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Efficacy of Low-Sodium Oxybate by Baseline Sleep Inertia in a Phase 3 Clinical Study in Patients With Idiopathic Hypersomnia

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Introduction

- Idiopathic hypersomnia is a chronic, debilitating neurologic sleep disorder[1,2]
- Sleep inertia (difficulty awakening) is a common symptom of idiopathic hypersomnia that can significantly impair functioning and quality of life[3,4]
- Calcium, magnesium, potassium, and sodium oxybates (low-sodium oxybate; LXB; Xywav®) is approved in the United States for the treatment of idiopathic hypersomnia in adults[5-8]
- In a phase 3 trial (NCT03533114), LXB demonstrated efficacy in treating multiple symptoms and impacts of idiopathic hypersomnia, including excessive daytime sleepiness, sleep inertia, overall symptom severity, functional impairment, and quality of life[9]

Objective

- This post hoc analysis evaluated response to LXB by baseline sleep inertia in adults with idiopathic hypersomnia

Methods

- Eligible participants were 18–75 years of age and had idiopathic hypersomnia and average nocturnal total sleep time (TST) of 7 hours or more
- Participants began LXB treatment with an open-label treatment titration and optimization period (10–14 weeks), followed by a 2-week stable-dose period (SDP); participants were then randomly assigned to placebo or continued LXB treatment during a 2-week, double-blind, randomized withdrawal period
- Baseline assessments of efficacy and disease severity included Clinical Global Impression of Severity (CGIs), Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire short version (FOSQ-10), Idiopathic Hypersomnia Severity Scale (IHSS), Patient Global Impression of Change (PGIc), visual analog scale for sleep inertia (VAS-SI), and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)
  - On the VAS-SI, participants rated their difficulty awakening on a 100-mm line with anchors at 0 (very easy) and 100 (very difficult)
- Baseline scores on IHSS items 3 and 4 were used to define sleep inertia categories of severe (≥2 on both items), absent (0 on both items), and mild (other scores)[4]
- Spearman correlation coefficients were used to assess correlations between VAS-SI scores and scores on IHSS items 3, 4, and 5 at baseline and end of SDP
  - IHSS item 3 ("Is it extremely difficult for you, or even impossible, to wake up in the morning without several alarm calls or the help of someone?") is scored 3 (always), 2 (often), 1 (sometimes), or 0 (never)
  - IHSS item 4 ("After a night sleep, how long does it take to feel like you are functioning properly [ie, fully functional, both physically and intellectually] after getting out of bed?") is scored 4 (≥2 hours), 3 (>1 hour but <2 hours), 2 (between 30 minutes and 1 hour), 1 (<30 minutes), or 0 (I feel I am functioning properly as soon as I wake up)
  - IHSS item 5 ("In the minutes after waking up, do you ever do irrational things and/or say irrational things, and/or are you very clumsy, for example, tripping, breaking, or dropping things?") is scored 3 (always), 2 (often), 1 (sometimes), or 0 (never)
  - Generally, correlation coefficients <0.3 are considered weak, ≥0.3 to <0.6 moderate, and ≥0.6 strong[10]

Results

Table 1. Demographics and Baseline Clinical Characteristics

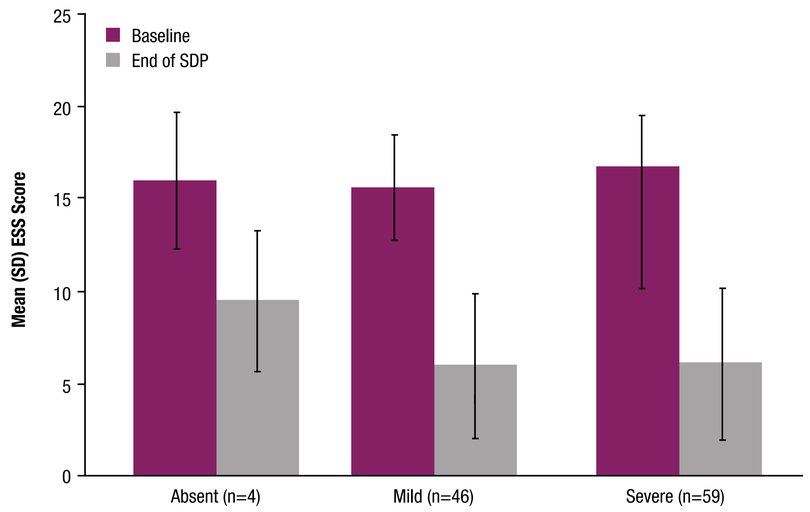
Characteristic	Sleep Inertia Severity[a] Absent (n=4)	Mild (n=46)	Severe (n=59)	Total (N=109)
Age, years, mean (SD)	46.0 (12.4)	43.7 (14.3)	38.1 (12.7)	40.8 (13.6)
Sex, female, n (%)	2 (50.0)	33 (71.7)	44 (74.6)	79 (72.5)
Region, n (%)				
North America	2 (50.0)	29 (63.0)	44 (74.6)	75 (68.8)
Europe	2 (50.0)	17 (37.0)	15 (25.4)	34 (31.2)
CGIs, n (%)				
Normal, not at all ill	0	0	0	0
Borderline ill	0	1 (2.2)	0	1 (0.9)
Mildly ill	0	2 (4.3)	1 (1.7)	3 (2.8)
Moderately ill	1 (25.0)	17 (37.0)	25 (42.4)	43 (39.4)
Markedly ill	2 (50.0)	21 (45.7)	15 (25.4)	38 (34.9)
Severely ill	1 (25.0)	5 (10.9)	17 (28.8)	23 (21.1)
Among the most extremely ill patients	0	0	1 (1.7)	1 (0.9)
ESS, mean (SD)	16.0 (3.7)	15.7 (2.8)	16.8 (2.7)	16.3 (2.8)
IHSS, mean (SD)	19.3 (7.5)	28.5 (6.2)	36.4 (5.4)	32.5 (7.4)
FOSQ-10, mean (SD)	13.7 (2.2)	12.7 (3.1)	10.6 (3.1)	11.6 (3.2)
WPAI:SHP, mean (SD)				
Percent work time missed due to IH (absenteeism)	0	3.4 (5.7)	10.4 (19.1)	7.2 (15.2)
Percent impairment while working due to IH (presenteeism)	40.0 (36.1)	50.6 (25.7)	59.8 (19.1)	55.3 (22.9)
Percent overall work impairment due to IH	40.0 (36.1)	50.6 (25.7)	62.5 (19.2)	56.9 (23.2)
Percent activity impairment due to IH	42.5 (29.9)	60.9 (23.5)	70.8 (17.7)	65.6 (21.6)
TST, mean (SD), minutes				
24 hour	514.7 (82.7)	509.2 (85.1)	551.6 (130.1)	531.7 (112.1)
Nocturnal	471.4 (49.8)	482.7 (77.0)	500.8 (97.9)	491.9 (87.9)
Idiopathic hypersomnia subtype, n (%)				
Long sleep	1 (25.0)	8 (17.4)	13 (22.0)	22 (20.2)
Without long sleep	3 (75.0)	38 (82.6)	46 (78.0)	87 (79.8)
Treatment at study entry, n (%)				
Non-SXB stimulant or alerting agent	2 (50.0)	28 (60.9)	32 (54.2)	62 (56.9)
Treatment-naive	2 (50.0)	18 (39.1)	27 (45.8)	47 (43.1)

[a]Baseline scores on IHSS items 3 and 4 were used to define sleep inertia categories: severe (≥2 on both items), absent (0 on both items), and mild (other scores).[4]

CGIs, Clinical Global Impression of Severity; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire short version; IH, idiopathic hypersomnia; IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation; SXB, sodium oxybate; TST, total sleep time; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

- Mean (SD) age of participants was 40.8 (13.6) years; a majority of participants were female (72.5%), and about two-thirds of participants were from North America (68.8%)
- Nearly all participants (105/109, 96.3%) experienced sleep inertia, either mild (46/109, 42.2%) or severe (59/109, 54.1%)

Figure 1. ESS Scores Over Time, by Baseline Sleep Inertia Severity[a]

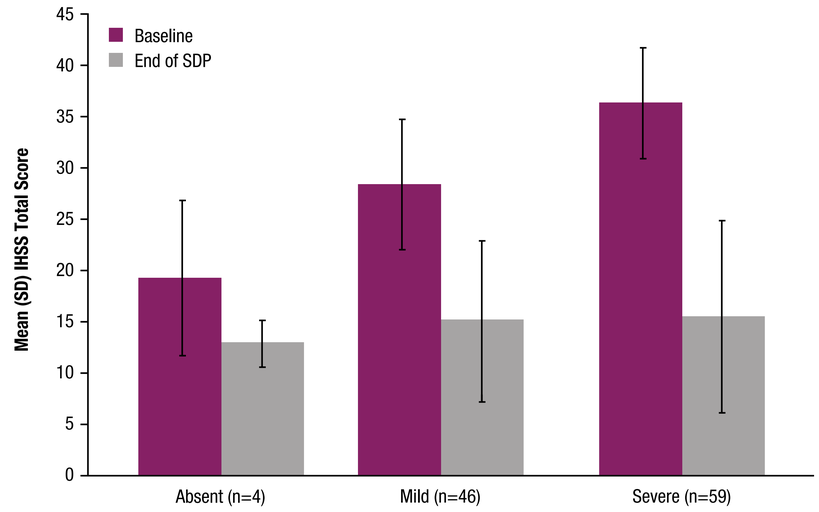


[a]Baseline scores on IHSS items 3 and 4 were used to define sleep inertia categories: severe (≥2 on both items), absent (0 on both items), and mild (other scores).[4]

ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation; SDP, stable-dose period.

- ESS scores improved during LXB treatment in each category of baseline sleep inertia severity

Figure 2. Total IHSS Scores Over Time, by Baseline Sleep Inertia Severity[a]

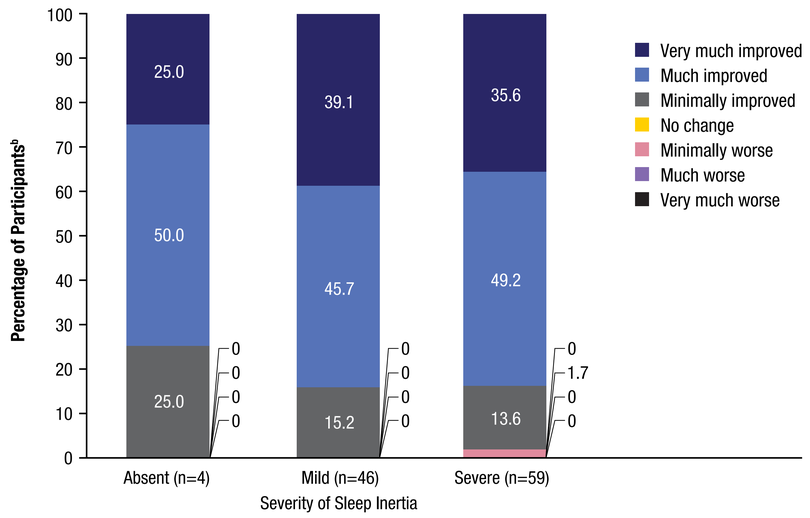


[a]Baseline scores on IHSS items 3 and 4 were used to define sleep inertia categories: severe (≥2 on both items), absent (0 on both items), and mild (other scores).[4]

IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation; SDP, stable-dose period.

- Total IHSS scores improved during LXB treatment in each category of baseline sleep inertia severity

Figure 3. PGIc Ratings at End of SDP, by Baseline Sleep Inertia Severity[a]



[a]Baseline scores on IHSS items 3 and 4 were used to define sleep inertia categories: severe (≥2 on both items), absent (0 on both items), and mild (other scores).[4]

[b]Due to rounding, percentages may not sum to 100%.

IHSS, Idiopathic Hypersomnia Severity Scale; PGIc, Patient Global Impression of Change; SDP, stable-dose period.

- After LXB treatment, participants rated themselves as improved (minimally, much, or very much) in each PGIc category of baseline sleep inertia severity (absent, 100%; mild, 100%; severe, 98.3%)

Table 2. VAS-SI Scores Over Time, by Baseline Sleep Inertia Severity

Weekly Mean VAS-SI Score	Sleep Inertia Severity[a] Absent (n=4)	Mild (n=46)	Severe (n=59)
Baseline			
n	4	41	54
Mean (SD)	12.4 (10.8)	47.7 (24.6)	65.5 (20.2)
Median (Q1, Q3)	7.7 (6.5, 18.4)	54.0 (31.2, 67.1)	69.0 (50.3, 81.1)
Min, max	5.7, 28.6	3.6, 89.7	10.6, 100.0
SDP Week 2			
n	4	43	49
Mean (SD)	9.7 (9.0)	25.5 (18.5)	32.3 (20.9)
Median (Q1, Q3)	5.7 (4.9, 14.5)	19.8 (13.0, 40.3)	25.8 (16.9, 45.7)
Min, max	4.1, 23.2	0.0, 74.0	0.0, 82.7
Change from baseline			
n	4	39	48
Mean (SD)	−2.7 (1.8)	−23.5 (20.4)	−33.1 (22.2)
Median (Q1, Q3)	−2.1 (−4.0, −1.5)	−17.4 (−40.8, −9.3)	−28.6 (−49.9, −18.3)
Min, max	−5.4, −1.4	−82.9, 14.6	−74.7, 23.9

[a]Baseline scores on IHSS items 3 and 4 were used to define sleep inertia categories: severe (≥2 on both items), absent (0 on both items), and mild (other scores).[4]

IHSS, Idiopathic Hypersomnia Severity Scale; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation; SDP, stable-dose period; VAS-SI, visual analog scale for sleep inertia.

- In participants with absent, mild, and severe baseline sleep inertia, respectively, VAS-SI improvements in sleep inertia at end of SDP (mean changes from baseline) were −2.7, −23.5, and −33.1

Table 3. Correlation Between VAS-SI Scores and IHSS Items Related to Sleep Inertia[a]

Time Point	Spearman Correlation Coefficient	Spearman 95% CI	Spearman *P* Value
Baseline			
IHSS items 3 and 4	0.556	0.403, 0.679	<0.0001
IHSS items 3, 4, and 5	0.566	0.414, 0.686	<0.0001
End of SDP			
IHSS items 3 and 4	0.569	0.416, 0.691	<0.0001
IHSS items 3, 4, and 5	0.592	0.445, 0.709	<0.0001
Change from baseline to end of SDP			
IHSS items 3 and 4	0.436	0.252, 0.589	<0.0001
IHSS items 3, 4, and 5	0.489	0.315, 0.631	<0.0001

[a]Participants taking sodium oxybate at baseline were excluded.

CI, confidence interval; IHSS, Idiopathic Hypersomnia Severity Scale; SDP, stable-dose period; VAS-SI, visual analog scale for sleep inertia.

- Correlations between total VAS-SI scores and IHSS items assessing sleep inertia at baseline and end of SDP, as well as change in score from baseline to end of SDP, were moderate (≥0.3 to <0.6)

Conclusions

- Participants with idiopathic hypersomnia and more severe baseline sleep inertia generally had greater baseline idiopathic hypersomnia disease burden
- LXB treatment was efficacious across baseline sleep inertia severity groups
- VAS-SI scores were moderately correlated with IHSS items related to sleep inertia

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