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Hypertension Onset Among Narcolepsy Patients Newly Treated With Sodium Oxybate

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Introduction

- Narcolepsy is a rare hypersomnolence disorder that requires long-term pharmacologic treatment[1]
- 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 in narcolepsy[2,3]
  - Sodium oxybate is a high sodium–containing drug and contains a warning in its FDA-approved labeling due to its high sodium content[3]
- The relationship between excess sodium intake and increased risk of hypertension, stroke, and cardiovascular disease is well established[4-6]

Objective

- This exploratory study compared the intermediate-term risk (ie, within 180 days) of incident hypertension among normotensive patients with narcolepsy newly treated with sodium oxybate versus comparable patients with narcolepsy not treated with sodium oxybate (controls)

Methods

- IBM® MarketScan® claims from January 2014 to February 2020[7] were analyzed
- Patient selection criteria included the following:
  - Sodium oxybate (SXB) cohort: Adults (≥18 years of age) with continuous insurance coverage (allowing up to 30-day gaps) 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 sodium oxybate
  - Control cohort: Adults (≥18 years of age) with continuous insurance coverage (allowing up to 30-day gaps) 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 claim for hypertension or use of antihypertensive medication within 13 months prior to cohort entry
- SXB and control cohorts were 1:2 propensity score (PS) matched to balance clinical and demographic characteristics at cohort entry date
- Outcomes of hypertension diagnosis and a composite of hypertension diagnosis or a new prescription for an antihypertensive were assessed
- Patients were followed for 180 days or until first occurrence of the outcome, discontinuation of sodium oxybate in the SXB cohort, or exposure to sodium oxybate in the control cohort

Results

- Of 118 million total patients in the database, 954 and 1908 were included in the SXB and matched control cohorts, respectively. Mean (standard deviation [SD]) age was 35 (12) years and most were female (67%)

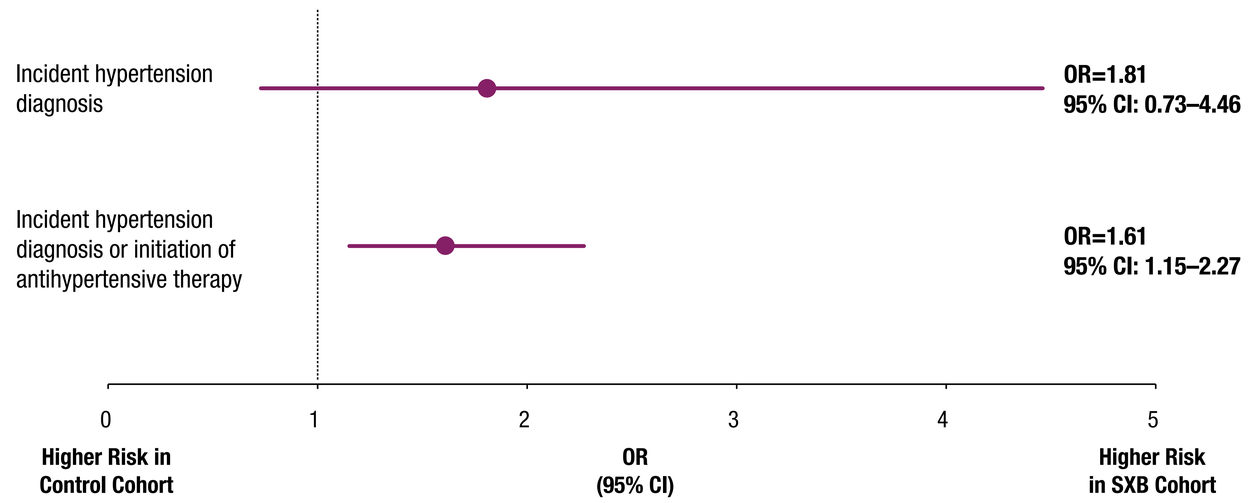
Table 1. Select Baseline Characteristics Before and After Propensity Score Matching

	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	10,890		954	1908[c]	
Demographics						
Age, years, mean (SD)	34.48 (11.59)	37.18 (13.28)	0.216	34.85 (11.66)	35.12 (12.33)	0.023
Female, n (%)	738 (67.77)	6897 (63.33)	0.093	641 (67.19)	1269 (66.51)	0.014
Select comorbidities, n (%)						
Sleep apnea	419 (38.48)	2592 (23.80)	0.321	334 (35.01)	699 (36.64)	0.034
Narcolepsy type 1	376 (34.53)	1215 (11.16)	0.580	253 (26.52)	495 (25.94)	0.013
History of CVD	48 (4.41)	409 (3.76)	0.033	37 (3.88)	85 (4.45)	0.029
Diabetes diagnosis	45 (4.13)	592 (5.44)	0.061	38 (3.98)	80 (4.19)	0.011
Treatment						
Use of CPAP machine, n (%)	122 (11.20)	879 (8.07)	0.106	95 (9.96)	205 (10.74)	0.026
Use of alerting agents, n (%)	587 (53.90)	3926 (36.05)	0.365	476 (49.90)	974 (51.05)	0.023
Outpatient visits, mean (SD)	29.99 (35.51)	23.45 (29.71)	0.200	28.30 (33.67)	27.45 (33.38)	0.026

ASD, absolute standardized difference; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; PS, propensity score; REM, rapid eye movement; SD, standard deviation; SXB, sodium oxybate.
[a]PS matching covariates were determined prior to outcome evaluation. The covariates included in the propensity score model were age, gender, region, insurance type, anxiety disorders, cataplexy, history of CVD, coronary revascularization, 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, hyperuricemia, use of alerting agents (wake-promoting agents or stimulants), use of CPAP, outpatient visits, and cohort entry date.
[b]The propensity match is considered adequate if the exposure and referent groups are balanced, with an absolute value of the standardized differences for all baseline factors used to generate the PS less than 0.1. The absolute value is the difference in means of a covariate across the treatment groups, divided by the SD in the treated group.
[c]Two patients were excluded from the control cohort outcome analysis due to initiating sodium oxybate on the first day of their follow-up period.

- After the 1:2 PS matching, the SXB and control cohorts were similar in all key measured baseline covariates

Figure 1. Elevated Odds Ratio for New Onset of Hypertension in Patients With Narcolepsy Treated With Sodium Oxybate



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

- Risk of incident (new) hypertension diagnosis per 100 patients was numerically higher in the SXB cohort (0.94) than the control cohort (0.52; odds ratio [OR]=1.81; 95% confidence interval [CI]: 0.73–4.46)
- Risk of the composite endpoint of either diagnosis of hypertension or initiation of antihypertensive therapy per 100 patients was higher in the SXB cohort (6.60) than the control cohort (4.20; OR=1.61; 95% CI: 1.15–2.27)
- Results remained robust through a series of sensitivity analyses

Conclusions

- This study detected a signal of increased risk of new-onset hypertension in normotensive patients with narcolepsy initiated on sodium oxybate
- These results are consistent with expert global consensus that excess sodium intake is associated with increased blood pressure[8-10]
- Clinicians should consider the cardiovascular risk associated with high-sodium oxybate

Limitations

- The limitations of this retrospective analysis are those inherent with this methodology when applied to orphan conditions
- The study's power was affected by a limited number of eligible patients and events in the database

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