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Review Article

The sodium in sodium oxybate: is there cause for concern?

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ABSTRACT

Sodium oxybate (SO), the sodium salt of γ-hydroxybutyric acid, is one of the primary pharmacologic agents used to treat excessive sleepiness, disturbed nighttime sleep, and cataplexy in narcolepsy. The sodium content of SO ranges from 550 to 1640 mg at 3–9 g, given in two equal nightly doses. Clinicians are advised to consider daily sodium intake in patients with narcolepsy who are treated with SO and have comorbid disorders associated with increased cardiovascular (CV) risk, in whom sodium intake may be a concern. It remains unclear whether all patients with narcolepsy treated with SO should modify or restrict their sodium intake. No data are currently available specific to the sodium content or threshold of SO at which patients might experience increased CV risk. To appraise attributable risk, critical evaluation of the literature was conducted to examine the relationship between CV risk and sodium intake, narcolepsy, and SO exposure. The findings suggest that increased CV risk is associated with extremes of daily sodium intake, and that narcolepsy is associated with comorbidities that may increase CV risk in some patients. However, data from studies regarding SO use in patients with narcolepsy have shown a very low frequency of CV side effects (eg, hypertension) and no overall association with CV risk. In the absence of data that specifically address CV risk with SO based on its sodium content, the clinical evidence to date suggests that SO treatment does not confer additional CV risk in patients with narcolepsy.

1. Introduction

There are substantial data confirming the clinical efficacy and favorable safety profile of sodium oxybate (SO) in patients with narcolepsy [1–14]. "Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin," an American Academy of Sleep Medicine report, designate SO as a standard of care for the treatment of cataplexy and disturbed nighttime sleep based on level 1 evidence [15].

The sodium content of SO at approved nightly doses of 3, 4.5, 6, 7.5, and 9 g is 550, 820, 1100, 1400, and 1640 mg, respectively [16]. The US Food and Drug Administration–recommended SO dose is 6–9 g/d, and approximately one third of patients are treated at the highest dose of 9 g nightly [4,6,16].

Current data do not support a causal relationship between dietary sodium intake and cardiovascular (CV) risk in those with normal blood pressure [17,18]. Many authoritative agencies recommend nearly universal reduction in daily sodium intake to levels <2300 mg/d [19]. However, substantive evidence to support the health benefit rationale behind this universal reduction is lacking [17,20–22]. Moreover, less than 5% of the population consumes sodium at or below this threshold—the average daily sodium intake in the US population is 3600 mg/d—and CV risk has been associated with much higher sodium levels than these recommended guidelines (>6000 mg/d) [23,24].

The clinical implications of sodium intake among patients with narcolepsy treated with SO have not been established. Prescribers of SO are advised to consider daily sodium intake in patients with narcolepsy who have disorders associated with increased CV risk, including heart failure, hypertension, or impaired renal function [16,25]. Questions remain about the need for calibration of sodium intake in narcolepsy management with SO and whether patients receiving SO and their physicians should be mindful of its sodium content [26]. This review examines relevant literature for evidence on CV risk in relation to daily sodium intake and narcolepsy, as well as CV risk in the setting of SO treatment in patients with narcolepsy.

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Abbreviations

AE	adverse event
BP	blood pressure
CPAP	continuous positive airway pressure
CV	cardiovascular
DC	discontinuation
EKG	electrocardiogram
MSNA	muscle sympathetic nerve activity
NR	not reported
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OR	odds ratio
OSA	obstructive sleep apnea
RCT	randomized, placebo-controlled trial
SO	sodium oxybate
US XMSG	US Xyrem Multicenter Study Group
XISG	Xyrem International Study Group

2. Methods

A literature search was performed in the National Institutes of Health/National Library of Medicine PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) using the following search strings: relationship between dietary sodium intake and CV morbidity and mortality ([sodium OR salt] AND [cardiovascular disease OR cardiovascular mortality OR cardiovascular risk]); CV risk factors in patients with narcolepsy ([narcolepsy] AND [comorbidities]) and ([narcolepsy] AND [cardiovascular risk]); CV risks associated with sodium oxybate ([sodium oxybate] AND [cardiovascular]) and ([sodium oxybate] AND [safety] AND [adverse events]). The search was limited to studies published in English and in human subjects. Bibliographies of review articles and meta-analyses identified through these searches were also examined for further pertinent sources. Data were included regardless of publication date up until June 2020. A total of 557 articles were identified, 102 of which were deemed relevant for consideration of inclusion. After careful review of the information included in each of these articles, data from 64 were identified to be of specific relevance for the topic and are included.

3. Results

3.1. Sodium, blood pressure, and cardiovascular risk

Sodium intake is associated with risk of hypertension and cardiovascular outcomes, particularly stroke and myocardial infarction, independent of blood pressure (BP) [27,28]. A number of organizations have recommended that all adults limit sodium intake to <2300 mg/d [19,26,29,30]. The rationale is that this could hopefully reduce these CV risks, and not only for older individuals or those with comorbidities, but for apparently healthy persons as well [19,26,29,30]. However, there is no empiric evidence that reducing sodium intake will reduce CV disease or otherwise improve health outcomes. The Institute of Medicine and the US Agency for Healthcare Research and Quality acknowledge that there is a lack of evidence to support the theory that reducing daily sodium intake to guideline levels reduces CV-related negative health outcomes [31,32]. Sodium, like most dietary nutrients, does not follow a linear but rather a J-shaped relationship to worsening health outcomes [33,34]. Risk of CV disease is increased when sodium intake is <3000 or >6000 mg/d [18,35]. In sum, available evidence suggests that optimal health outcomes are achieved when sodium intake is maintained between 3000 and 6000 mg/d, which is the range consumed by roughly 80% of Americans [24,36].

3.2. Narcolepsy and cardiovascular risk

Heterogeneous data reported across various geographic regions have identified an increased prevalence of CV and cardiometabolic comorbidities in patients with narcolepsy [37–40]. Compared with matched controls, patients with narcolepsy have been found to have an increased risk for “heart diseases” (odds ratio [OR], 2.1, 95% CI, 1.2–3.5; mean age, 46 years) and “diseases of the circulatory system” (OR, 2.6, 95% CI, 2.5–2.8; mean age, 40 years) [37,39]. Specific CV diagnoses that have been reported to be more prevalent in patients with narcolepsy include stroke, myocardial infarction, cardiac arrest, heart failure, hypertension, and hyperlipidemia [37,39]. Obesity and diabetes have been found to be twice as prevalent in patients with narcolepsy (OR, 2.3, 95% CI, 2.1–2.5; OR, 1.8, 95% CI, 1.7–1.8, respectively; mean age, 46 years) [37]. In addition, obstructive sleep apnea (OSA) has been observed to be much more common in patients with narcolepsy, with an OR of 18.7 (95% CI, 17.5–20.0; mean age, 46 years) compared with matched controls [37]. Only one study has looked at the evolution of comorbidities over time in patients with narcolepsy [38]. It was found that over a 14-month observation period, endocrine/metabolic comorbidities remained more prevalent, whereas prevalence of CV comorbid conditions, such as hypertension and hyperlipidemia, decreased to that of matched controls [38]. No study has directly looked at how treatment with SO affects comorbidity prevalence.

Interactions between the orexin/hypocretin system, appetite, energy expenditure, CV autonomic function, and sleep are complex [41]. Increased prevalence of CV and cardiometabolic comorbidities in narcolepsy may be linked to the neuropathophysiology of orexin/hypocretin deficiency [42–48]. Metabolic dysfunction in patients with narcolepsy appears to be independent of body mass index, and CV autonomic dysfunction has been documented in patients with narcolepsy type 1 (NT1), including blunted nocturnal dipping in BP, reduced cardiac vagal modulation, reduced cardiac baroreflex sensitivity, blunted negative heart period trough, decreased sympathetic activation during sleep, and decreased muscle sympathetic nerve activity (MSNA) [39,42,45,46,49]. Although much emphasis has been placed on the nocturnal “non-dipping” phenotype (defined by a BP decrease of <10% during nighttime sleep) in patients with narcolepsy as a predictor of mortality in the general population, the clinical significance of these findings and/or their contribution to CV risk in this population of patients is unclear and conflicting [42,50]. Additionally, ambulatory BP has been observed to be lower in patients with narcolepsy during wakefulness than in control subjects [51].

3.3. Sodium oxybate and cardiovascular risk in patients with narcolepsy

In more than two decades of SO use, neither the sodium content nor any CV risk associated with the sodium content of SO has been established or identified as a therapeutic concern. In clinical trials to date, there were no noted differences in BP between SO treatment and placebo [1,10,12,13,16]. There is only one published record of small increases in BP and MSNA 6 months after initiation of SO (6 g) in a case series of two subjects [52]. In the absence of any noted BP changes from SO studies, adverse event (AE) data from clinical trials can be used to assess CV risk. Randomized, controlled, open-label, and long-term observational studies in the real world and clinical settings, as well as in postmarketing surveillance

Table 1
Cardiovascular system adverse events reported in patients treated with sodium oxybate for narcolepsy: Published safety data.

Study	Type of Study (N)	CV System Event	Patients with Event, n (%)	Related to Study Drug, Y/N	Serious, Y/N	Led to DC, Y/N
US XMSG, 2002 [1]	RCT (n = 136 adults)	None reported	–	–	–	–
US XMSG, 2004 [10]	RCT withdrawal (n = 55 adults)	None reported	–	–	–	–
XISG, 2005 [12]	RCT (n = 228 adults)	None reported	–	–	–	–
XISG, 2005 [13]	RCT (n = 228 adults)	None reported	–	–	–	–
US XMSG, 2003 [3]	Open-label, 12-week extension (n = 118 adults)	Recurrent chest pain with normal EKG	1 (0.9)	N	Y	Y
Mamelak et al., 2015 [6]	Open-label, 12-week (n = 202)	None reported	–	–	–	–
Drakatos et al., 2017 [4]	Observational, 6-year retrospective single-center (n = 90)	Hypertension	1 (1.1)	NR	NR	Y
		"Palpitations"	1 (1.1)	NR	NR	Y
Mayer et al., 2018 [7]	Post-authorization, 10-year surveillance (n = 730)[a]	Hypertension	3 (0.4)	NR	N	Y
		Angina pectoris	2 (0.3)	NR	Y	N
		Cerebrovascular disorder	1 (0.1)[b]	NR	N	N
		Circulatory collapse	1 (0.1)	NR	N	N
Wang et al., 2011 [11,14]	Worldwide surveillance, 2002–2011[c]	Cardiac events	17	NR	NR	NR
		Cerebrovascular accident	6	NR	NR	NR
Plazzi et al., 2018 [8]	RCT withdrawal and open-label titration (n = 106 children; 104 took study drug)	None reported	–	–	–	–

CV, cardiovascular; DC, discontinuation; EKG, electrocardiogram; NR, not reported; RCT, randomized placebo-controlled trial; SO, sodium oxybate; US XMSG, US Xyrem Multicenter Study Group; XISG, Xyrem International Study Group.
[a] 670 patients had narcolepsy type 1, 60 had other diagnoses.
[b] Occurred in a patient with a diagnosis other than narcolepsy type 1.
[c] Includes all patients who received SO via prescription; total n not reported.

studies (Table 1), have been conducted and demonstrated no increased association between SO and CV risk [1,3–7,9–14].

In the pivotal short-term randomized controlled studies conducted in 611 patients with narcolepsy (398 treated with SO and 213 with placebo; age range, 36–48 years), SO was well tolerated with no CV concerns [1,10,12,16,53]. Serious AEs were infrequent, and treatment discontinuations due to AEs related to SO treatment over all studies of varying duration occurred in 10.3% of patients [16,54]. The most frequent AEs associated with SO treatment in studies of adult and pediatric patients were nausea, dizziness, vomiting, somnolence, enuresis, tremor, headache, decreased weight, and decreased appetite [8,54,55]. Most AEs occurred at the start of treatment and decreased with continued treatment [1]. Overall, there were no clinically meaningful changes in vital signs, including BP, which were similar in control and treatment groups [1,10,12,53]. Hypertension was noted on vital sign monitoring in one patient randomized to SO plus modafinil combination therapy; modafinil is known to cause AEs of hypertension [53,56]. Similarly, in a longer 12-week study of open-label SO in 202 patients with narcolepsy, only one patient (0.5%) experienced hypertension, but this was not recorded as an AE [6].

The reporting of CV AEs in observational studies using SO in clinical practice was similar to controlled interventional trials. In a retrospective study constituting 3116 patient treatment-months (most common dose of SO was 9 g in 33% of patients; mean age, 43 years), there was only one patient with an AE of hypertension [4]. In a prospective observational study constituting 800 patient-years of exposure to SO (median dose, 6 g; mean age, 39 years), no specific CV AEs related to SO treatment were reported [7]. Similarly, in SO postmarketing observational surveillance in the United States and European Union from 2002 to 2008 in 26,000 patients (including patients with narcolepsy, insomnia, and fibromylagia), hypertension was reported in 0.4% of patients [11]. There was one fatality attributed to heart attack in a patient with narcolepsy who had concomitant OSA and was noncompliant with continuous positive airway pressure (CPAP) use [11]. Only one study has looked at older patient subpopulations and patients with OSA, and it found the safety profile for patients treated with SO to be similar to that of the patient population as a whole, suggesting no conferred increased risk with age or comorbidity [7].

4. Discussion

We conducted this literature review to determine whether the sodium content of SO, particularly at higher doses, increases CV risk in patients with narcolepsy. Narcolepsy is associated with CV risk factors [37–39]. Obesity, diabetes, OSA, hypertension, and hyperlipidemia have all been shown to be more common in patients with narcolepsy than in the general population, based on uncontrolled data [37–39]. Because dietary sodium has been associated with increased CV risk at extremes of intake (ie, <3000 or >6000 mg/d), it is possible that sodium intake could be of greatest concern in patients with narcolepsy who have comorbidities that predispose individuals for increased CV risk [23,34]. No studies have specifically reported safety profiles for SO-treated patient subgroups with baseline comorbidities that may predispose them to increased CV risk. However, clinical trials examining the use of SO in narcolepsy have not reported specific exclusion criteria for baseline hypertension or other stable medical comorbidities, apart from sleep apnea, which suggests that patients with these underlying conditions may have been included in randomized controlled trials with SO. Examination of clinical trial data from controlled, observational, and post-marketing surveillance studies showed that the incidence of CV AEs, particularly hypertension, is extremely low in patients treated with SO, regardless of age [1,3,4,6–8,10–12,14,53]. SO has been approved in the United States for the treatment of excessive sleepiness and cataplexy in patients with narcolepsy for almost 20 years, and at no time has increased CV risk been identified as a therapeutic issue in the vast majority of patients [16].

Evidence suggests that extremes of sodium intake are associated with increased CV morbidity and mortality in individuals who have clinically significant preexisting risk factors for CV disease as well as for individuals without those risk factors [23,57]. Any sodium-containing drug is an additional contribution to total daily sodium intake [57]. Therefore, sodium intake and SO treatment in patients with narcolepsy who have comorbidities associated with CV risk could theoretically be a cause for concern.

The relationship between sodium intake, BP, and CV risk is complex. Accurate measurement of an individual's sodium intake is difficult because intake varies day to day, and although urinary sodium excretion reflects dietary sodium intake, it does not reflect

plasma sodium levels [35,58]. However, it is possible to determine average intakes for large groups of individuals and therefore it has been possible to compare CV outcomes in groups with different average intakes [36]. When renal function is normal, sodium economy is under neural control [36]. This neural system modulates sodium retention and/or excretion to maintain total body sodium and water balance, upon which human life depends [35,36,58]. Normal total body and plasma sodium levels are maintained over a wide range of daily sodium intake levels [59]. Thus, urinary excretion increases when intake is too high, and decreases when total body stores are deficient [18,35]. Under normal physiologic conditions with intact homeostatic mechanisms, BP is also maintained over a wide range of dietary sodium intake levels [58,60,61]. It is only at extremes of sodium intake that these homeostatic mechanisms become challenged.

The upper limit of sodium intake beyond which increased CV risk is conferred (6000 mg/d) is far higher than guideline levels (<2300 mg/d) [23,26]. The majority of the US population consumes 3600 mg/d, the midpoint of the range associated with optimal health outcomes [24,36]. Currently, there is no supportive evidence that the sodium content of SO, even at the 9-g dose, is a cause for concern for most patients with narcolepsy; no associated CV risk has been found [1,3,4,6–8,10–12,14,53]. Thus, there is no current evidence that treatment with SO increases CV risk or that reducing SO-related sodium intake would alleviate CV risk in patients with narcolepsy. However, there have been no studies that directly examined the effect of dietary sodium intake or urinary sodium levels on CV safety in patients with narcolepsy treated with SO.

Narcolepsy is associated with predisposing CV risk factors of obesity; diabetes; OSA; hypertension; hyperlipidemia; and, to some degree, cardiovascular autonomic dysregulation [37–39]. Although evidence exists to support the notion that narcolepsy is associated with CV and cardiometabolic comorbidities, these studies were largely based on claims data, which inherently lack control for disease severity. Furthermore, the observed high prevalence of OSA, in particular, may be due in part to misdiagnosis of sleep disorders as sleep apnea [37–40]. Increased CV risk associated with any of these comorbidities is attenuated with adequate treatment, including maintaining BP within normal limits, stabilizing blood glucose levels, instituting effective CPAP ventilation, and weight loss [62]. No studies specifically following the evolution of these comorbidities after initiation of SO treatment were identified. In addition, no conclusion can be drawn about the clinical relevance of CV autonomic dysregulation in patients with narcolepsy until further studies are conducted to evaluate effects of narcolepsy medications, obesity, sleep-disordered breathing, periodic limb movements, smoking, and potential differences between NT1 and NT2 on CV autonomic control [51].

It is worth noting that SO treatment has been observed to decrease body weight in both adults and children with narcolepsy [63,64]. It is unclear whether this observed weight loss is because patients may become more active with SO treatment or because of the direct metabolic effect of SO on lipolysis [63,64]. Further research is warranted in this area to determine whether the weight loss observed with SO treatment could potentially contribute to a reduction in overall CV risk [62].

Upon critical evaluation of the existing literature on the topics of sodium intake levels and SO treatment and the hypothetical association with CV risk, we identified several limitations of these data that should be noted. Most notably, no studies have prospectively examined SO treatment on CV outcomes or in subgroups of patients with baseline comorbidities that predispose them to elevated CV risk to evaluate the possible effects of increased sodium load on CV outcomes. Furthermore, the short study period of some pivotal studies (12 weeks) may be insufficient to conclude absence of CV events. Although the multiyear retrospective and surveillance data are more robust and corroborate the lack of evidence of CV AEs with SO treatment, such analyses may introduce recall bias.

5. Conclusions

The use of SO for the treatment of narcolepsy is supported by robust clinical evidence demonstrating its efficacy and safety. Existing evidence does not support a model whereby exposure to SO leads to increased CV risk. Patients with narcolepsy and comorbidities that place them at elevated risk for CV disease should receive appropriate treatment for such comorbidities, as appropriate for any patient without narcolepsy. There is no evidence that, in general, patients receiving SO treatment for narcolepsy should alter or discontinue their therapy because of the sodium content of SO.

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Conflict of interest

AA: Consultant: Avadel Pharmaceuticals; Balance Therapeutics [Idiopathic hypersomnia]; Harmony Biosciences [Narcolepsy]; Eisai Pharma [Insomnia]; Merck Pharmaceuticals [Insomnia].

CK: Consultant: Avadel Pharmaceuticals, Merck & Co., Inc., XWPharma.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.09.017.

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