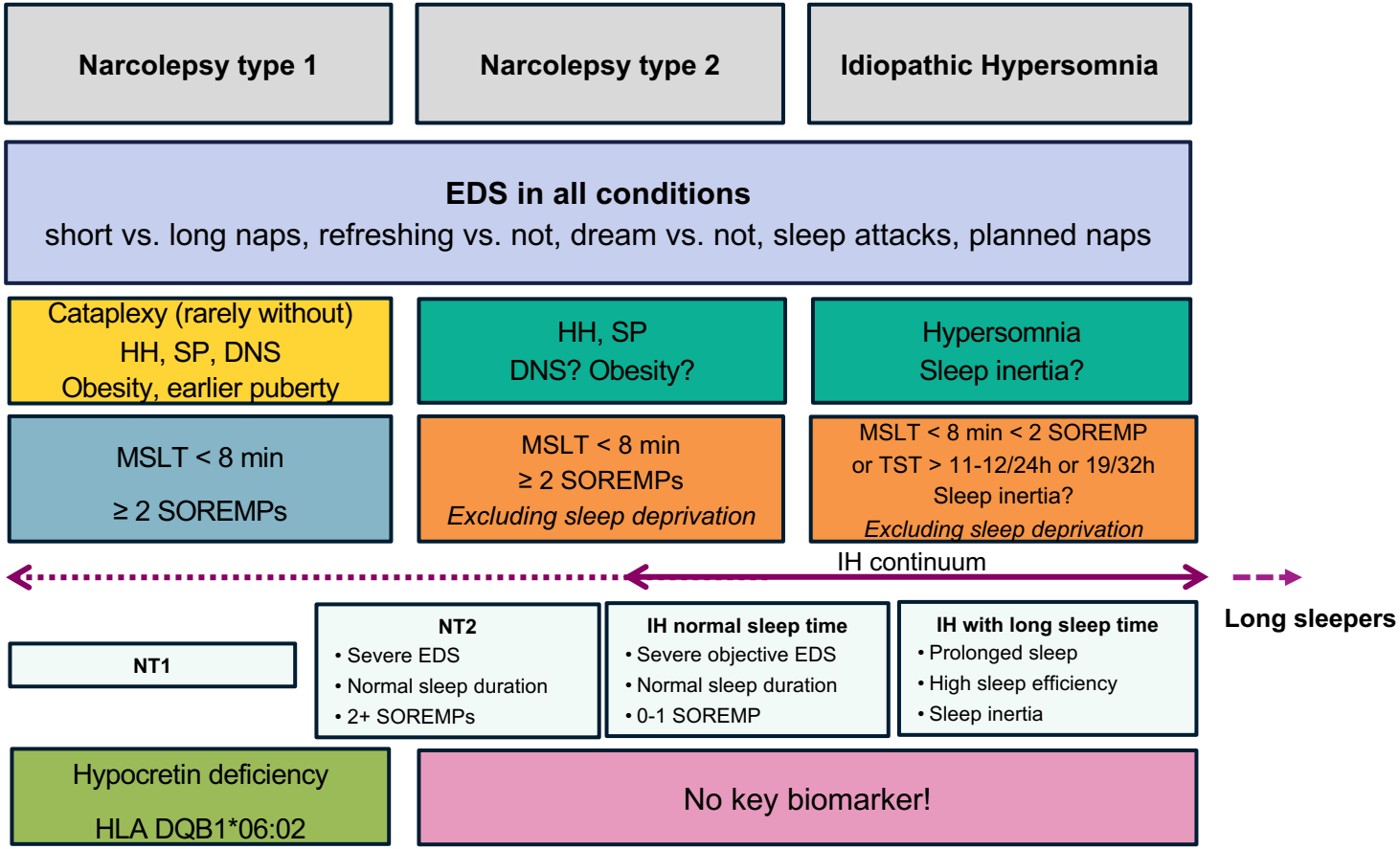
→ Same item A for NT1/2!
Unidimensional aspect? No hypersomnia?

→ Number of SOREMPs variable between tests

→ Wrist actigraphy: Not objective sleep assessment

→ **Which causes? How to be ruled out?**
Sleep restriction, mild AHI, mild PLMS,
Low sleep efficiency, low TST on PSG?
NT2: Diagnosis because of MSLT
Depressive symptoms: Consequences?
Obesity, CNS drugs intake

CNS = central nervous system; TST = total sleep time
Sateia MJ. *Chest.* 2014;146(5):1387-1394.

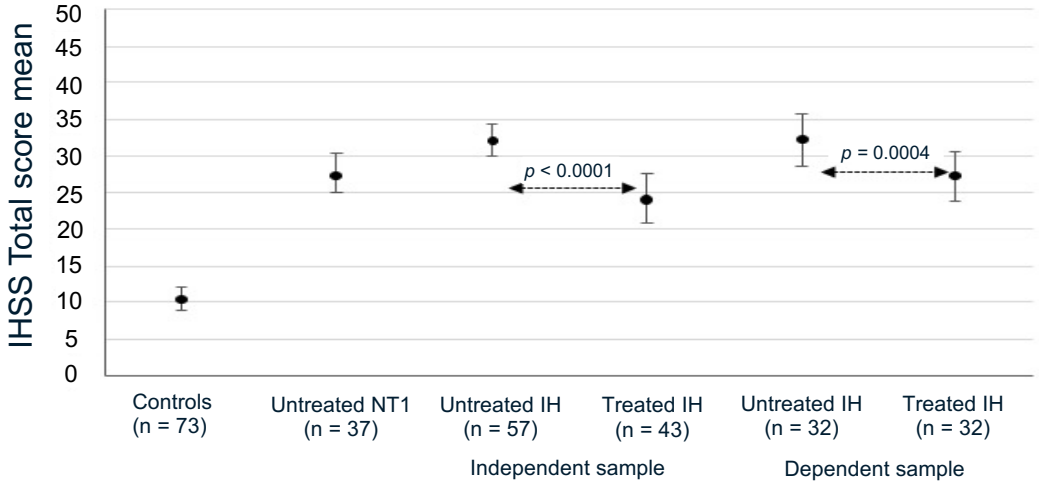


Courtesy of Yves Dauvilliers, MD, PhD

DNS = disrupted nighttime sleep; HH = hypnagogic hallucinations; SP = sleep paralysis

Idiopathic Hypersomnia Severity Scale (IHSS)

- 14-item questionnaire that assesses the severity of IH
  - 5 on nighttime sleep symptoms and related sleep inertia
  - 4 on daytime sleep symptoms and related sleep inertia
  - 5 on daytime function
- Total score 0 to 50, higher score indicating more severe and frequent symptoms



- Higher scores in drug-free IH patients than NT1 and controls
- No ceiling effect
- **Cut off to discriminate IH and controls: 22**
  Sensitivity: 91.1%
  Specificity: 94.5%
- **Untreated and treated IH: 26**
  Sensitivity: 55.8%
  Specificity: 78.9%
- **Treatment difference:**
  5-8 units

IHSS is a reliable, valid clinical tool for the quantification of IH symptoms; sensitive enough to detect clinical changes in symptoms following treatment!

Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762.

The Case of Savannah: A Recap

- Presentation/Symptoms:
  - Symptoms began in mid-teenage years
  - Constantly feels the need to take a nap
  - 3-4 awakenings during the night but does not have trouble going back to sleep
  - Often awakened with sensation of inability to move and impending doom and panic
  - No history of snoring, periodic leg movements, or muscle weakness or “melting” with emotion
- Results:
  - Paroxysmal extremity movements and talking episodically during the night
  - ESS = 19/24; ISI = 19/28; FOSQ = 9.5/20
  - MSLT = Mean 3.5 mins; 3 SOREMP during 4 naps

Audience Response

Now, what diagnosis would you give Savannah?

A. Idiopathic hypersomnia
B. Narcolepsy type 1
C. Narcolepsy type 2
D. None of the above
E. I am not sure

The Case of Janet: A Recap

- Presentation/Symptoms:
  - EDS since at least 10 years of age (difficult to remember age of onset)
  - Very long sleep times: 12-15 hours/day; never refreshing
  - No history of depression
  - No cataplexy or sleep paralysis

- Results:
  - ESS = 12/24; BDI = 13/63
  - Good sleep efficiency, AHI, PLMS < 5/h
  - MSLT = Mean 10.8 mins; 0 SOREMP
  - Total sleep time = 20.5hrs/32hrs

Audience Response

Now, what diagnosis would you give Janet?

A. Idiopathic hypersomnia
B. Narcolepsy type 1
C. Narcolepsy type 2
D. None of the above
E. I am not sure

Treatment Considerations for Narcolepsy

Audience Response

How confident are you developing an effective treatment plan for patients like Savannah with NT2 to improve their EDS, quality of life, and functioning?

A. Extremely confident
B. Confident
C. Somewhat confident
D. Not at all confident

Back to Savannah: Treatment Goals in Narcolepsy

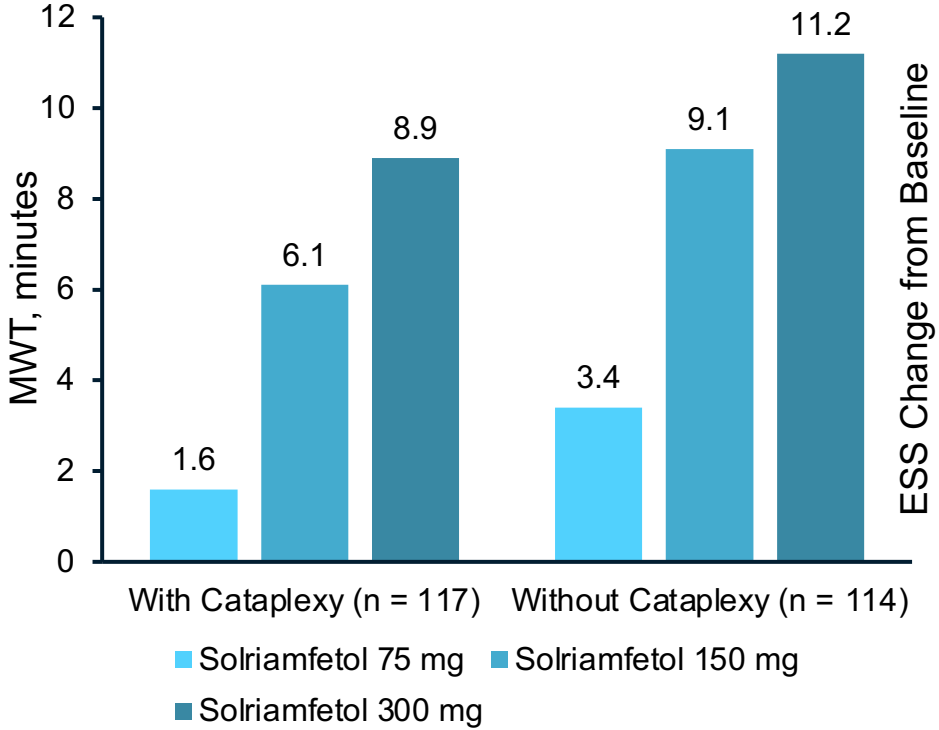
- Reduce EDS
- Control ancillary symptoms
  - Cataplexy
  - Nightmares and hallucinations
  - Sleep paralysis
  - Disturbed nocturnal sleep
- Reduce psychosocial and work dysfunction and improve quality of life
- Improve safety of patient and public
- Prevent adverse medication effects
- Standardize the follow-up and optimize risk/benefit of pharmacotherapies

Thorpy MJ, et al. *Sleep Med*. 2015;16(1):9-18.

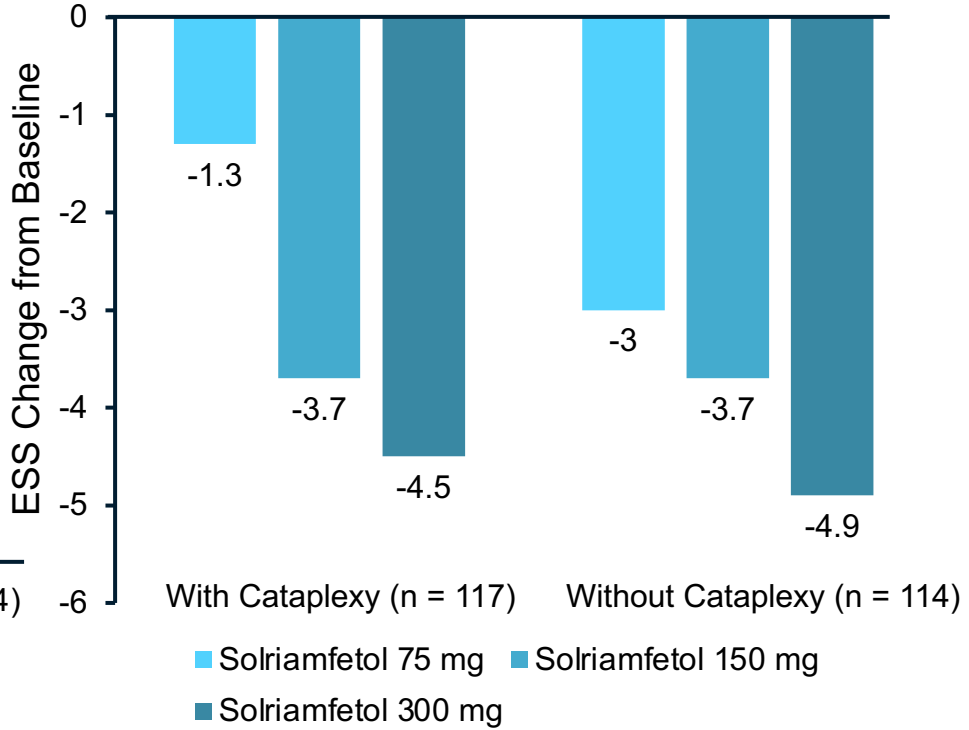
Potential Treatment Options

- Schedule 2 stimulants (e.g., methylphenidate)
- Armodafinil/Modafinil
- Solriamfetol
- Pitolisant
- Lower-sodium oxybate
- Sodium Oxybate

Solriamfetol: Efficacy in Narcolepsy



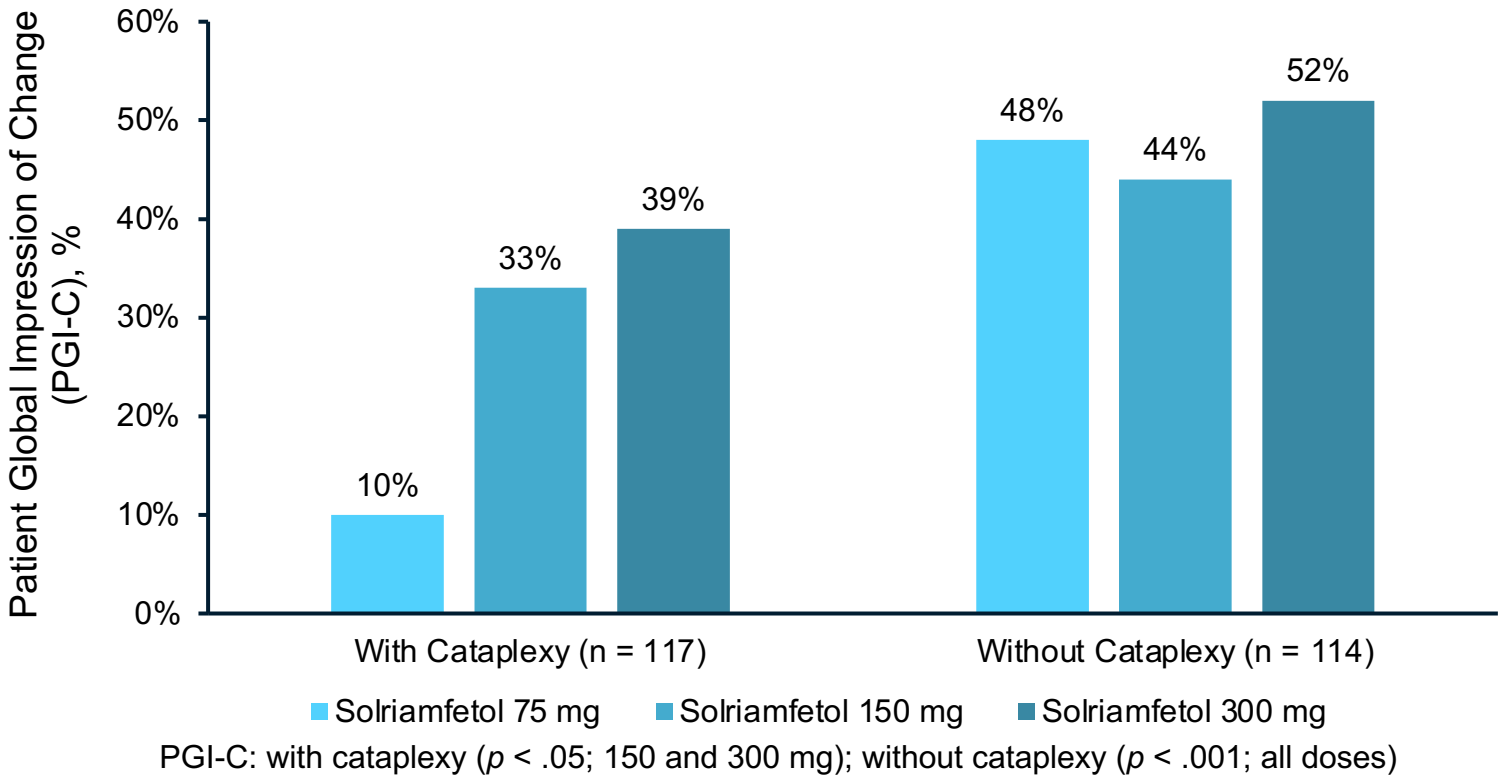
MWT: with cataplexy ($p < .05$; 150 and 300 mg); without cataplexy ($p < .001$; 150 and 300 mg)



ESS: with cataplexy ($p < .01$; 150 and 300 mg); without cataplexy ($p < .05$; all doses)

Dauvilliers Y, et al. *CNS Drugs*. 2020; 34:773-784.

Solriamfetol: Efficacy in Narcolepsy (cont.)



PGI-C: with cataplexy ($p < .05$; 150 and 300 mg); without cataplexy ($p < .001$; all doses)

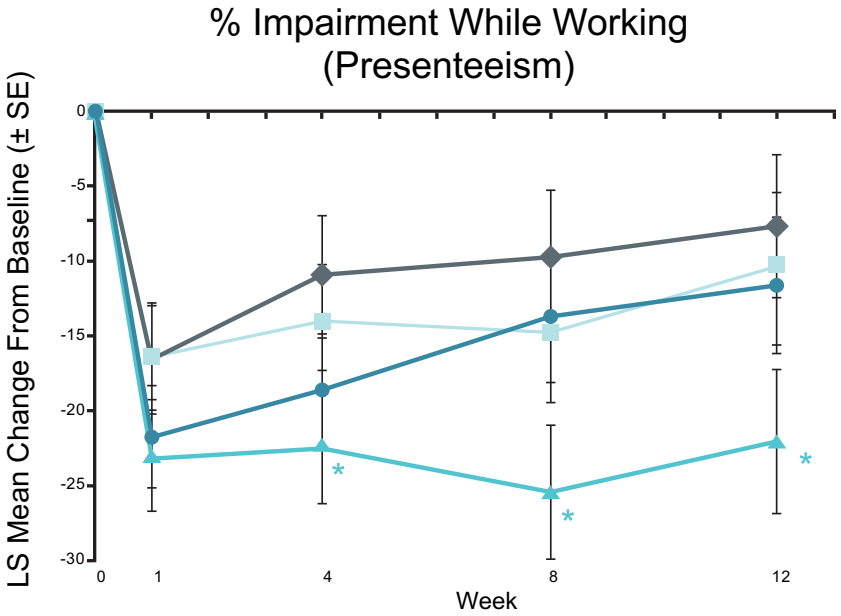
Dauvilliers Y, et al. *CNS Drugs*. 2020; 34:773-784.

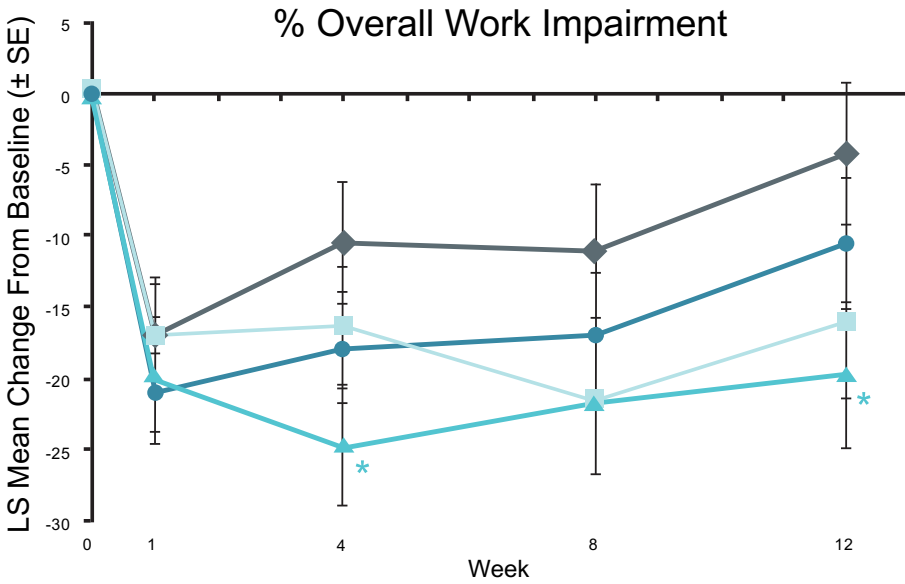
Audience Response

How often do you assess treatment efficacy on functional status in your patients with narcolepsy or IH?

A. 0% of the time
B. 1% - 25% of the time
C. 26% - 50% of the time
D. 51% - 75% of the time
E. 76% - 100% of the time

Solriamfetol: Efficacy on Work Productivity in Narcolepsy



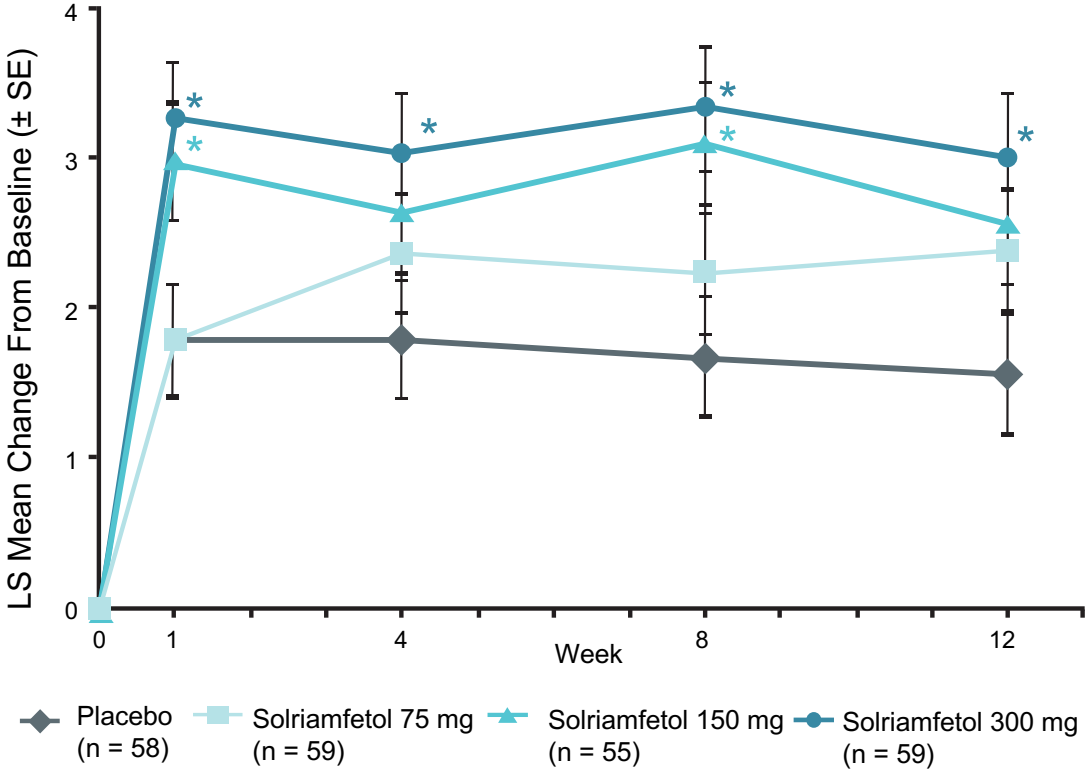


Placebo (n = 58)
Solriamfetol 75 mg (n = 59)
Solriamfetol 150 mg (n = 55)
Solriamfetol 300 mg (n = 59)

Emsellem HA, et al. Sleep Med. 2020;67:128-136.

CME OUTFITTERS

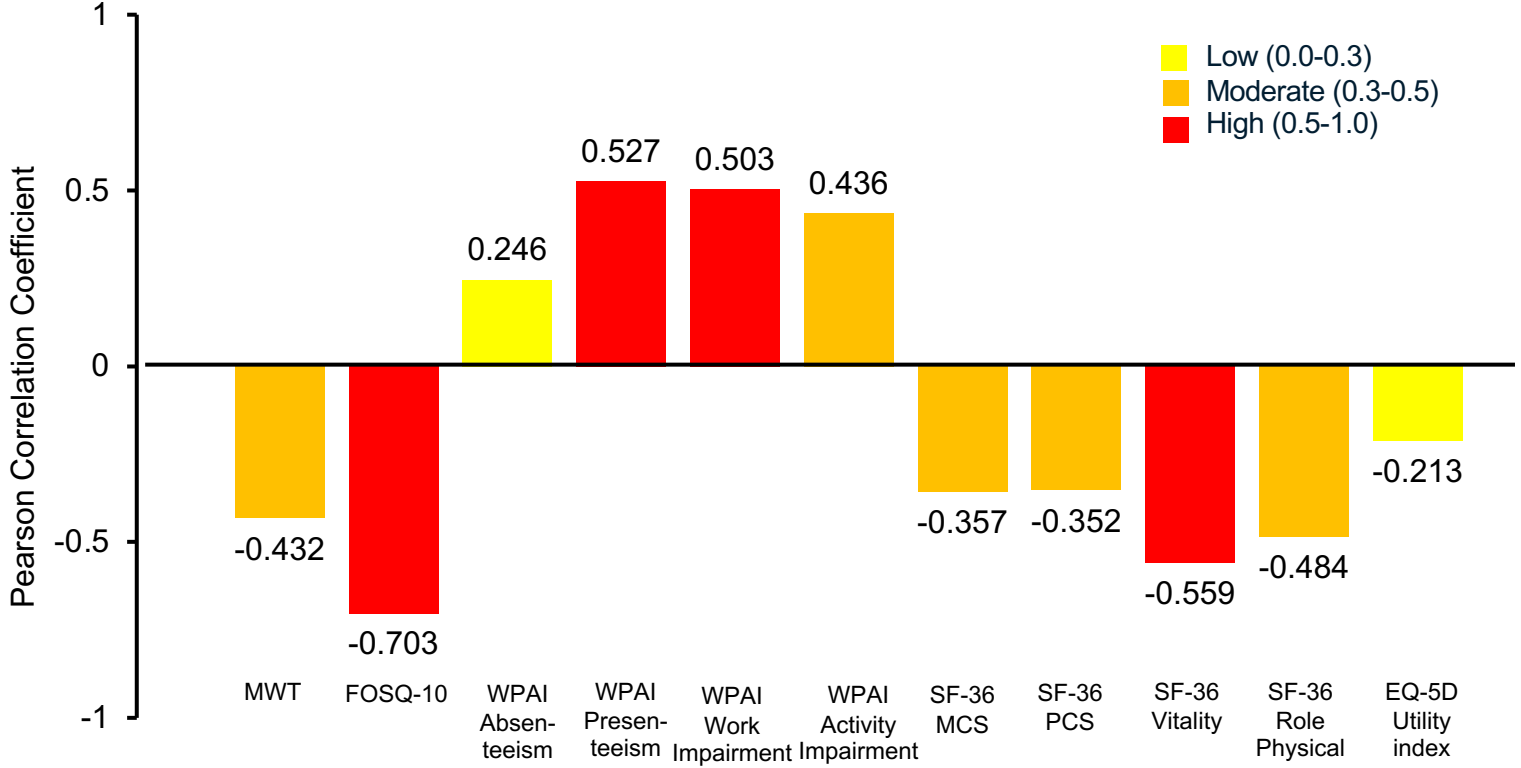
Solriamfetol: Efficacy on Functional Outcomes (FOSQ-10) in Narcolepsy



Emsellem HA, et al. *Sleep Med*. 2020;67:128-136.

Solriamfetol: Correlations Between Change in ESS and MWT Scores, Measures of Functioning, and HRQoL

N = 132
Data depicts from baseline to week 12 for participants with narcolepsy



EQ-5D = EuroQoL 5-Dimension; MCS = Mental Component Survey; PCS = Physical Component Survey; SF-36 = 36-Item Short Form Health Survey; WPAI = Work Productivity and Activity Impairment Questionnaire

Weaver TE, et al. *J Sleep Res*. 2020;00:e13210.

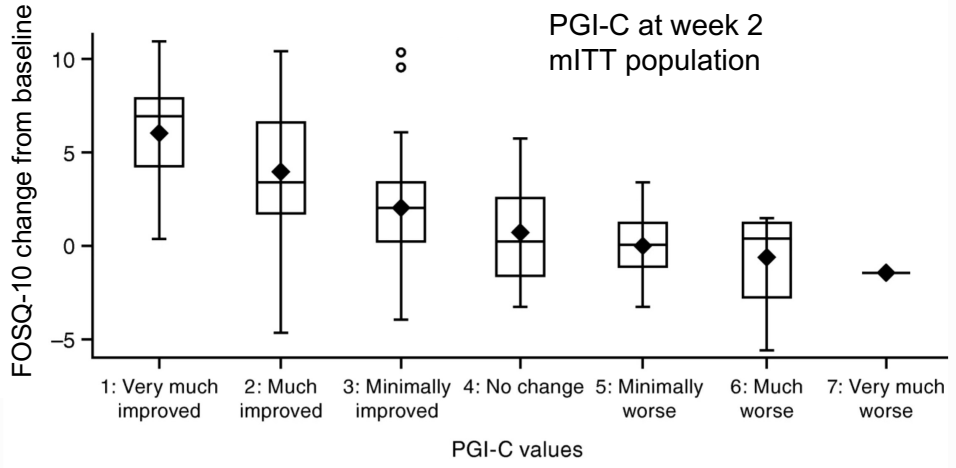
Audience Response

How would you interpret Savannah's FOSQ-10 score of 9.5/20?

A. No difficulty with sleepiness affecting functioning
B. A little difficulty with sleepiness affecting functioning
C. Moderate difficulty with sleepiness affecting functioning
D. Extreme difficulty with sleepiness affecting functioning

Interpreting FOSQ-10: Clinically Meaningful Changes

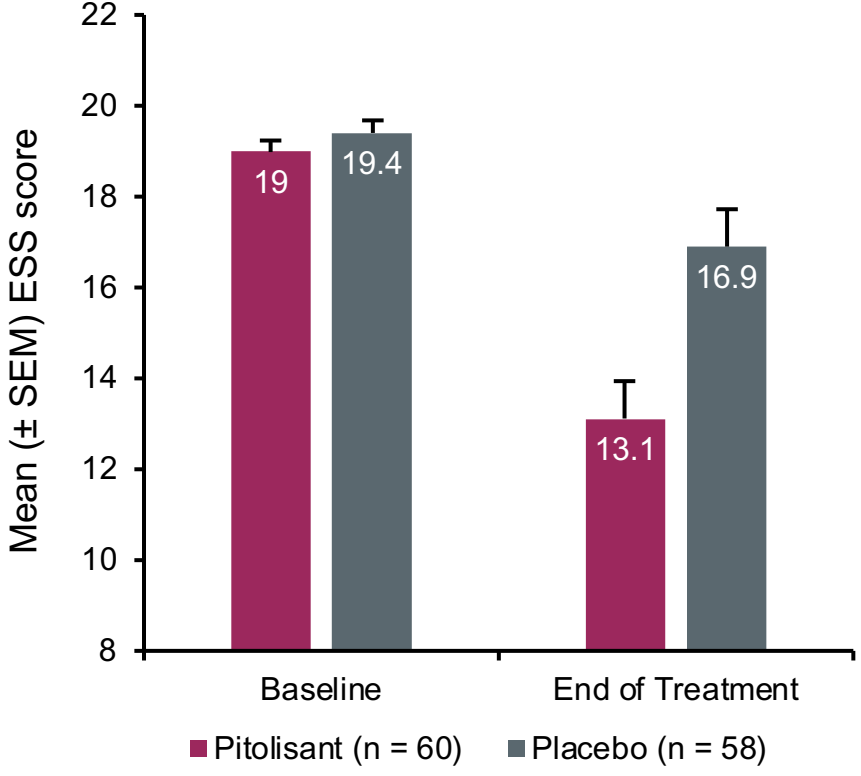
	Mean change in FOSQ-10 scores				
	Very much improved	Much improved	Minimally improved	No change	Worse
PGI-C	6.15 (2.98) [n = 17]	4.03 (2.95) [n = 55]	2.05 (2.76) [n = 56]	0.98 (2.42) [n = 41]	-0.08 (2.05) [n = 22]
CGI-C	4.43 (3.00) [n = 18]	4.28 (3.00) [n = 58]	1.74 (2.85) [n = 60]	0.85 (2.35) [n = 45]	0.80 (3.25) [n = 14]

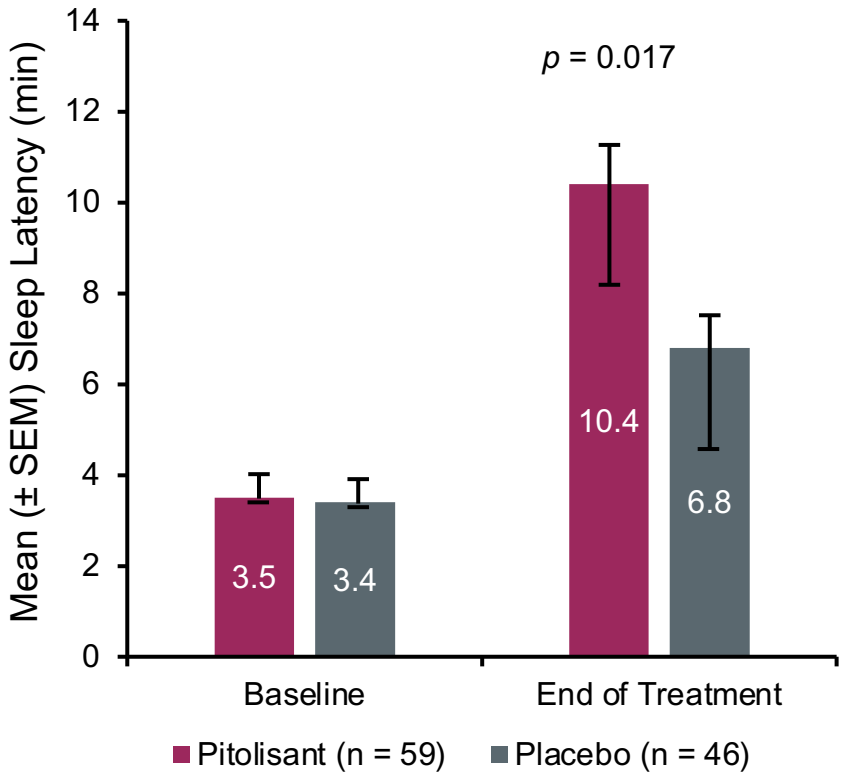


CGI-C = Clinical Global Impressions Scale; mITT = modified intention-to-treat

Weaver TE, et al. *Sleep Breath*. 2021 Jan 4; [Epub ahead of print].

Pitolisant: Post Hoc Analysis of Efficacy in Narcolepsy with High EDS Burden – ESS and Sleep Latency



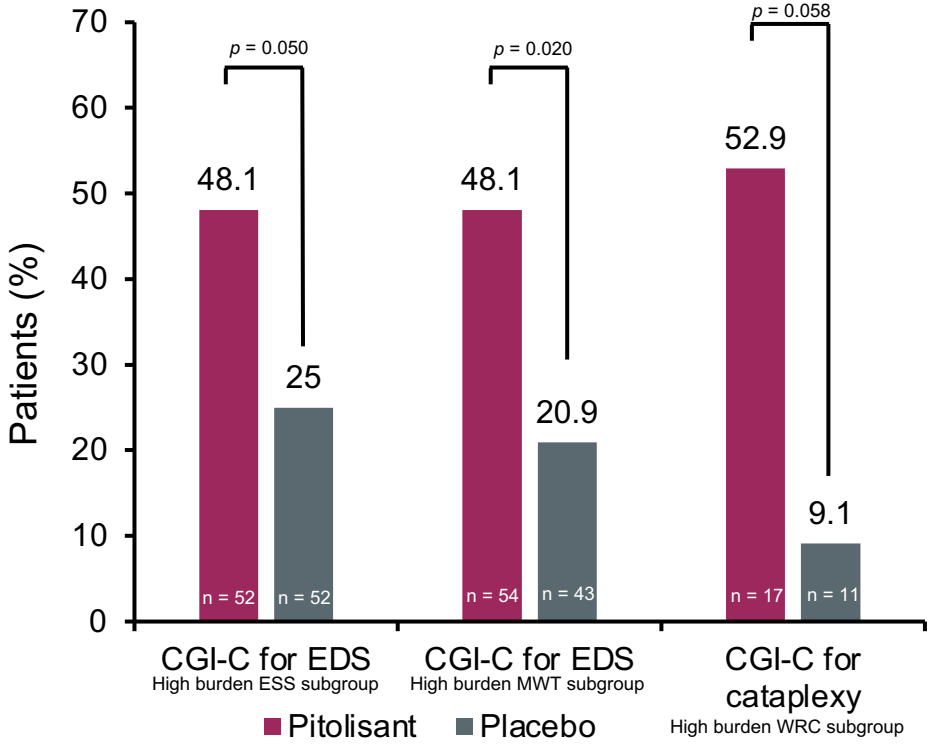


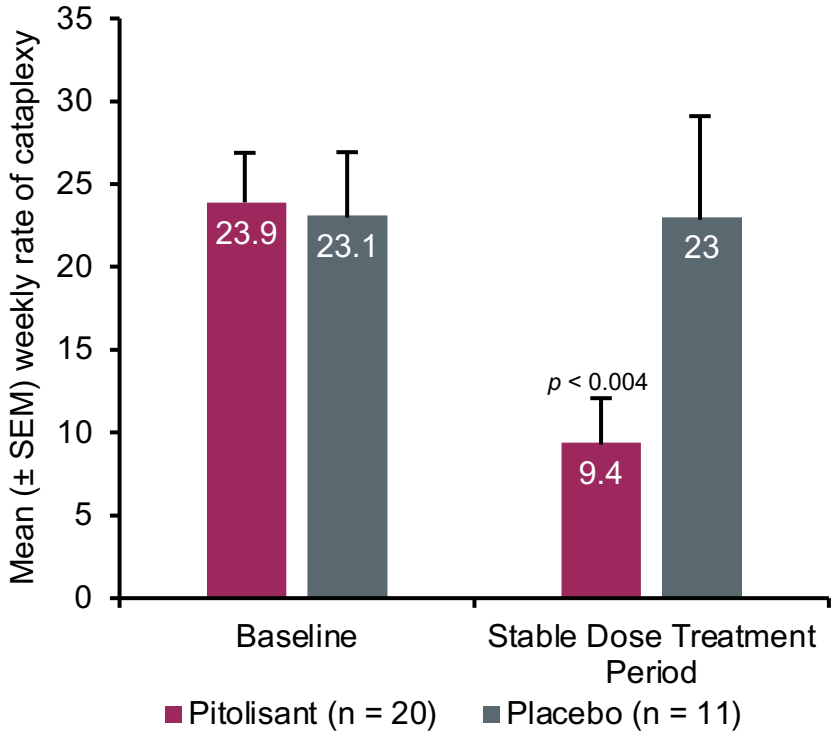
Inclusion criteria: baseline score of ≥ 16 on the ESS and baseline sleep latency of ≤ 8 min on the MWT

SEM = standard error of measurement

Davis CW, et al. Sleep Med. 2021;81:210-217.

Pitolisant: Efficacy in Narcolepsy with High EDS Burden – CGI-C and Cataplexy

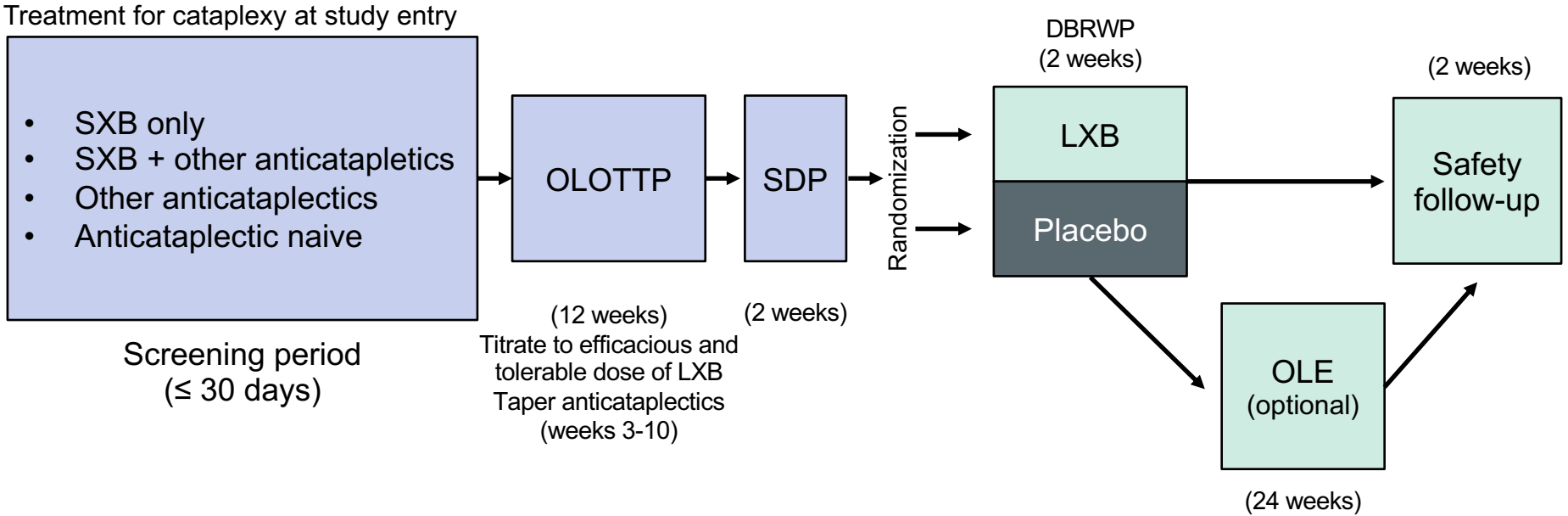




Inclusion criteria: baseline score of ≥ 16 on the ESS, baseline sleep latency of ≤ 8 min on the MWT, and baseline frequency of cataplexy attacks ≥ 15 per week.

Davis CW, et al. Sleep Med. 2021;81:210-217.

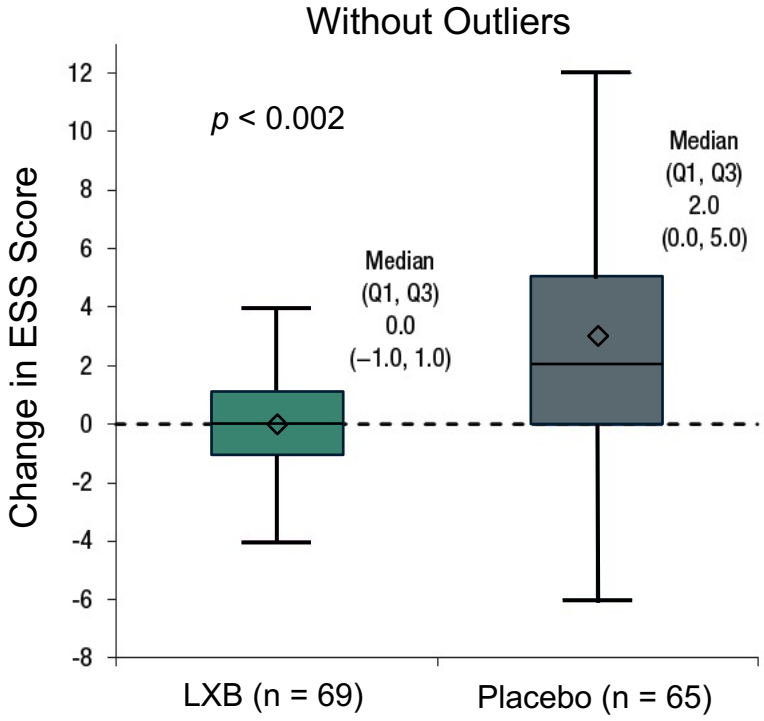
Lower-Sodium Oxybate (LXB): Efficacy in Narcolepsy Study Design

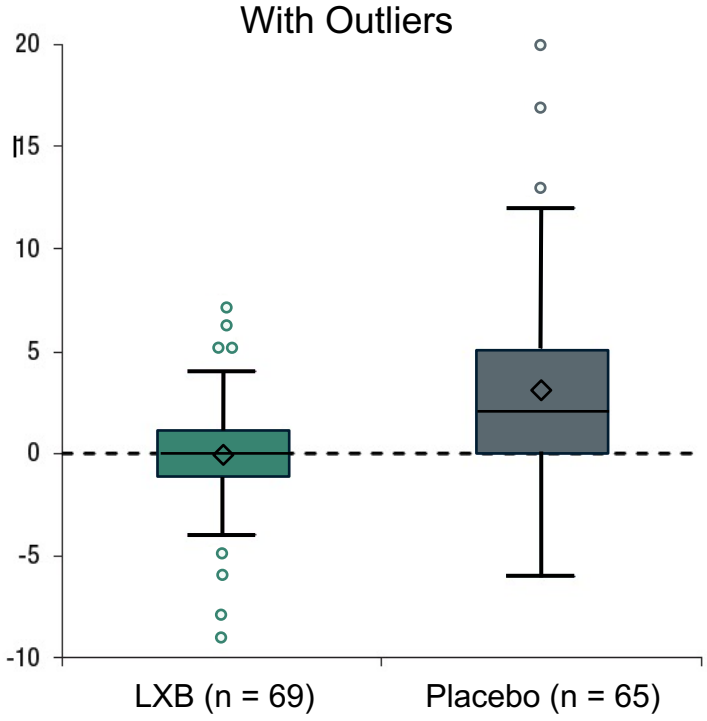


OLE = open-label safety extension period; OLOTTP = optimized treatment and titration period; SDP = stable-dose period

Folvary-Schaefer N, et al. AAN Virtual Annual Meeting; 2021. Abstract No. S9.002.

Lower-Sodium Oxybate (LXB): Efficacy in Narcolepsy – Change in ESS Scores





Folvary-Schaefer N, et al. ANA Virtual Annual Meeting; 2020. Abstract No. 436.

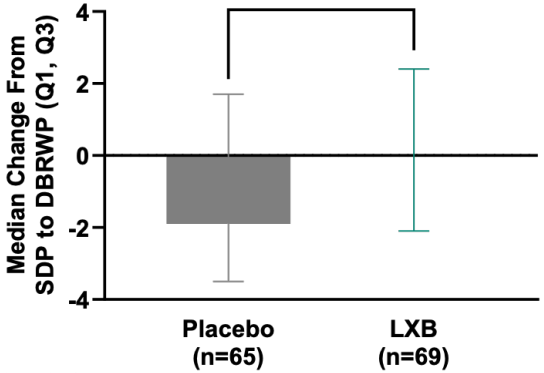
Lower-Sodium Oxybate (LXB): Efficacy in Narcolepsy

Change in SF-36 Scores From End of Stable-Dose Period (SDP) to End of Double-Blind Randomized Withdrawal Period (DBRWP)

- On the SF-36, PCS, and MCS scores declined in participants randomized to placebo vs participants randomized to continue LXB treatment during the 2-week DBRWP

Physical Component Summary

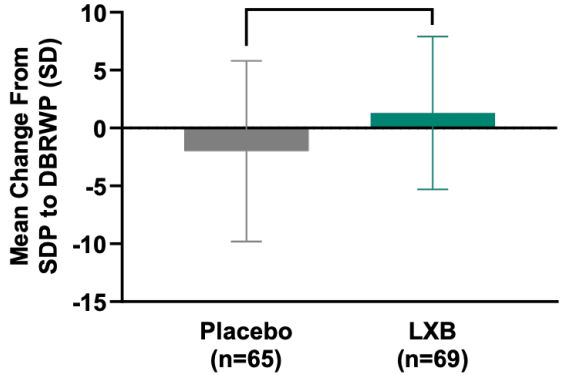
Location shift (95% CI):
1.4 (-0.1, 2.8)
Nominal *P* value: 0.0174



Median (Q1, Q3):	Placebo (n=65)	LXB (n=69)
End of SDP	51.5 (44.0, 57.4)	53.9 (46.9, 58.3)[a]
End of DBRWP	50.7 (43.2, 55.8)	53.7 (47.2, 58.6)

Mental Component Summary

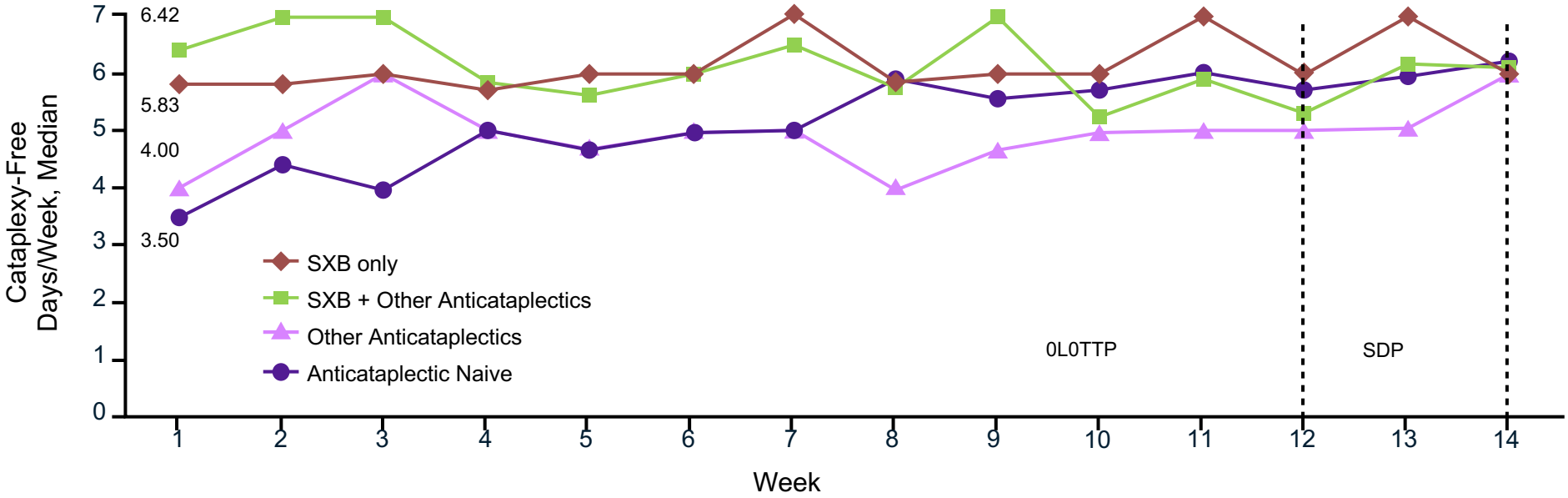
LS mean difference (SE; 95% CI):
2.5 (1.2; 0.2, 4.8)
Nominal *P* value: 0.0331



Mean (SD):	Placebo (n=65)	LXB (n=69)
End of SDP	48.1 (9.9)	45.2 (12.2)[a]
End of DBRWP	46.0 (9.9)	46.8 (11.2)

Folvary-Schaefer N, et al. AAN Virtual Annual Meeting; 2021. Abstract No. S9.002.

LXB: Efficacy on Cataplexy-Free Days/Week

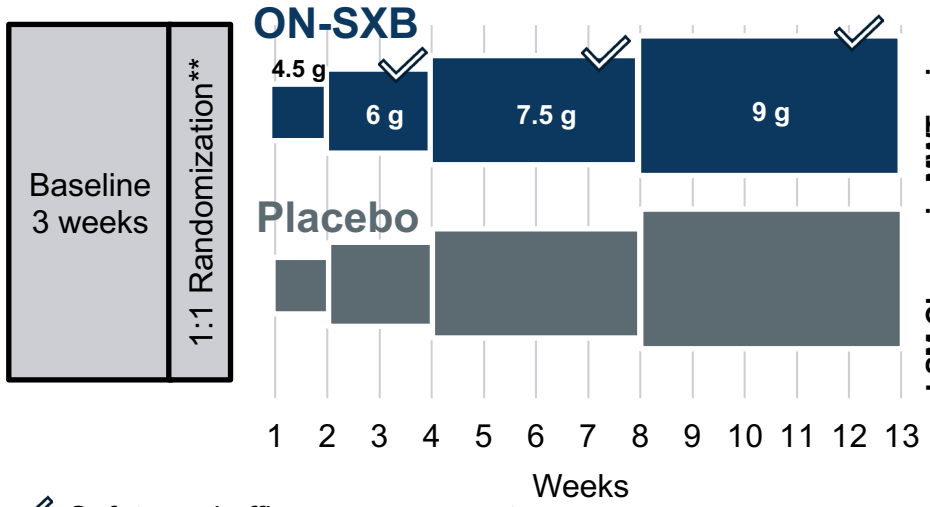


- At the end of SDP (when all participants were on a stable, optimized dose of LXB), median (Q1, Q3) cataplexy-free days/week were: SXB only, 6.0 (3.5, 7.0); SXB + other anticataplectic(s), 6.1 (1.4, 7.0); other anticataplectic(s), 6.0 (2.6, 7.0); anticataplectic naive 6.2 (4.0, 7.0)

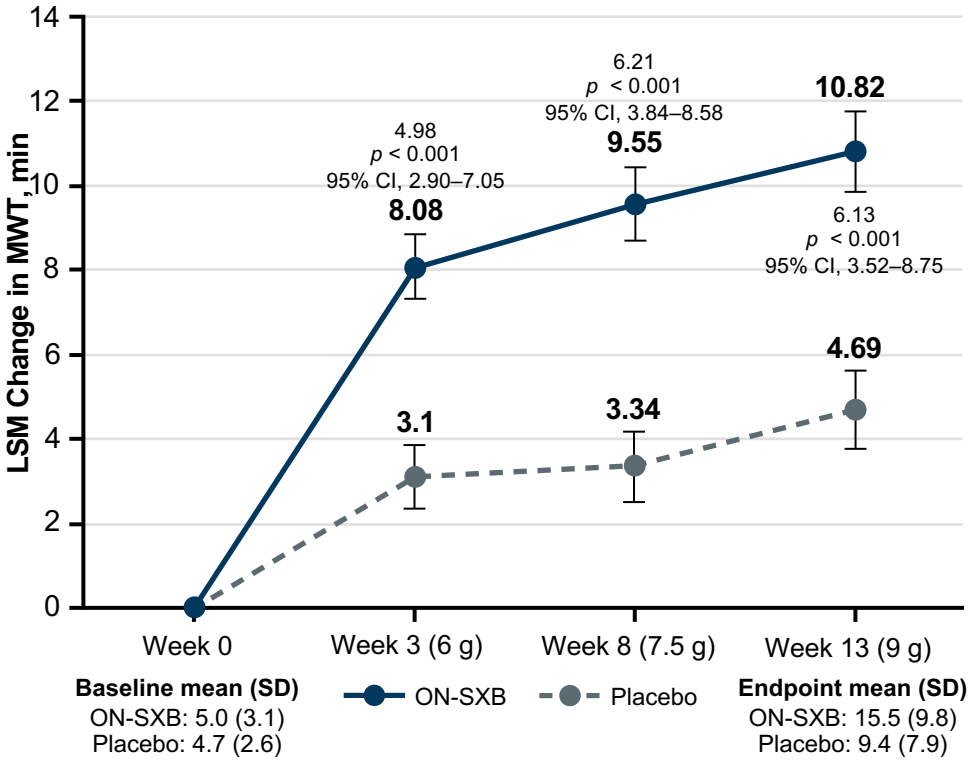
Dauvilliers Y, et al. Sleep 2021, 35th Annual Meeting of APSS; 2021.

FT-218:* Efficacy in Narcolepsy – MWT

Study Design



✓ Safety and efficacy assessment



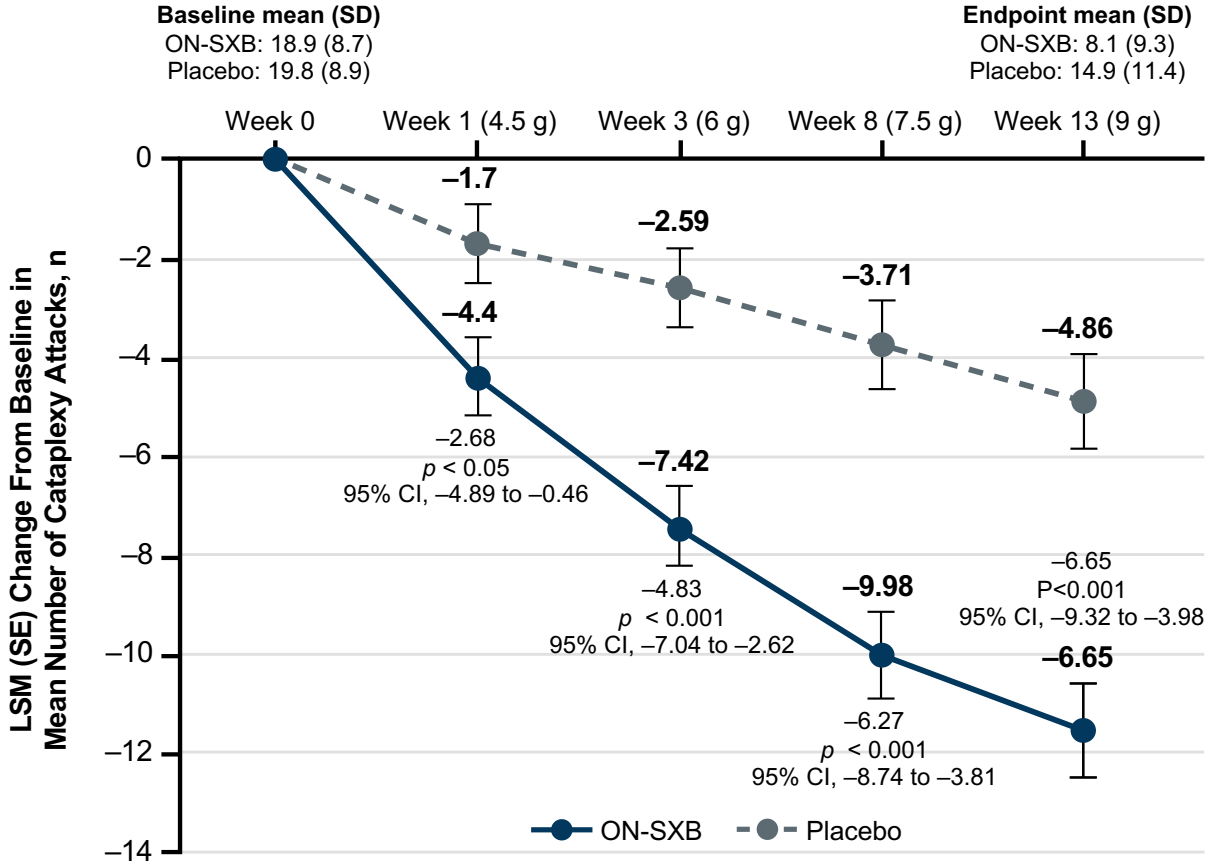
*FT-218 is not FDA-approved for the treatment of cataplexy or EDS associated with narcolepsy.

**randomization stratified by narcolepsy type

LSM = least squares mean; ON-SXB = once-nightly sodium oxybate (FT218)

Kushida C, et al. *Sleep*. 2021;44(Supp2):A193.

FT-218:* Efficacy in Narcolepsy – Weekly Cataplexy Attacks



*FT-218 is not FDA-approved for the treatment of cataplexy or EDS associated with narcolepsy.

Kushida C, et al. *Sleep*. 2021;44(Supp2):A193.

Safety: Common AEs (≥ 5%)

- **Modafinil:**
  - Anxiety, back pain, diarrhea, dizziness, dyspepsia, headache, insomnia, and nausea
- **Armodafinil**:
  - Dizziness, headache, insomnia, and nausea
- **Sodium oxybate:**
  - Decreased appetite, dizziness, enuresis, headache (in peds), and nausea (in peds), somnolence (adults), tremor (adults), vomiting, and weight decrease (peds)
- **Solriamfetol:**
  - Anxiety, decreased appetite, headache, insomnia, and nausea
- **Pitolisant:**
  - Anxiety, insomnia, and nausea
- **Lower-sodium oxybate**
  - Anxiety (adults), decreased appetite, diarrhea (adults), dizziness, enuresis (peds), headache, hyperhidrosis (adults), parasomnia (adults), vomiting, and weight decrease (peds)

Drugs@FDA Website.

Safety: Other Considerations

Agent	Additional Considerations
Modafinil/ Armodafinil[1,2,3]	• May reduce effectiveness of hormonal contraceptive agents • May increase heart rate and diastolic and systolic blood pressure (BP)
Methylphenidate[3]	• Schedule II controlled substance • High potential for abuse
Solriamfetol[4,5,6]	• Precautions regarding blood pressure and heart rate increases • Unlikely to reduce effectiveness of birth control • Renally secreted • Abuse potential ≤ phentermine in recreational drug users • 300 mg dose not available in U.S.

1. Volkow ND, et al. *JAMA*. 2009;301(11):1148-1154.; 2. Black JE, et al. *J Clin Sleep Med*. 2010;6(5):458-466.; 3. Drugs@FDA Website.
4. Meskill GJ, et al. *Sleep*. 2020;43(Suppl 1):A291.; 5. Zomorodi K, et al. *J Clin Pharmacol*. 2019;59(8):1120-1129.;
6. Carter LP, et al. *JPsychopharmacol.* 2018;32(12):1351-1361.

Safety: Other Considerations (cont.)

Agent	Additional Considerations
Pitolisant[1-3]	• May reduce effectiveness of hormonal contraceptive (???) • In a study of 303 patients, no clinically relevant effects on vital signs, laboratory findings, or electrocardiogram (ECG) parameters were noted • Lower abuse potential compared to phentermine and overall profile to placebo • Not a controlled substance
Sodium Oxybate[4]	• High sodium formulation may be contraindicated in patients at risk for CVD events • May decrease body mass index • Common, early onset AEs are generally of short duration and decrease over time
LXB[5]	• Lower-sodium oxybate formulation may be ideal in those with CVD risks • AEs same as with sodium oxybate except CVD impact

1. Drugs@FDA Website.; 2. Scart-Gres C, et al. *Sleep*. 2019;42(Suppl 1):A244-245.; 3. Setnik B, et al. *Sleep*. 2020;43(4):zsz252.; 4. Husain AM, et al. *J Clin Sleep Med*. 2020;16(9):1469-1474.; 5. Dauvilliers Y, et al. *Sleep*. 2020;43:A286.

Decision-Making Strategies for Patients with Narcolepsy Like Savannah

- **In favor of LXB as first step:**
  - Moderate EDS
  - Severe cataplexy
  - DNS, obesity (if no OSAS)
  - Able to comply with drug
  - Comorbid CVD

- **In favor of PITOLISANT as first step:**
  - Moderate EDS and cataplexy
  - CVD, untreated OSAS
  - Psychiatric problems

- **In favor of SODIUM OXYBATE as first step:**
  - Moderate EDS
  - Severe cataplexy
  - DNS, obesity (if no OSAS)
  - Able to comply with drug

- **In favor of MODAFINIL as first step:**
  - Severe EDS
  - Mild cataplexy
  - Low cardiovascular risk
  - Untreated SAS

- **In favor of SOLRIAMFETOL as first step:**
  - Resistant cases and severe EDS
  - Mild cataplexy, if any
  - Low cardiovascular risk

- **In favor of METHYLPHENIDATE:**
  - Resistant cases and severe EDS
  - Young female with oral contraception
  - Comorbid ADHD…

Courtesy of Yves Dauvilliers, MD, PhD

Personalized medicine ► Benefit/risk **ratio** needs to be assessed regularly ► Unmet needs in EDS remain

OSAS = obstructive sleep apnea syndrome; SAS = sleep apnea syndrome

Lopez R, et al. *Rev Neurol (Paris).* 2017;173(1-2):8-18.

Audience Response

Now, how confident are you developing an effective treatment plan for patients like Savannah with NT2 to improve their EDS, quality of life, and functioning?

A. Extremely confident
B. Confident
C. Somewhat confident
D. Not at all confident

Treatment Considerations for Idiopathic Hypersomnia

Audience Response

How confident are you developing an effective treatment plan for patients like Janet with IH to improve their EDS, quality of life, and functioning?

A. Extremely confident
B. Confident
C. Somewhat confident
D. Not at all confident

How to Treat IH

- No approved drugs for the treatment of IH
- Treatment approaches for EDS in IH similar to narcolepsy
- AASM 2021 draft guideline updates recommends the following for IH:
  - Use modafinil for the treatment of idiopathic hypersomnia in adults. (Strong)
  - Use clarithromycin for the treatment of idiopathic hypersomnia in adults. (Conditional)
  - Use methylphenidate for the treatment of idiopathic hypersomnia in adults. (Conditional)
  - Use pitolisant for the treatment of idiopathic hypersomnia in adults. (Conditional)
  - Use sodium oxybate for the treatment of idiopathic hypersomnia in adults. (Conditional)

Maski K, et al. *J Clin Sleep Med*. 2021 Mar 15. [Epub ahead of print].

Overview of Pharmacological Trials in IH*

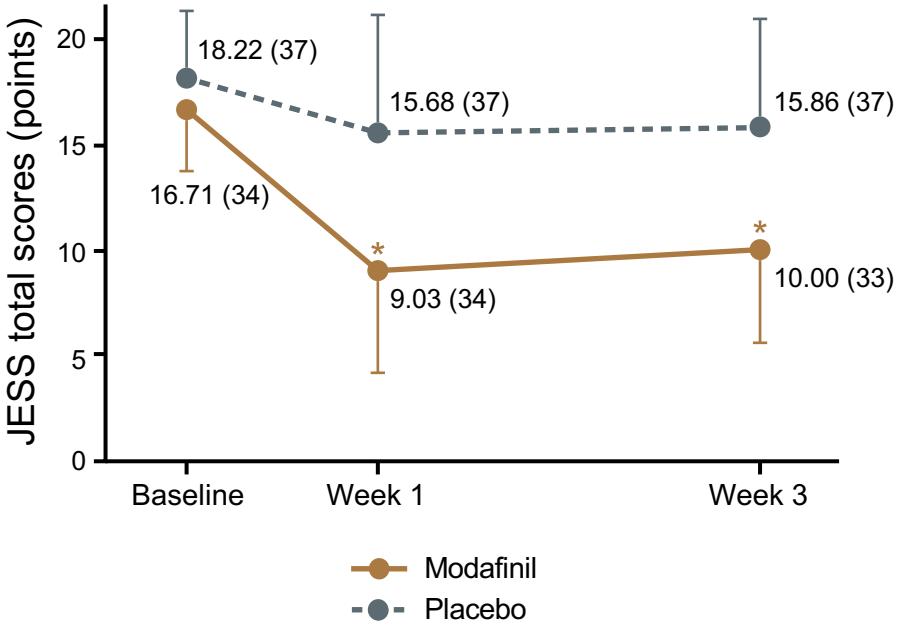
Treatment	Author	Dose	Patient population	Conclusion
Modafinil	Mayer et al. 2015	2 × 100 mg	IH without long sleep time (ICSD-2; n = 31)	Improvement on ESS: 6.0 points; on CGI: 1.0 point
	Yaman et al. 2015	200 mg per day	IH (n = 18)	Improvement mean P300 amplitudes
Methylphenidate	Thakrar et al. 2018	19 ± 10 mg per day	IH (ICSD-3; n = 9); NT1 (ICSD-3; n = 70), NT2 (ICSD-3; n = 47)	Improvement on ESS: 3.1 points
Dextroamphetamine	Ali et al. 2009	36 ± 44 mg per day	IH (ICSD-2; n = 2)	0% complete or partial response
Sodium oxybate	Leu-Semenescu et al. 2016	4.3 ± 2.2 g	Treatment-refractory IH (ICSD-2/3; n = 46)	65% responders; improvement on ESS: 3.5 points
Pitolisant	Leu-Semenescu et al. 2014	5–50 mg	Treatment-refractory IH (ICSD-2/3; n = 65)	35% responders; improvement on ESS: 1.5 points
Mazindol	Nittur et al. 2013	1–6 mg	Treatment-refractory IH (ICSD-2/3; n = 37)	Improvement on ESS: 4.8 points
Flumazenil	Kelty et al. 2014	0.35–4 mg/day (subcutaneous)	IH (n = 1)	Improvement on ESS: 10 points
	Trotti et al. 2016	24–60 mg/day (oral)	Refractory hypersomnolence (n = 153)	62.8% responders
Clarithromycin	Trotti et al. 2014	2 × 500 mg	Primary hypersomnia (DSM-IV; n = 41), narcolepsy without cataplexy (DSM-IV; n = 12)	64% improvement in daytime sleepiness
	Trotti et al., 2015	2 × 500 mg	IH (ICSD-2; n = 10); NT2 (ICSD-2; n = 4); subjective hypersomnia (n = 6)	Improvement on ESS: 3.9 points
Transcranial direct current stimulation	Galbiati et al., 2016	12 stimulations	IH (ICSD-3; n = 8)	Improvement on ESS: 5.8 points

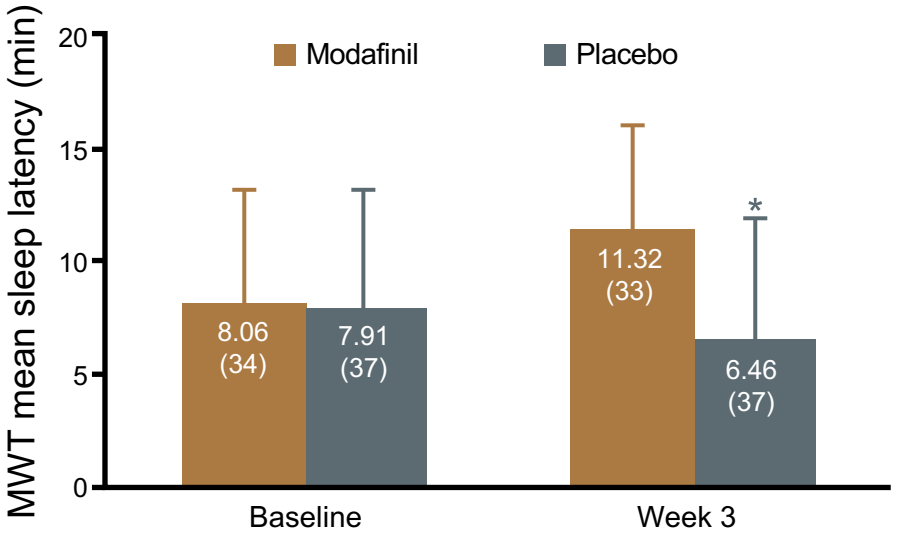
*These agents are not FDA-approved for the treatment of IH.

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; ICSD = International Classification of Sleep Disorder

Schinkelshoek MS, et al. *Curr Sleep Medicine Rep*. 2019;5:207-214.

Modafinil:*
Efficacy in IH without Long Sleep Time

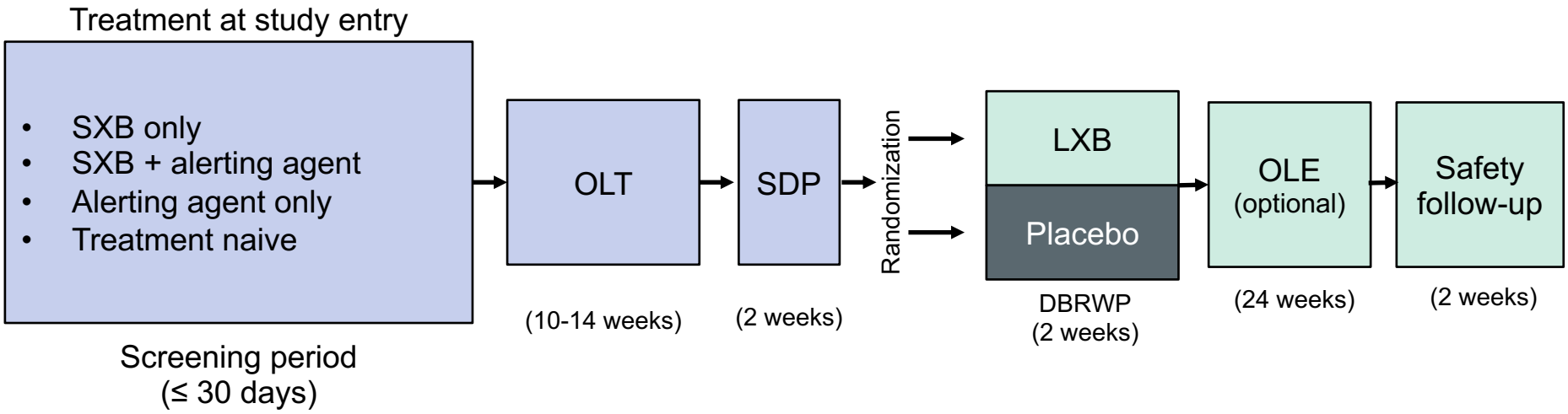




*Modafinil is not FDA-approved for the treatment of IH.

JESS = Japanese version of the Epworth Sleepiness Scale
Inoue Y, et al. *Sleep Med*. 2021;80:315-321.

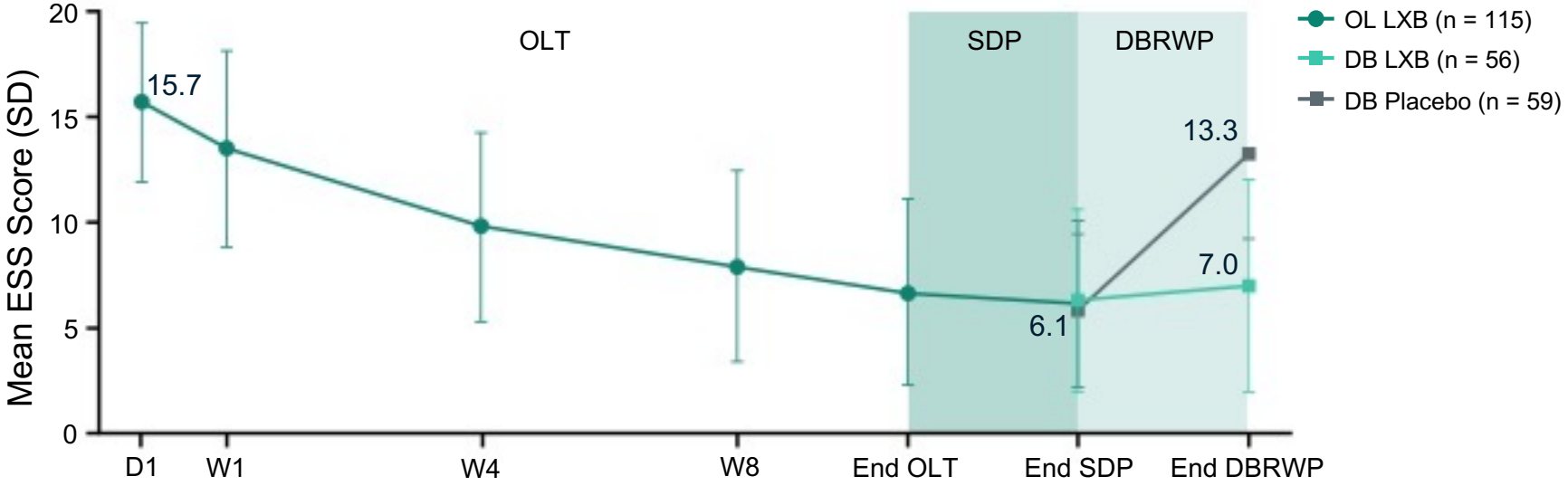
LXB:* Efficacy in IH Study Design



*LXB is not FDA-approved for the treatment of IH.

Folvary-Schaefer N, et al. AAN Virtual Annual Meeting; 2021. Abstract No. S9.002.

LXB:* Efficacy in IH - ESS



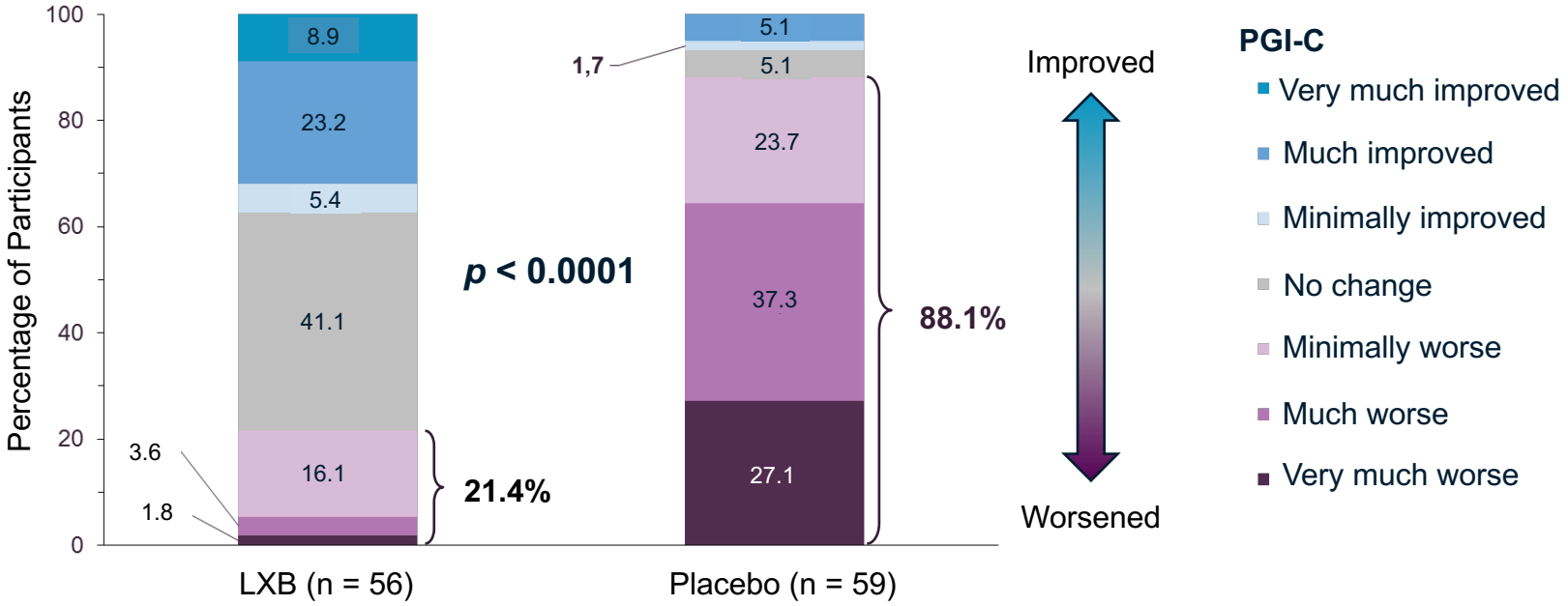
- Improvement in mean ESS score from study entry to end of SDP
- Worsening in mean ESS score from end of SDP to end of DBRWP with placebo; maintenance of improvement with LXB
- LS mean difference (95% CI) in change from end of SDP to end of DBRWP: −6.51 (−7.99, −5.03)

*LXB is not FDA-approved for the treatment of IH.

DBRWP = double-blind, randomized withdrawal period; OLT = titration and optimization period

Dauvilliers Y, et al. AAN Virtual Annual Meeting; 2021.

LXB:* Efficacy in IH – PGI-C



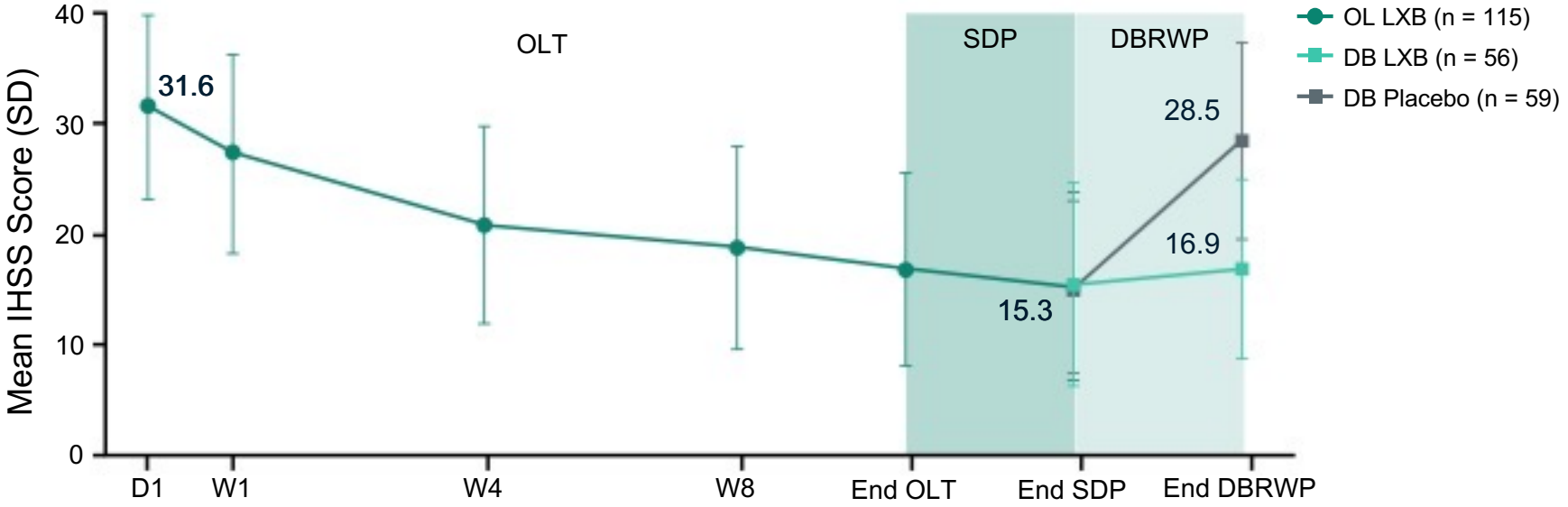
- At the end of DBRWP, significant worsening in PGI-C ratings was observed in participants randomized to placebo vs. LXB (88.1% vs. 21.4% rated minimally/much/very much worse)

*LXB is not FDA-approved for the treatment of IH.

PGI-C = patient global impression of change

Dauvilliers Y, et al. AAN Virtual Annual Meeting; 2021.

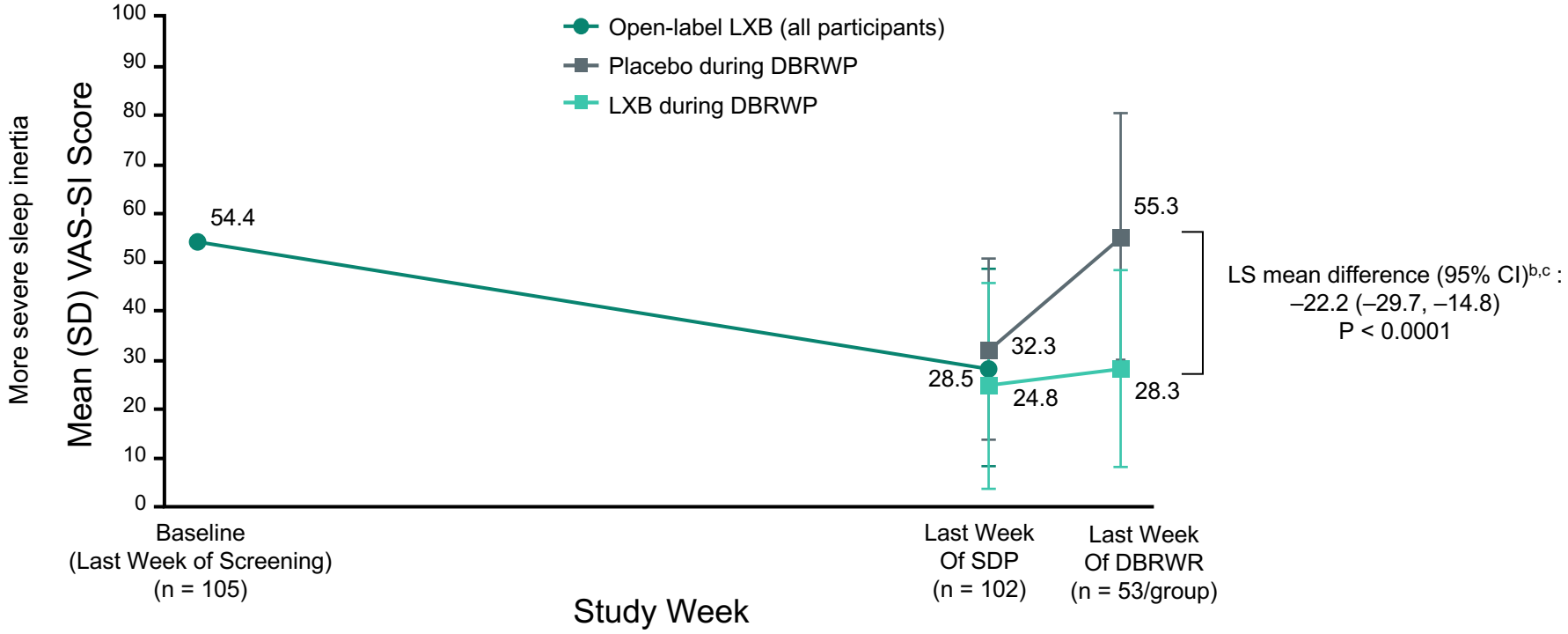
LXB: Efficacy in IH – IHSS



- Improvement in mean IHSS score from study entry to end of SDP
- Worsening in mean IHSS score from end of SDP to end of DBRWP with placebo; maintenance of improvement with LXB
- Estimated median difference (95% CI) in change from end of SDP to end of DBRWP: −12.00 (−15.00, −8.00)

Dauvilliers Y, et al. AAN Virtual Annual Meeting; 2021.

LXB: Efficacy in IH – Visual Analog Scale for Sleep Inertia (VAS-SI)



[a]Modified intent-to-treat population.
[b]Difference in change from end of SDP to end of DBRWP. [c]LXB, n = 49; placebo, n = 51.

*LXB is not FDA-approved for the treatment of IH.

Bogan RK, et al. Sleep 2021, 35th Annual Meeting of APSS; 2021. Abstract 487.

Audience Response

Now, how confident are you developing an effective treatment plan for patients like Janet with IH to improve their EDS, quality of life, and functioning?

A. Extremely confident
B. Confident
C. Somewhat confident
D. Not at all confident

Audience Response

Now, how often will you assess treatment efficacy on functional status in your patients with narcolepsy or IH?

A. 0% of the time
B. 1% - 25% of the time
C. 26% - 50% of the time
D. 51% - 75% of the time
E. 76% - 100% of the time

Conclusions

- The diagnosis of NT2 and IH is challenging and laden with missed diagnoses, misdiagnosis, and considerable diagnostic delays.
- Treatment options for narcolepsy have expanded and include therapies that may be more ideal for patients with medical comorbidities.
- While there are currently no FDA-approved therapies for IH, lower-sodium oxybate may soon become the first agent to be approved.
- When making treatment decisions for narcolepsy and IH, therapeutic efficacy on QoL and functional outcomes must also be considered.
- As treatment outcomes are not stable, follow-up is important

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Utilize evidence-based strategies to improve the differential diagnosis of narcolepsy and IH
- Assess a patients' daytime sleepiness at each visit
- Assess the impact of treatment options on quality of life and functioning, facilitated by patient reported outcomes such as ESS, FOSQ, and IHSS
- Consider patient-specific factors such as cardiovascular risk when making treatment decisions for patients with narcolepsy or IH

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QUESTIONS & ANSWERS

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