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Nocturnal Sleep Features as a Candidate Mechanism for Improvements in Daytime Sleepiness and Disease Severity in Idiopathic Hypersomnia or Narcolepsy

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Objective

- To characterize how changes in polysomnography (PSG) features were associated with changes in Epworth Sleepiness Scale (ESS) scores and Patient Global Impression of Change (PGI-C) ratings in participants with idiopathic hypersomnia or narcolepsy from baseline to end of treatment (on optimized low-sodium oxybate [LXB])

Conclusions

- Prior evidence supported parallel improvements in sleep and daytime outcomes with LXB; these analyses identify a positive association between increased slow-wave sleep (N3) and clinically meaningful symptom improvement
- Increased N3 sleep with LXB treatment was associated with higher odds of achieving normal ESS scores and meaningful improvement ("much" or "very much") in patient-reported disease severity
- These data support increased nocturnal N3 sleep specifically as a potential mechanism associated with improvements in daytime sleepiness in idiopathic hypersomnia and narcolepsy

References: 1. Schneider LD, et al. *Neurol Ther.* 2026; In Press. **2.** Plante DT, et al. *CNS Drugs.* 2026; Mar 14 Online Ahead of Print. **3.** Ruoff C, et al. *Sleep.* 2025;48(suppl 1):A374. **4.** Cairns A, et al. *Sleep.* 2025;48(suppl 1):A370.

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Introduction

- Prior findings from the DUET study (NCT05875974) showed that LXB (Xywav®) improves nighttime sleep (as assessed by PSG) and multiple daytime symptoms (including ESS and PGI-C) in participants with idiopathic hypersomnia or narcolepsy (type 1 [NT1] and type 2 [NT2])[1,2]; however, the association between changes in sleep and improvements in daytime symptoms has not yet been evaluated[1-4]
- These analyses aimed to advance understanding of the association between nocturnal sleep PSG changes and improved daytime symptoms with analysis of changes in ESS scores and PGI-C ratings for overall disease symptoms in idiopathic hypersomnia or narcolepsy

Methods

- Changes in PSG (centrally scored using current American Academy of Sleep Medicine [AASM] criteria) and patient-reported outcomes (ESS and PGI-C) were assessed from baseline (BL; off LXB) to end of treatment (EOT; on optimized LXB)
- Logistic regression models, adjusting for total sleep time and age, were used to identify PSG predictors of improvements in ESS outcomes (**Model 1**) and PGI-C outcomes (**Model 2**)
  - Changes in clinically relevant PSG features reflecting sleep disruption or consolidation evaluated were: 1) percentage of N3 sleep (%N3); 2) percentage of N1 sleep (%N1); 3) stage transition index (defined as total number of transitions from deeper to lighter stages—ie, from rapid eye movement [REM]/N3/N2/N1 to wake and from REM/N3/N2 to N1—divided by sleep period duration [sleep onset latency subtracted from time in bed]); and 4) arousal index
    - PSG features were removed using a backward selection procedure using Wald chi-square tests with parameter retention criteria of *P*<0.1; **for both models, only %N3 was retained**
  - For the ESS model, ESS was dichotomized as:
    - "clinically meaningful decrease + normalization" (CMDN): a stringent composite endpoint requiring both an ESS score decrease from BL of 3 or more points plus an EOT ESS score ≤10; ie, in the normal range)
    - "non-CMDN": an ESS decrease from BL of 2 points or less and/or EOT ESS >10
  - For the PGI-C model, PGI-C was dichotomized as:
    - "≥much improved": *very much improved and much improved*
    - "≤minimally improved": *minimally improved, no change, minimally worse, much worse, and very much worse*
- Models were evaluated in the pooled analysis group (idiopathic hypersomnia and narcolepsy combined) and stratified by cohort and subcohort:
  - Idiopathic hypersomnia: with and without long sleep need (LSN), based on response to Idiopathic Hypersomnia Severity Scale, Item 1: "*What for you is the ideal duration of nighttime sleep (at the weekend or on holiday, for example)?*" (Response options: "11 hours or more," "more than 9 hours and less than 11 hours," "between 7 hours and 9 hours," "less than 7 hours")
  - Narcolepsy: NT1 and NT2
  - In addition, sensitivity analyses were conducted adjusting for dose and subcohort

Results

Table 1. Demographics and Baseline Characteristics

Characteristic	Idiopathic Hypersomnia (n=37)	Narcolepsy (n=34)	Pooled Analysis Group (N=71)
Age, years			
Mean (SD)	38.4 (11.8)	35.7 (14.2)	37.1 (13.0)
Median (min, max)	38.0 (20, 68)	31.0 (20, 75)	34.0 (20, 75)
Sex at birth, n (%)			
Male	9 (24.3)	9 (26.5)	18 (25.4)
Female	28 (75.7)	25 (73.5)	53 (74.6)
Race, n (%)			
White	32 (86.5)	27 (79.4)	59 (83.1)
Black or African American	2 (5.4)	4 (11.8)	6 (8.5)
Asian	1 (2.7)	2 (5.9)	3 (4.2)
Native Hawaiian or other Pacific Islander	1 (2.7)	0	1 (1.4)
Multiple[a]	1 (2.7)	0	1 (1.4)
Unknown	0	1 (2.9)	1 (1.4)
Ethnicity, n (%)			
Hispanic or Latino	9 (24.3)	3 (8.8)	12 (16.9)
Not Hispanic or Latino	27 (73.0)	31 (91.2)	58 (81.7)
Body mass index (kg/m²), mean (SD)	29.0 (6.3)	29.1 (6.2)	29.0 (6.2)
Total twice-nightly LXB dosage (g), mean (SD)	7.7 (1.3)[b]	7.0 (1.7)[c]	7.3 (1.6)

[a]Participant reported ≥1 race. [b]n=24; mean (SD) total nightly LXB dosage for participants taking LXB once nightly (n=13) was 4.6 (1.0) g. [c]All took twice-nightly LXB.
LXB, low-sodium oxybate; SD, standard deviation.

For participants with idiopathic hypersomnia who completed the IHSS

18 (50.0%) had LSN (>9 hours of sleep need at BL)

18 (50.0%) did not have LSN (≤9 hours of sleep need at BL)

For participants with narcolepsy

16 (47.1%) had NT1

18 (52.9%) had NT2

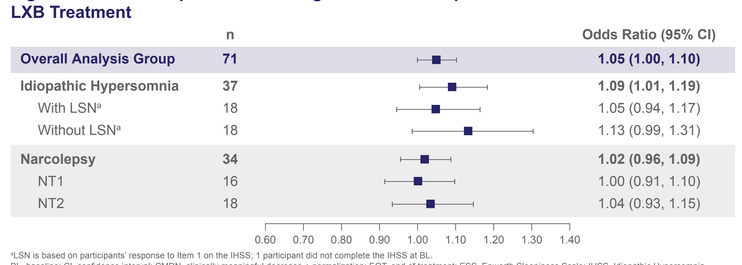
Mean %N3 Change From BL to EOT

- In the pooled analysis, mean (SE) %N3 increased by 10.3% points (1.3% points) from BL to EOT (from 12.2% [1.0%] to 22.5% [1.7%])
  - In participants with idiopathic hypersomnia (n=37), mean (SE) %N3 increased by 10.3% points (1.7% points) (from 10.9% [1.4%] to 21.2% [2.1%])
  - In participants with narcolepsy (n=34), mean (SE) %N3 increased by 10.3% points (2.0% points) (from 13.7% [1.4%] to 24.0% [2.8%])[1]
- Additional details on demographics/clinical characteristics and LXB dosages by subcohorts and %N3 change by outcome category can be found in the Supplemental Tables 1–3, accessed via the QR code

Model 1: ESS Modeling

- In the pooled analysis group, mean (SE) ESS score decreased by 8.1 (0.6) points from BL to EOT (from 16.4 [0.4] to 8.4 [0.6])
  - In participants with idiopathic hypersomnia, mean (SE) ESS score decreased by 8.4 (0.8) points (from 16.6 [0.5] to 8.2 [0.7])
  - In participants with narcolepsy, mean (SE) ESS score decreased by 7.7 (0.9) points (from 16.3 [0.5] to 8.6 [1.0])[1]
- At EOT, 45 (63%) participants met/achieved the stringent composite endpoint of ESS CMDN; 26 (37%) did not

Figure 1. Relationship Between Change in %N3 and Improvement in ESS Scores After LXB Treatment

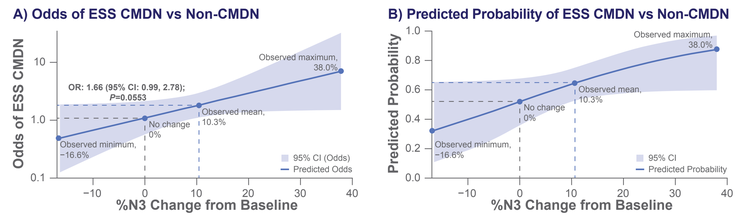


[a]LSN is based on participants' response to Item 1 on the IHSS; 1 participant did not complete the IHSS at BL.
BL, baseline; CI, confidence interval; CMDN, clinically meaningful decrease + normalization; EOT, end of treatment; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; LSN, long sleep need; LXB, low-sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

- Each 1% increase in %N3 sleep from BL to EOT was associated with a 5% increase in the odds of achieving a CMDN in ESS scores (ie, normal ESS scores) after LXB treatment

Model 1: ESS Modeling (continued)

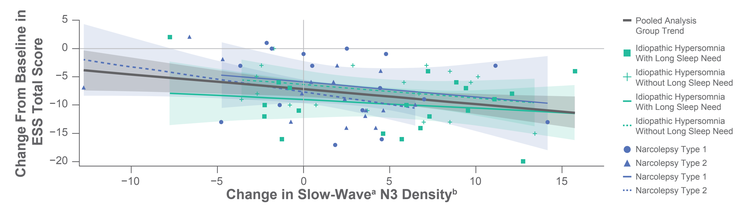
Figure 2. Odds and Predicted Probability of Improvement in ESS Scores



BL, baseline; CI, confidence interval; EOT, end of treatment; ESS, Epworth Sleepiness Scale; CMDN, clinically meaningful decrease + normalization; OR, odds ratio; PGI-C, Patient Global Impression of Change.

- For a participant with idiopathic hypersomnia or narcolepsy and average %N3 increase, the odds of achieving ESS CMDN were 1.66 times that of a participant with no %N3 increase
- A greater increase in %N3 sleep from BL to EOT was associated with a higher odds of symptom improvement based on ESS
- At the observed mean %N3 increase of 10.3% points, the model predicts approximately a 64% probability of achieving ESS CMDN

Figure 3. Change from Baseline in Sleepiness as a Function of Increased Slow-Wave[a] Density[b]



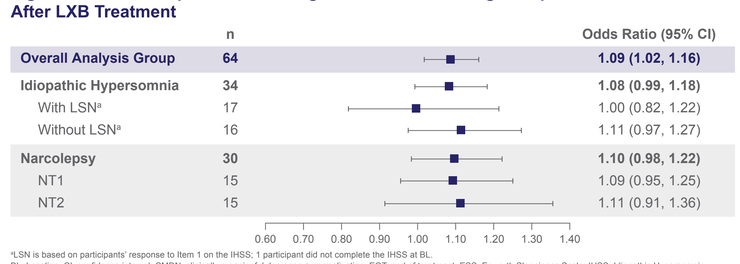
[a]Per the American Academy of Sleep Medicine (2023). *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications (Version 3)*. Darien, IL. [b]The number of slow waves per minute of N3 sleep, reflecting N3 intensity.
AASM, American Academy of Sleep Medicine; ESS, Epworth Sleepiness Scale; LSN, long sleep need.

- Change in slow-wave N3 density showed a modest inverse correlation with changes in ESS scores (r=−0.29, *P*=0.014; n=71); these data suggest that greater slow-wave intensity at EOT was associated with improvements in daytime sleepiness
- Sensitivity models adjusting for dose and subcohort yielded similar conclusions (data not shown); final outcomes did not change

Model 2: PGI-C Modeling

- PGI-C data were available for 64 participants (idiopathic hypersomnia, n=34; narcolepsy, n=30); demographic and clinical characteristics for this pooled analysis group can be accessed in Supplemental Table S4
- At EOT, 47 (73.4%) participants reported much/very much improved on the PGI-C
  - In participants with idiopathic hypersomnia, 24 (70.6%) participants reported much/very much improved and 10 (29.4%) reported minimally improved or worse categories on the PGI-C
  - In participants with narcolepsy, 23 (76.7%) participants reported much/very much improved and 7 (23.3%) reported minimally improved or worse categories on the PGI-C[1]

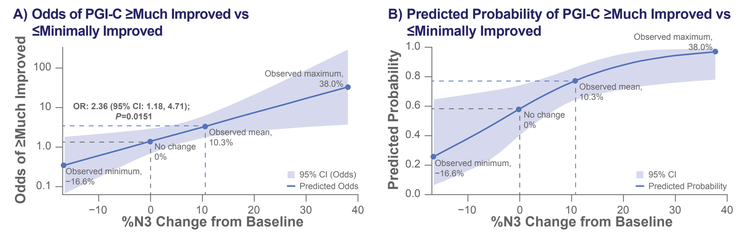
Figure 4. Relationship Between Change in %N3 and Meaningful Improvement on the PGI-C After LXB Treatment



[a]LSN is based on participants' response to Item 1 on the IHSS; 1 participant did not complete the IHSS at BL.
BL, baseline; CI, confidence interval; CMDN, clinically meaningful decrease + normalization; EOT, end of treatment; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; LSN, long sleep need; LXB, low-sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PGI-C, Patient Global Impression of Change.

- Each 1% increase in %N3 sleep at EOT vs BL was associated with a 9% increase in the odds of achieving much/very much improved category on the PGI-C after LXB treatment

Figure 5. Odds and Predicted Probability of Meaningful Improvement on the PGI-C



BL, baseline; CI, confidence interval; EOT, end of treatment; OR, odds ratio; PGI-C, Patient Global Impression of Change.

- For a participant with idiopathic hypersomnia or narcolepsy and average %N3 increase, the odds of achieving ≥much improved PGI-C were 2.36 times that of a participant with no %N3 increase
- A greater increase in %N3 sleep from BL to EOT was associated with a higher odds of meaningful improvement based on PGI-C
- At the observed mean %N3 increase of 10.3% points, the model predicts approximately a 79% probability of reporting ≥much improved on the PGI-C
- Sensitivity models adjusting for dose and subcohort yielded similar conclusions (data not shown); final outcomes did not change

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Supplemental Material

Supplemental Table S1. Demographics and Baseline Characteristics By Idiopathic Hypersomnia or Narcolepsy Cohorts and Subcohorts

Characteristic	Idiopathic Hypersomnia (n=37)		Narcolepsy (n=34)	
	With LSN[a] (n=18)	Without LSN[b] (n=18)	NT1 (n=16)	NT2 (n=18)
Age, years				
Mean (SD)	38.6 (11.8)	37.2 (11.4)	35.6 (14.2)	35.9 (14.7)
Median (min, max)	36.5 (20, 62)	38.0 (22, 68)	30.5 (20, 68)	31.0 (22, 75)
Sex at birth, n (%)				
Male	0	8 (44.4)	3 (18.8)	6 (33.3)
Female	18 (100)	10 (55.6)	13 (81.3)	12 (66.7)
Race, n (%)				
White	17 (94.4)	14 (77.8)	10 (62.5)	17 (94.4)
Black or African American	0	2 (11.1)	3 (18.8)	1 (5.6)
Asian	0	1 (5.6)	2 (12.5)	0
Native Hawaiian or other Pacific Islander	0	1 (5.6)	0	0
Multiple[c]	1 (5.6)	0	0	0
Unknown	0	0	1 (6.3)	0
Ethnicity, n (%)				
Hispanic or Latino	7 (38.9)	2 (11.1)	1 (6.3)	2 (11.1)
Not Hispanic or Latino	11 (61.1)	15 (83.3)	15 (93.8)	16 (88.9)
Body mass index (kg/m^2), mean (SD)	28.5 (7.7)	29.4 (5.0)	28.9 (6.5)	29.2 (6.0)

[a]>9 hours of sleep at BL. [b]≤9 hours of sleep at BL. [c]Participant reported ≥1 race.
BL, baseline; LSN, long sleep need; max, maximum; min, minimum; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation.

Supplemental Table S2. Average Total Nightly Dose During the Stable-Dose Period By Idiopathic Hypersomnia or Narcolepsy Cohorts and Subcohorts

Dosage, mean (SD)	Idiopathic Hypersomnia (n=37[a])		Narcolepsy (n=34)	
	With LSN, >9 hours at BL (n=18)	Without LSN, ≤9 hours at BL (n=18)	NT1 (n=16)	NT2 (n=18)
Twice nightly (g/night)	7.8 (1.2), n=11	7.4 (1.4), n=12	7.3 (1.2), n=16	6.8 (2.0), n=18
Once nightly (g/night)	4.6 (1.0), n=7	4.5 (1.2), n=6	N/A	N/A

[a]LSN is based on participants' response to Item 1 on the IHSS; 1 participant did not complete the IHSS at BL and could not be included in LSN subcohorts but was counted in the total idiopathic hypersomnia cohort.
BL, baseline; IHSS, Idiopathic Hypersomnia Severity Scale; LSN, long sleep need; N/A, not applicable; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation.

Supplemental Table S3. Change in %N3 by Outcome

Category	n	Change in %N3 Mean (SE)
ESS		
CMDN (decrease 3+ points and EOT ESS ≤10)	45	12.2 (1.6)
non-CMDN (change ≤2 points or EOT ESS >10)	26	7.0 (2.2)
PGI-C		
≥much improved (*very much improved + much improved*)	47	12.4 (1.6)
minimally improved (*minimally improved + no change + minimally worse + much worse + very much worse*)	17	4.5 (2.1)

CMDN, clinically meaningful decrease + normalization EOT, end of treatment; ESS, Epworth Sleepiness Scale; SE, standard error.

Supplemental Table S4. Demographics and Baseline Characteristics in Participants with PGI-C Data

Characteristic	Idiopathic Hypersomnia (n=34)	Narcolepsy (n=30)	Pooled Analysis Group (N=64)
Age, years			
Mean (SD)	38.1 (12.1)	34.8 (12.7)	36.6 (12.4)
Median (min, max)	38.0 (20, 68)	31.0 (22, 68)	32.5 (20, 68)
Sex at birth, n (%)			
Male	8 (23.5)	9 (30.0)	17 (26.6)
Female	26 (76.5)	21 (70.0)	47 (73.4)
Race, n (%)			
White	29 (85.3)	23 (76.7)	52 (81.3)
Black or African American	2 (5.9)	4 (13.3)	6 (9.4)
Asian	1 (2.9)	2 (6.7)	3 (4.7)
Native Hawaiian or other Pacific Islander	1 (2.9)	0	1 (1.6)
Multiple[a]	1 (2.9)	0	1 (1.6)
Unknown	0	1 (3.3)	1 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	9 (26.5)	2 (6.7)	11 (17.2)
Not Hispanic or Latino	24 (70.6)	28 (93.3)	52 (81.3)
Body mass index (kg/m^2), mean (SD)	29.4 (6.4)	28.5 (6.0)	29.0 (6.2)
Total twice nightly LXB dosage (g), mean (SD)	7.7 (1.3)[b]	7.1 (1.6)[c]	7.4 (1.5)[d]

[a]Participant reported ≥1 race. [b]n=23; data for participants taking LXB once nightly are not available. [c]All took twice-nightly LXB. [d]n=53; data for participants taking LXB once nightly are not available.
LXB, low-sodium oxybate; PGI-C, Patient Global Impression of Change; SD, standard deviation.