The Importance of Sodium Reduction in Patients With Narcolepsy

Cardiologist and Sleep Specialist Perspectives

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This white paper reviews the role sodium plays in modifying cardiometabolic and cardiovascular risk present in patients with narcolepsy. It includes important insights from experts in sleep medicine and cardiology who were convened to provide perspectives on cardiometabolic and cardiovascular risk management in patients with narcolepsy and how sodium and other factors play a role in mediating these risks.

Introduction

Narcolepsy is a chronic neurologic condition that requires lifelong management.[1] Although narcolepsy can begin at any age from infancy to older adulthood, symptom onset typically occurs at 15 years old, and there is a smaller peak at approximately 35 years old.[2] It is important for healthcare professionals (HCPs) to consider each patient's medical history, comorbidities, and additional risk factors when prescribing a treatment for narcolepsy.[3] A comprehensive management strategy goes beyond symptom control and takes into account overall long-term health implications of narcolepsy.[1,2,4,5]

"Narcolepsy is a chronic condition. It's not just here for a couple of months. Patients are affected for years and presumably decades. So, long-term health needs to be considered in all management decisions we make for our patients."

– Daniel Barone, MD
Sleep Specialist

"This is not just taking care of our patients' excessive daytime sleepiness and cataplexy. It's caring about the whole patient. We should take preventive measures seriously and counsel our patients appropriately at any age to prevent chronic accumulation of disease burden over time."

– Logan Schneider, MD
Sleep Specialist

Patients with narcolepsy have increased risk of cardiometabolic (CM) and cardiovascular (CV) comorbidities

Research has demonstrated an increased prevalence of certain comorbid conditions, including CM and CV conditions, in patients with narcolepsy compared with matched controls.[6,7]

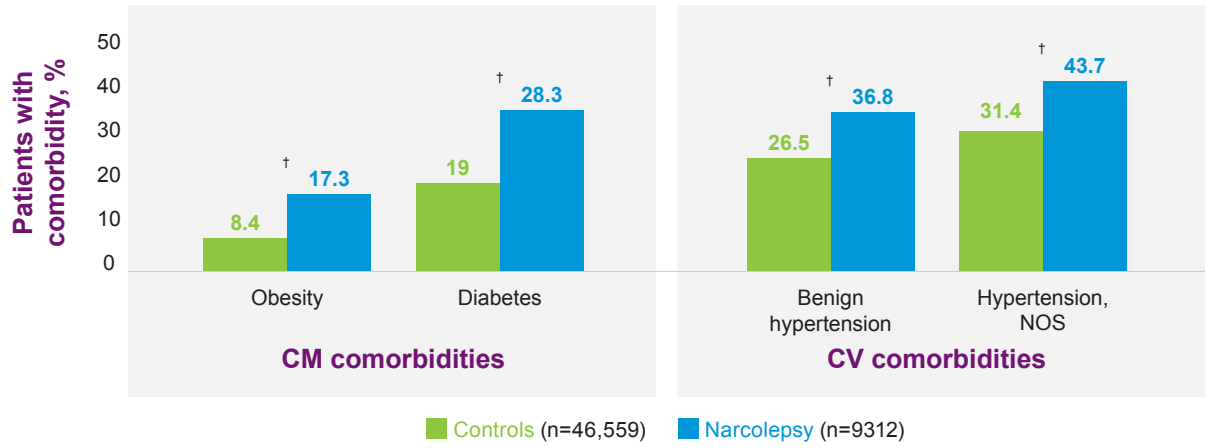
"It's important for anyone who's taking care of a patient with narcolepsy to inform them of the increased risk of cardiovascular disease."

– Akinyemi Ajayi, MD
Sleep Specialist

The Burden of Narcolepsy Disease (BOND) study was a retrospective medical claims data analysis evaluating medical comorbidity patterns in patients with narcolepsy vs controls matched for age, gender, region, and payer. The mean age of participants at baseline was approximately 46 years. Narcolepsy was identified by the presence of at least 1 occurrence of a diagnosis code of narcolepsy with or without cataplexy at any time during the 5-year study interval. Comorbid conditions were defined by diagnosis code and grouped by category using a single-level and multilevel Clinical Classifications Software (CCS). Overall comorbidity was evaluated by comparing the prevalence of 17 CCS multilevel categories between the narcolepsy and control groups. Conditions of interest assigned to heterogeneous CCS categories were analyzed separately by diagnosis codes.[7]

In the BOND study, patients with narcolepsy had claims evidence in the 5-year period suggesting substantially higher comorbidity burden compared with controls, including presence of CM and CV conditions **(Figure 1)**.[7]

Figure 1: *Increased Rates of CM and CV Comorbidities in Patients With Narcolepsy in the BOND Study*[7,*]



BOND, Burden of Narcolepsy Disease; CM, cardiometabolic; CV, cardiovascular; NOS, not otherwise specified.
*The BOND study was a retrospective medical claims data analysis that included a total of 9312 people with narcolepsy (≥18 years of age, continuously insured between 2006 and 2010) and 46,559 matched controls. Controls without narcolepsy were matched 5:1 for age, sex, region, and payer. The objective of the study was to evaluate medical comorbidity patterns in people with narcolepsy.
†P<0.0001 for all comparisons.

CM comorbidities

CM disease comprises a wide array of diseases that typically begin early in life and progress later into conditions that can be identified clinically as metabolic syndrome, prediabetes, type 2 diabetes mellitus, and CV disease (CVD). Metabolic syndrome is defined as a cluster of risk factors for CVD and type 2 diabetes mellitus. It involves elevated blood pressure, dyslipidemia (high triglycerides and low HDL [high-density lipoprotein] cholesterol), high fasting glucose, and central obesity.[8]

In the BOND study, patients with narcolepsy had increased rates of diabetes mellitus (28.3%) compared with controls (19%, P<0.0001) **(Figure 1)**.[7] Interestingly, narcolepsy and type 1 diabetes mellitus share genetic and environmental risk factors, including the HLA-DQB1*0602 allele and mutations in the cathepsin (*CTSH*) gene.[9-11]

Multiple studies have shown that weight gain often coincides with the onset of narcolepsy in adolescence.[12,13] In fact, 60% of patients were reported to gain weight around narcolepsy onset.[14] The BOND study also found that 17.3% of adult patients with narcolepsy had obesity vs 8.4% of controls (P<0.0001) **(Figure 1)**. However, it is important to note that the prevalence of obesity reported in the BOND study in both the control and narcolepsy populations was significantly lower than obesity rates reported by US sources relying on data other than voluntarily reported diagnosis codes. This limitation may exist because obesity is commonly neglected as a coded diagnosis for medical visits in the United States.[7]

"Obesity and cardiometabolic syndromes are more prevalent in patients with narcolepsy, so efforts should be made to remind patients of the importance of weight management, appropriate dietary modifications, and reduced sodium intake."

– Akinyemi Ajayi, MD
Sleep Specialist

Another study by Ohayon evaluated the prevalence of comorbidities in 320 patients with narcolepsy and 1464 participants from the general population matched with the narcolepsy sample for age, gender, and body mass index (BMI). All participants were interviewed by telephone using the Sleep-EVAL system, a computer software specially designed to conduct epidemiologic studies, and administered questionnaires about sociodemographic information and sleep-wake schedule, physical health queries, and questions related to sleep and mental disease symptoms. This study showed that hypercholesterolemia, another CM abnormality, was among 5 diseases whose frequency was greater (at a statistically significant level) in patients with narcolepsy after adjusting for age and sex. Specifically, hypercholesterolemia was present in 10.3% of patients with narcolepsy, compared with 6.8% in the general population (P<0.05).[6]

"Many cardiometabolic comorbidities are risk factors that we're trying to manage to mitigate future CV events like heart failure, stroke, and heart attack. We need to take a look at the entire patient and make sure these things are under control."

– Logan Schneider, MD
Sleep Specialist

CV comorbidities

The BOND study found that CVD occurred at higher rates in the narcolepsy group compared with the control group, including hypertension not otherwise specified (43.7% vs 31.4%, narcolepsy vs controls) and benign hypertension (36.8% vs 26.5%) **(Figure 1)**.[7] A separate study by Ohayon (described above) also observed hypertension more frequently in patients with narcolepsy compared with a matched general population sample after adjusting for age and sex (19.2% vs 14.7%; adjusted odds ratio [AOR] [95% CI], 1.32 [1.02-1.70], P<0.05).[6] Hypertension is related to CM disease and is often associated with metabolic disorders, including insulin resistance, obesity, and dyslipidemia.[8]

"Based on data, it's reasonable for sleep specialists to highlight cardiovascular risks when counseling patients with narcolepsy. Don't forget to cover the basics, like blood pressure and weight. These are simple yet powerful parameters."

– Younghoon Kwon, MD
Cardiologist and Sleep Specialist

It is well established that hypertension is one of the major modifiable risk factors for CVD. Short-term consequences of hypertension may include stroke, coronary heart disease, heart failure, and CV death. However, long-term consequences of high blood pressure should not be overlooked, as they may include hypertensive cardiomyopathy, heart failure with preserved ejection fraction, atrial fibrillation, valvular heart disease, aortic syndromes, and peripheral arterial disease, among others.[15]

"We're all in the job of primary prevention. Nutrition, managing obesity, caloric excess, exercise, good sleep hygiene, etc. It's just a part of the broader discussion around well-being for patients with narcolepsy."

– Roy Artal, MD
Sleep Specialist

CV events

An increased prevalence of CM and CV comorbidities, including obesity, diabetes, hypercholesterolemia, and hypertension, may partially explain increased rates of CV events in patients with narcolepsy.[6,7,16] The BOND study demonstrated this relationship, showing that in a population with a mean age of 46 years, the odds [95% CI] of certain CV events were higher in patients with narcolepsy compared with matched controls, including stroke (2.5 [2.3-2.7], *P*<0.0001), myocardial infarction (1.6 [1.3-1.8], *P*<0.0001), cardiac arrest (1.6 [1.1-2.3], *P*=0.326), and heart failure (2.6 [2.3-2.9], *P*<0.0001).[7]

> "Sometimes I hear that modifying risks in young people doesn't matter. But young people grow up to be older people who have more of these risks and conditions. Sitting down and talking to our patients with narcolepsy about risk is something we need to do, even early on."
>
> **– W. Christopher Winter, MD**
> Sleep Specialist

Additionally, a separate retrospective medical claims analysis (CV-BOND) showed an increased incidence of CV events in even younger patients with narcolepsy (mean age of 38 years) when compared with matched controls. Controls were matched to patients with narcolepsy by calendar date of cohort entry, age, sex, US geographic region, and insurance type.[17]

Figure 2: *Increased CV Events in Patients With Narcolepsy in the CV-BOND Study*[17,*]

Mean age of study participants = **38 years**

Adapted from Ben-Joseph RH et al. *Sleep*. 2023. Published online ahead of print June 12, 2023. doi:10.1093/sleep/zsad161. Available under a Creative Commons Attribution 4.0 License (https://creativecommons.org/licenses/by/4.0/legalcode.en#).
CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiac event.
*The CV-BOND (Cardiovascular BOND) study was a retrospective medical claims analysis designed to estimate the incidence of cardiovascular or renal comorbidities or events in adult patients with narcolepsy in the United States between January 1, 2014, and June 30, 2019. Eligible patients were 18 years of age and older with continuous medical and prescription coverage. Patients without narcolepsy were matched 3:1 to patients with narcolepsy by calendar date of cohort entry, age, gender, US geographic region, and insurance type.

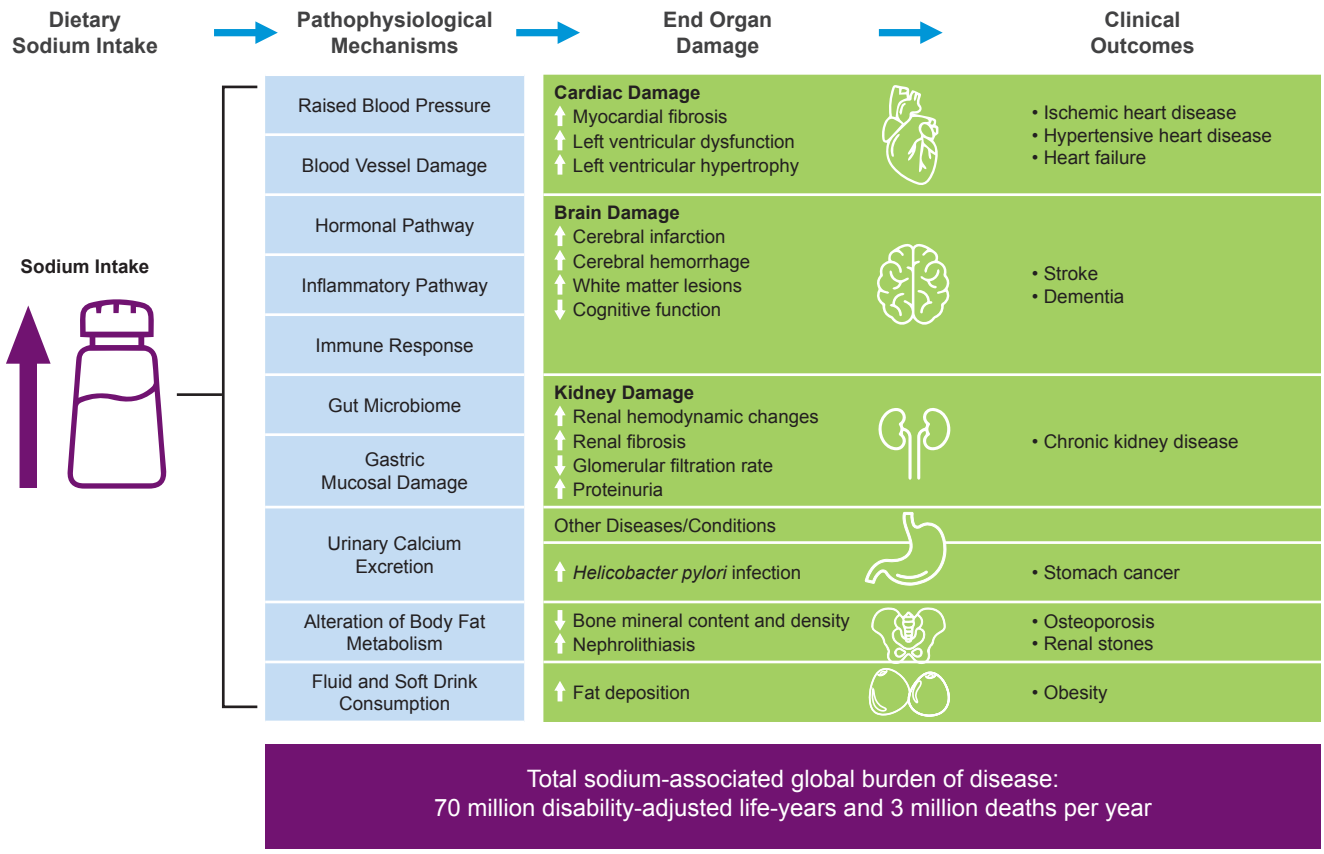
At baseline, patients with narcolepsy (n=12,816) had more comorbidities compared with controls (n=38,441), including diabetes or diabetes/obesity medication, hyperlipidemia, and prior CVD (*P*<0.001 for all comparisons). During the follow-up period of the CV-BOND study, patients with narcolepsy demonstrated a greater risk for new-onset CV events, including any stroke; heart failure; ischemic stroke; major adverse cardiac event (MACE); grouped instances of stroke, atrial fibrillation, and edema; and CVD (grouped instances of stroke, atrial fibrillation, heart failure, and myocardial infarction) **(Figure 2)**.[17]

Sodium intake is a modifiable risk factor for CV and CM disease

Sodium is a modifiable risk factor for CV and CM disease.[18] In fact, elevated dietary sodium intake can have widespread effects on the body and may contribute to disease development over time **(Figure 3)**.[19]

> "Excessive sodium is not good for us on multiple levels, whether it's our cardiovascular health or other areas of health."
>
> **– Roy Artal, MD**
> Sleep Specialist

Figure 3: *Elevated Dietary Sodium Can Have Widespread Effects on the Body and Contribute to Disease Development Over Time*[19]

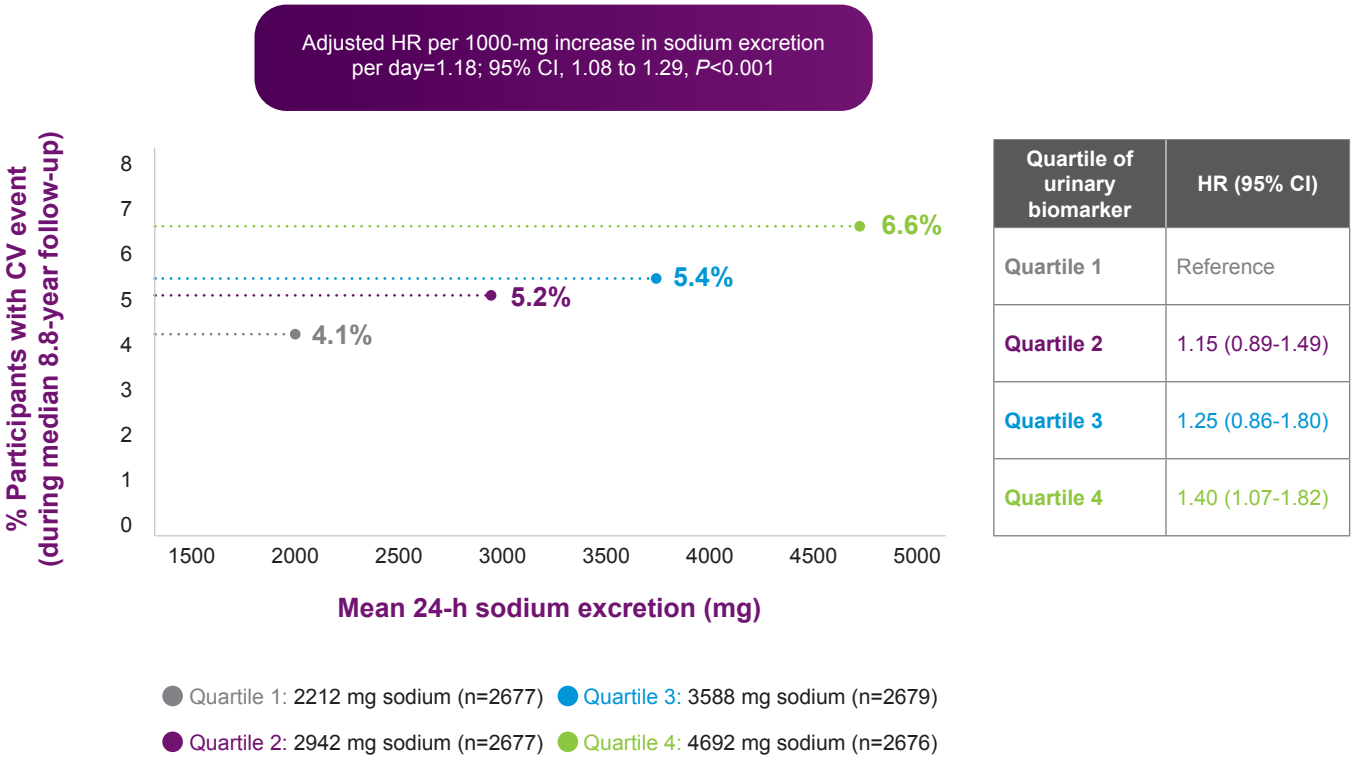


Adapted from *Journal of the American College of Cardiology*, Vol 75, He FJ et al, Salt Reduction to Prevent Hypertension and Cardiovascular Disease, 632-647, © 2020, with permission from Elsevier.

Several randomized, controlled studies have shown the impact of dietary sodium on blood pressure and control of hypertension. Among them, the Dietary Approaches to Stop Hypertension (DASH)-Sodium study had 412 prehypertensive individuals consume 3 different diets with various sodium content for 30 days. The 3 sodium levels were defined as high (a target of 150 mmol per day with an energy intake of 2100 kcal, reflecting typical consumption in the United States), intermediate (a target of 100 mmol per day, reflecting the upper limit of national recommendations at the time of the study) and low (a target of 50 mmol per day, reflecting a level hypothesized to produce additional lowering of blood pressure). They found a dose-dependent relationship between sodium consumption and blood pressure regulation in which higher sodium intake led to decreased blood pressure regulation.[20] Reduction of salt intake for longer than 30 days was also found to have a positive linear effect on blood pressure regulation in people with and without hypertension.[21]

A recent meta-analysis of 10,709 participants from 6 prospective cohort studies across the United States and Europe examined the association between 24-hour sodium secretion and the risk for CVD. In this study, multiple 24-hour urine samples, the most accurate method for assessing sodium intake, were obtained for each participant. Each daily increment of 1000 mg in sodium excretion was associated with an 18% increase in CV risk **(Figure 4)**. In addition, there was a 24% increase in CV risk for each unit increase in the sodium-to-potassium ratio. These associations were consistent regardless of age, sex, baseline hypertension, weight status, and years of follow-up, highlighting that sodium intake is associated with CV risk in a dose-response manner, with a daily sodium intake of approximately 2000 to 6000 mg.[22]

Figure 4: *Rates of CV Events Based on Amount of Urinary Sodium Excretion (N=10,709)*[22,*]



Quartile of urinary biomarker	HR (95% CI)
Quartile 1	Reference
Quartile 2	1.15 (0.89-1.49)
Quartile 3	1.25 (0.86-1.80)
Quartile 4	1.40 (1.07-1.82)

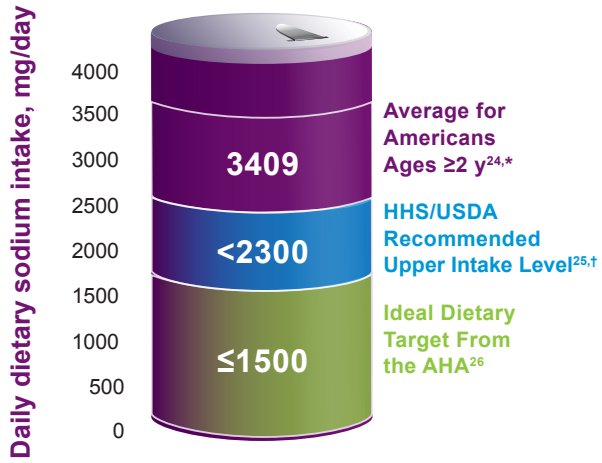
CV, cardiovascular; CVD, CV disease; HR, hazard ratio; DASH, Dietary Approach to Stop Hypertension.
*A meta-analysis of individual-participant data from 6 prospective cohorts of generally healthy adults. Sodium excretion was assessed with the use of at least 2 24-hour urine samples per participant. The primary outcome measure was a CV event, including coronary revascularization or fatal or nonfatal myocardial infarction or stroke. Hazard ratios were estimated from models adjusted for potential confounding factors, including age, sex, race, educational level, height, body mass index, smoking status, alcohol consumption, physical activity, history of diabetes and elevated cholesterol status, family history of CVD, 24-hour urinary potassium excretion, total energy intake, and modified DASH diet quality score.

It has been projected that a population-wide reduction in dietary sodium of 1200 mg of sodium per day would reduce the annual number of new cases of coronary heart disease by 60,000, stroke by 32,000, and myocardial infarction by 54,000, and the annual number of deaths from any cause by 44,000. However, even a more modest reduction of 1000 mg of sodium per day is projected to result in large declines in annual rates of CV events and deaths. Importantly, a nationwide effort to reduce sodium intake by 3 g per day would result in an estimated annual savings of up to $24 billion in healthcare costs, underscoring the importance of reducing sodium intake in the United States.[23]

Sodium intake in the United States

In the United States, the intake of sodium, primarily consumed as sodium chloride (NaCl), is generally above the threshold recommended by medical organizations and governmental agencies. The data collected as part of the National Health and Nutrition Examination Survey (NHANES) in 2013-2014 show that Americans (aged ≥2 years) consume approximately 3409 mg of sodium per day on average.[24] This far exceeds the upper limit of 2300 mg per day recommended by the US Department of Health and Human Services (HHS) and the US Department of Agriculture (USDA), as well as the 1500 mg per day ideal sodium intake target endorsed by the American Heart Association (AHA).[18,25,26] Among hypertensive adults, 86% exceed 2300 mg of dietary sodium per day **(Figure 5)**.[18]

Figure 5: *Sodium Intake in the US Exceeds the Recommended Upper Intake Limit*



*Based on 2013 to 2014 NHANES data from 8067 participants aged ≥2 years.[24]
†For people aged ≥14 years.[25]

In 2021, recognizing the impact of dietary sodium on diseases like hypertension and CVD, the US Food and Drug Administration (FDA) released voluntary guidance for industry regarding sodium content in commercially processed, packaged, and prepared foods. The guidance has a short-term goal of helping Americans to reduce their average sodium intake by 12% over 2.5 years, and it plans for further iterative reductions in the future.[27]

In addition to food and drink, sodium in both prescription and over-the-counter medications can contribute to patients' total daily sodium intake.[24,28] Although no FDA guideline exists, according to the European Medicines Agency (EMA), high-sodium–containing drugs (ie, ≥391 mg sodium) can add considerably to an individual's daily sodium intake.[28]

"We speak with our patients about blood pressure, pulse, and comorbid conditions that can increase those metrics and, in turn, increase cardiovascular risk. When we think through what medicines we will prescribe, we're also thinking about how those medications impact these cardiometabolic factors."

– Vikas Jain, MD
Sleep Specialist

"Most physicians recognize that dietary consumption of sodium is very high. We need to emphasize that sodium is not just coming from diet."

– Younghoon Kwon, MD
Cardiologist and Sleep Specialist

CV health is impacted by a combination of risk factors

Limiting excess sodium intake is important for everyone, including patients with narcolepsy. However, some people may have risk factors that contribute to a greater urgency around sodium reduction. In addition to sodium intake, there are several other modifiable risk factors for CV health that can also contribute

to risk. The AHA parameters for improving and maintaining CV health, formerly the "Simple 7," recently added sleep health to become "Life's Essential 8."[29] AHA President Dr Donald Lloyd-Jones explained that this update was because "sleep is related to every single one of the other seven elements—it's closely tied to weight, blood pressure, glucose metabolism, what we choose to eat."[30]

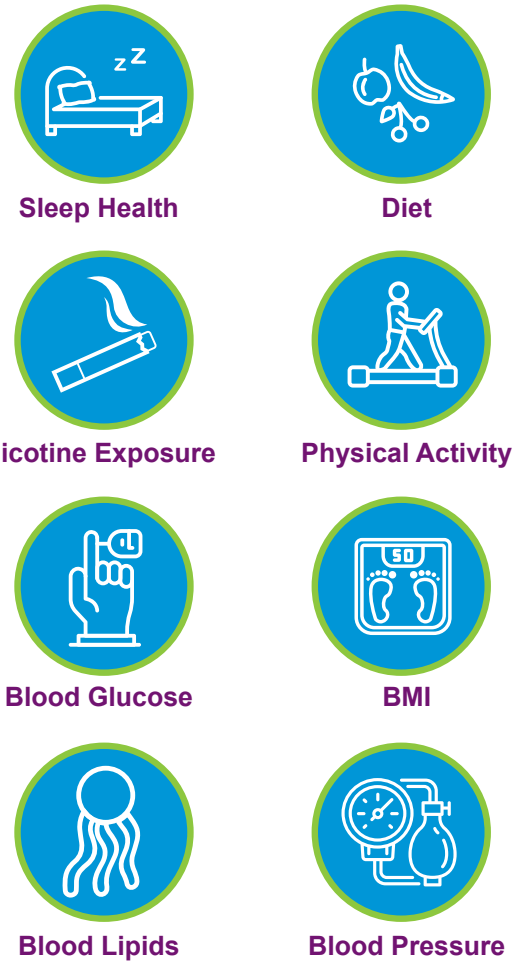
> "The fact that sleep has been included in the AHA Essential 8 gives recognition to the fact that we, as sleep specialists, are one part of overall health management. We shouldn't be too narrow in our management or care of our patients. There are healthy life factors that they need to account for in order to reduce their cardiovascular risk and prevent those long-term consequences."
>
> **– Logan Schneider, MD**
> Sleep Specialist

"Life's Essential 8" also includes diet, physical activity, nicotine exposure, BMI, blood lipids, blood glucose, and blood pressure **(Figure 6)**.[29] Staying healthy along these 8 essential parameters promotes CV health,[29] and they work in conjunction with each other. Patients with unhealthy levels in one or more of these parameters may require additional counseling about the urgency for sodium reduction.

Some risk factors, such as a high-fat diet, hypertension, and obesity, often co-occur and impact one another. The prevalence of obesity-related CVD is increasing and greatly compounds the likelihood of CM multimorbidity.[31] For example, a high-fat diet or obesity can lead to hypertension in a positive feedback loop of the renin-angiotensin system and sympathetic nervous system.[32]

A cohort study of almost 20,000 adults in Chicago with 22 years of follow-up found that when 2 or 3 of the top health risk factors were present (high cholesterol: serum cholesterol ≥200 mg/dL [≥5.2 mmol/L]; hypertension: elevated systolic and diastolic blood pressure [≥120/80 mm Hg]; and cigarette smoking), men and women had marked increases in the relative risk of coronary heart disease, CVD, and all-cause mortality. The study also suggested that risk factors often occur in combination, not in isolation.[33] Discussion and evaluation of all known modifiable risk factors are therefore necessary to provide a detailed total CVD and metabolic risk-status profile and ensure appropriate treatment of each factor within the context of a multifactorial, global approach to prevention of CV and CM diseases.[34]

Figure 6: *Life's Essential 8 — AHA-Recommended Metrics for Measurement and Quantitative Assessment of CV Health*[29]



AHA, American Heart Association; BMI, body mass index; CV, cardiovascular.

"These discussions are part of the long-term conversation we have with patients during follow-up appointments. That's where we can start to introduce smoking cessation, weight management, etc. Is the increased energy you have now that you're not so sleepy all the time translating into more time in the gym, more time being active? That's how I introduce this dialogue over time."

– W. Christopher Winter, MD
Sleep Specialist

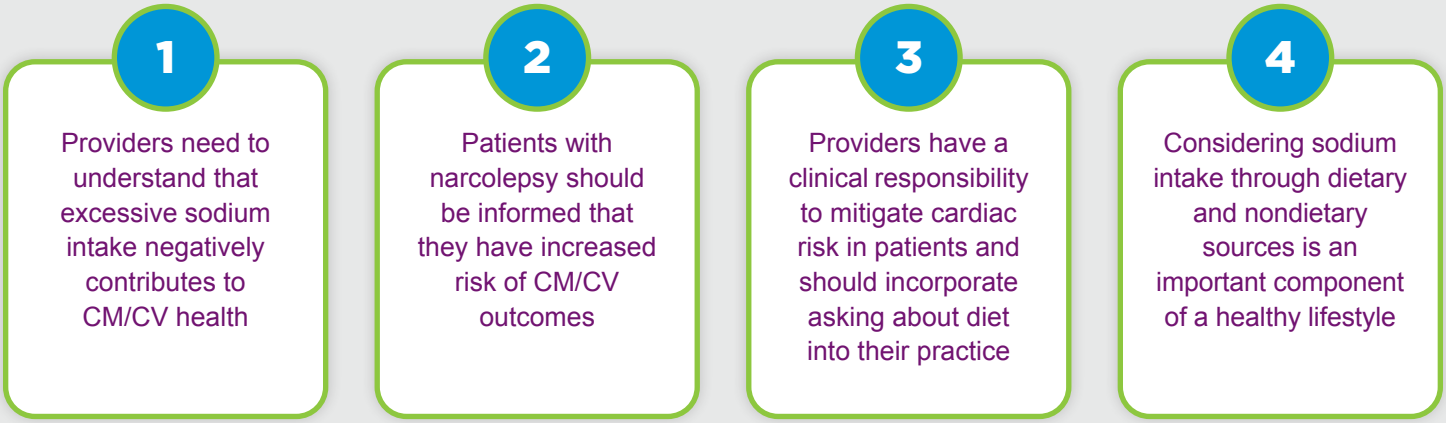
Conclusions

The importance of sodium reduction is increasingly being included in recommendations from leading national and international health organizations, including the AHA and World Health Organization (WHO).[29,35-38] It is important to counsel all patients with narcolepsy on the benefits of sodium reduction.[39] Current comorbidities and additional risk factors should all be considered as additional reasons to lower sodium intake in this patient population.[7,34] In summary, this expert panel provides treaters of narcolepsy with a consensus of key recommendations related to sodium intake **(Figure 7)**.

"Research continues to demonstrate that people with sleep disorders like narcolepsy may face even greater risk for heart disease and stroke than the general population. As the scientific community continues to explore this important topic, it's critical that people with sleep disorders and those who care for them recognize the connection and optimally manage the cardiovascular complications."[40]

– Mitch Elkind, MD, MS, FAHA, FAAN, chief clinical science officer at the American Heart Association

Figure 7: *Key Recommendations for Treaters of Narcolepsy Related to Sodium Intake and CM/CV Health*



CM, cardiometabolic; CV, cardiovascular.

"Emerging data suggest that cardiovascular risk needs to be taken more seriously in patients with narcolepsy. In addition to the narcolepsy itself, its management, types of medication, lifestyle behaviors, and sodium intake can all synergistically impact cardiovascular health."

– Younghoon Kwon, MD
Cardiologist and Sleep Specialist

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