002 Increased Risk of Hypertension Onset Among Patients With Narcolepsy Newly Treated With High-Sodium Oxybate

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Introduction

- Narcolepsy is a rare hypersomnolence disorder that requires long-term pharmacologic treatment[1]
- High-sodium oxybate (Xyrem®) is approved by the US Food and Drug Administration (FDA) for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients ≥7 years of age with narcolepsy and is strongly recommended by the American Academy of Sleep Medicine for treatment of EDS and cataplexy[2,3]
- High-sodium oxybate contains a high-sodium content warning in its FDA-approved labeling[2]
- The relationship between excess sodium intake and increased risk of hypertension, stroke, and cardiovascular disease is well established[4-6]
- A recently published study showed that patients with narcolepsy have a higher risk of cardiovascular disease (CVD)[7]

Objective

- This study compared the intermediate-term risk (within 180 days) of new-onset hypertension diagnosis among normotensive patients with narcolepsy initiating high-sodium oxybate (SXB cohort) versus comparable patients with narcolepsy not initiating high-sodium oxybate (control cohort)

Methods

- Claims from Merative™ MarketScan® (formerly IBM® MarketScan®) from January 2014 to February 2020 were analyzed
- Patient selection criteria included the following:
  - SXB cohort: Adults (≥18 years of age) with continuous insurance coverage from at least 180 days prior to cohort entry until 180 days after cohort entry, and ≥1 inpatient or outpatient narcolepsy claim (narcolepsy type 1 [NT1] or narcolepsy type 2 [NT2]) or a prescription for high-sodium oxybate
  - Control cohort: Adults with continuous insurance coverage from at least 180 days prior to cohort entry until 180 days after cohort entry and ≥1 inpatient or outpatient narcolepsy claim (NT1 or NT2)
  - Patients were excluded for prior use of sodium oxybate or antihypertensive medication, or having a claim for hypertension within 13 months prior to cohort entry
  - In a sensitivity analysis, patients with a history of CVD were excluded
- Cohorts were propensity score (PS) matched 1:2 to balance baseline characteristics, including age, sex, region, insurance type, medical conditions, therapeutic intervention, healthcare resource utilization, and year of cohort entry
- Two endpoints were assessed: 1) a composite of new-onset hypertension diagnosis or initiation of antihypertensive medication, and 2) new-onset hypertension diagnosis
- Patients were followed for 180 days or until first occurrence of the outcome, discontinuation of high-sodium oxybate in the SXB cohort, or initiation of high-sodium oxybate in the control cohort
- Risk per 100 patients was reported and differences were evaluated using multivariable logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs)

Conclusions

- This study detected increased intermediate-term risk (within 180 days) of new-onset hypertension diagnosis among normotensive patients with narcolepsy initiating treatment with high-sodium oxybate, even among patients without a history of CVD
- These results are consistent with expert global consensus that excess sodium intake is associated with increased blood pressure[8-10]
- Clinicians should consider the risk of hypertension associated with high-sodium oxybate in patients with and without a history of CVD

Results

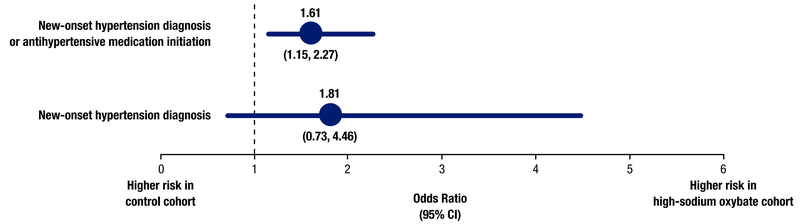
Table 1. Select Baseline Characteristics Before and After Propensity Score Matching

	Before 1:2 PS Matching			After 1:2 PS Matching[a]		
	SXB Cohort	Control Cohort	ASD[b]	SXB Cohort	Control Cohort	ASD[b]
Number of patients, n	1089	10,882[c]		954	1908[d]	
Demographics						
Age, years, mean (SD)	34.48 (11.6)	37.17 (13.3)	0.216	34.85 (11.7)	35.12 (12.3)	0.023
Female, n (%)	738 (67.8)	6895 (63.4)	0.093	641 (67.2)	1269 (66.5)	0.014
Select medical conditions, n (%)						
Sleep apnea (including OSA)	419 (38.5)	2589 (23.8)	0.321	334 (35.0)	699 (36.6)	0.034
Narcolepsy type 1	376 (34.5)	1213 (11.2)	0.580	253 (26.5)	495 (25.9)	0.013
History of CVD	48 (4.4)	408 (3.8)	0.033	37 (3.9)	85 (4.5)	0.029
Diabetes diagnosis	45 (4.1)	591 (5.4)	0.061	38 (4.0)	80 (4.2)	0.011
Therapeutic intervention, n (%)						
Use of CPAP machine	122 (11.2)	877 (8.1)	0.106	95 (10.0)	205 (10.7)	0.026
Use of alerting agents	587 (53.9)	3923 (36.1)	0.365	476 (49.9)	974 (51.1)	0.023
Healthcare resource use						
Outpatient visits, mean (SD)	29.99 (35.51)	23.45 (29.72)	0.200	28.30 (33.67)	27.45 (33.38)	0.026

[a]PS matching covariates were determined prior to outcome evaluation. The covariates included in the PS model were age, sex, region, insurance type, anxiety disorders, cataplexy, history of CVD, diabetes, headache/migraine, hypersomnia, mood disorders, periodic limb movement disorder, pulmonary fibrosis or interstitial lung disease, REM behavior disorder, restless legs syndrome, sleep apnea, hyperlipidemia, renal impairment, use of alerting agents (wake-promoting agents or stimulants), use of CPAP, outpatient visits, and cohort entry date.
[b]The PS is considered adequate if the cohorts are balanced, with an absolute value of the standardized differences for all baseline factors used to generate the PS less than 0.1. Propensity scores for continuous variables were calculated as the absolute value in the difference in means of a covariate across the treatment groups, divided by the standard deviation in the treated group.
[c]Covariates coronary vascularization and hyperuricemia captured zero patients in the SXB cohort, but 1 and 5 patients in the control group, respectively. These covariates were removed from propensity score calculations, and patients with these covariates (n=6) were removed from the control cohort. Two additional patients were removed from the control cohort due to missing demographic data.
[d]Two patients were excluded from the control cohort outcome analysis due to initiating sodium oxybate on the first day of their follow-up period.
ASD, absolute standardized difference; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; OSA, obstructive sleep apnea; PS, propensity score; REM, rapid eye movement; SD, standard deviation; SXB, sodium oxybate.

- Of 118 million total patients in the MarketScan database, 954 and 1908 were included in the SXB and matched control cohorts, respectively
- After 1:2 PS matching, baseline balance was achieved

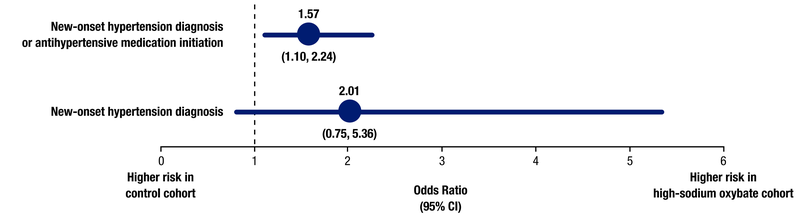
Figure 1. Results of Main Analysis: Elevated Odds Ratios in Patients With Narcolepsy Treated With High-Sodium Oxybate



A multivariable logistic regression model to estimate ORs and corresponding 95% CIs included all covariates used in the calculation of the propensity score as independent variables.
CI, confidence interval; OR, odds ratio.

- Risk of the composite endpoint (new-onset hypertension diagnosis or antihypertensive medication initiation) was higher in the SXB cohort (6.60 per 100 patients) than in the control cohort (4.20 per 100 patients), with a 61% increased odds of new-onset hypertension or antihypertensive medication initiation in the SXB cohort (OR=1.61; 95% CI, 1.15–2.27)
- Risk of new-onset hypertension diagnosis was numerically higher in the SXB cohort (0.94 per 100 patients) than in the control cohort (0.52 per 100 patients), with an 81% increased odds of new-onset hypertension diagnosis in the SXB cohort (OR=1.81; 95% CI, 0.73–4.46)

Figure 2. Results of Sensitivity Analysis Excluding Patients With CVD at Baseline: Elevated Odds Ratio in Patients With Narcolepsy Treated With High-Sodium Oxybate



A multivariable logistic regression model to estimate ORs and corresponding 95% CIs included all covariates used in the calculation of the propensity score as independent variables.
CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio.

- In the sensitivity analysis, which excluded patients with a history of CVD, a total of 900 and 1798 patients in the SXB and matched control cohorts, respectively, were included
- Risk of the composite endpoint was higher in the SXB cohort (6.22 per 100 patients) than in the control cohort (4.06 per 100 patients), with a 57% increased odds of new-onset hypertension diagnosis or antihypertensive medication initiation in the SXB cohort (OR=1.57; 95% CI, 1.10–2.24)
- Risk of new-onset hypertension diagnosis was numerically higher in the SXB cohort (0.89 per 100 patients) than in the control cohort (0.44 per 100 patients); the odds of new-onset hypertension diagnosis in the SXB cohort was twice that of controls (OR=2.01; 95% CI, 0.75–5.36)

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Support and Acknowledgments: This study was supported by Jazz Pharmaceuticals. Under the direction of the authors, Diana Arper, MSc and Joseph Mansonet, MPH of Peloton Advantage, LLC, an OPEN Health company, provided medical writing and editorial support for this poster, which was funded by Jazz Pharmaceuticals.
In memoriam of Michael N. Cook, a former Jazz Pharmaceuticals employee who passed during the development of this poster.

Disclosures: RH Ben-Joseph and **R Saad** are former full-time employees of Jazz Pharmaceuticals who, in the course of their employment, received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **VK Somers** and **RB D'Agostino, Jr.** provide paid consulting services to Jazz Pharmaceuticals. **J Black** is a part-time employee of Jazz Pharmaceuticals and shareholder of Jazz Pharmaceuticals plc. **M Davis, W Macfadden,** and **W Ni** are full-time employees of Jazz Pharmaceuticals who, in the course of their employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **KE Mues, C Jackson, J Pitino, H Latimer,** and **EC Dabrowski** are full-time employees of Aetion, Inc. and hold stock options or equity in Aetion. **WB White** is a cardiovascular safety consultant to Jazz Pharmaceuticals, plc.

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The 75th Annual Meeting of the American Academy of Neurology (AAN); April 22-27, 2023; Boston, MA