





ORIGINAL RESEARCH

# Cardiovascular Risks in People With Narcolepsy: Expert Panel Consensus Recommendations

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**BACKGROUND:** Observational and retrospective studies suggest that people with narcolepsy may have an increased prevalence of cardiovascular and cardiometabolic comorbidities and may be at greater risk for future cardiovascular events. An expert consensus panel was formed to establish agreement on the risk of hypertension and cardiovascular/cardiometabolic disease in people with narcolepsy and to develop strategies to mitigate these risks.

**METHODS AND RESULTS:** Experts in sleep medicine and cardiology were selected to participate in the panel. After reviewing the relevant literature, the experts identified key elements, drafted recommendation statements, and developed discussion points to provide supporting evidence for the recommendations. The draft and final recommendations were rated on a scale from 0 (not at all agree) to 4 (very much agree). All experts had an agreement rating of 4.0 for all 14 revised recommendation statements for patients with narcolepsy. These statements comprised 3 themes: (1) recognize the risk of hypertension and cardiovascular/cardiometabolic disease, (2) reduce the risk of hypertension and cardiovascular/cardiometabolic disease, and (3) reduce sodium intake to lower the risk of hypertension and cardiovascular disease.

**CONCLUSIONS:** These consensus recommendations are intended to increase awareness of potential cardiovascular/cardiometabolic risks in patients with narcolepsy for all clinicians. Early monitoring for, and prevention of, cardiovascular risks in this population are of great importance, especially as narcolepsy usually develops in adolescents and young adults, who will be exposed to adverse effects of the disease for decades. Prospective systematic studies are needed to determine association and causation of narcolepsy with cardiovascular/cardiometabolic disorders.

**Key Words:** heart disease ■ hypertension ■ narcolepsy ■ sleep ■ sodium

Narcolepsy is a chronic, neurologic sleep/wake disorder characterized by excessive daytime sleepiness, disrupted nighttime sleep, cataplexy (sudden loss of voluntary muscle tone), and symptoms such as sleep paralysis and hallucinations upon awakening (hypnopompic) or falling asleep (hypnagogic) (Figure 1A).<sup>1</sup> People with narcolepsy type 1 (NT1) have cataplexy or very low or absent cerebrospinal fluid orexin levels.<sup>1</sup> NT1 is caused by a loss of the orexin-producing neurons in the hypothalamus.<sup>2</sup> People with narcolepsy type 2 (NT2) do not have cataplexy and

have normal cerebrospinal fluid orexin levels. The underlying pathophysiology of NT2 is unknown.<sup>1</sup>

Observational and retrospective studies suggest that people with narcolepsy (NT1 or NT2) may have a higher-than-average prevalence of cardiovascular and cardiometabolic comorbidities, including obesity, diabetes, dyslipidemia, and hypertension (Figure 1B).<sup>3,4</sup> Additionally, a retrospective cohort study of administrative claims data suggested that people with narcolepsy had higher incidence rates of new-onset cardiovascular events than those without narcolepsy, although

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This manuscript was sent to Peng Li, PhD, Assistant Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 12.

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## CLINICAL PERSPECTIVE

### What Is New?

- Potential cardiovascular and cardiometabolic risks in people with narcolepsy encompass risks related to having the condition of narcolepsy, as well as those related to certain narcolepsy treatments.
- A panel of experts in sleep and cardiology developed consensus recommendations for reducing the risk of cardiovascular and cardiometabolic comorbidities in people with narcolepsy.

### What Are the Clinical Implications?

- All clinicians should increase their awareness of the potential cardiovascular/cardiometabolic risks for people with narcolepsy.
- Behavioral, therapeutic, and dietary strategies are recommended to mitigate these potential risks.

## Nonstandard Abbreviations and Acronyms

<b>AHA</b>	American Heart Association
<b>NT1</b>	narcolepsy type 1
<b>NT2</b>	narcolepsy type 2
<b>SSaSS</b>	Salt Substitute and Stroke Study
<b>TOHP</b>	Trials of Hypertension Prevention

insurance claims database studies are limited in their generalizability<sup>5</sup> and presence of unknown confounding issues could influence the results and conclusions.

While sleep specialists may often be the primary physicians managing narcolepsy, it is also beneficial for primary care providers and non-sleep specialists, including cardiologists, to be aware of the potentially higher cardiovascular risks in this patient population. Narcolepsy typically develops in adolescents and young adults, a group that may not be routinely evaluated for cardiovascular risks. Sleep disruption has been increasingly implicated in elevated blood pressure (BP) and cardiovascular risk,<sup>6,7</sup> suggesting that therapies achieving optimal sleep duration and quality in these patients may be important in improving long-term cardiovascular outcomes. Stimulant medications are common first-line treatments in these young patients, which may, in and of themselves, increase the risk of elevated BP and cardiac arrhythmias (Figure 1B).<sup>8,9</sup> Other treatments used as second-line for cataplexy include selective serotonin reuptake inhibitors and

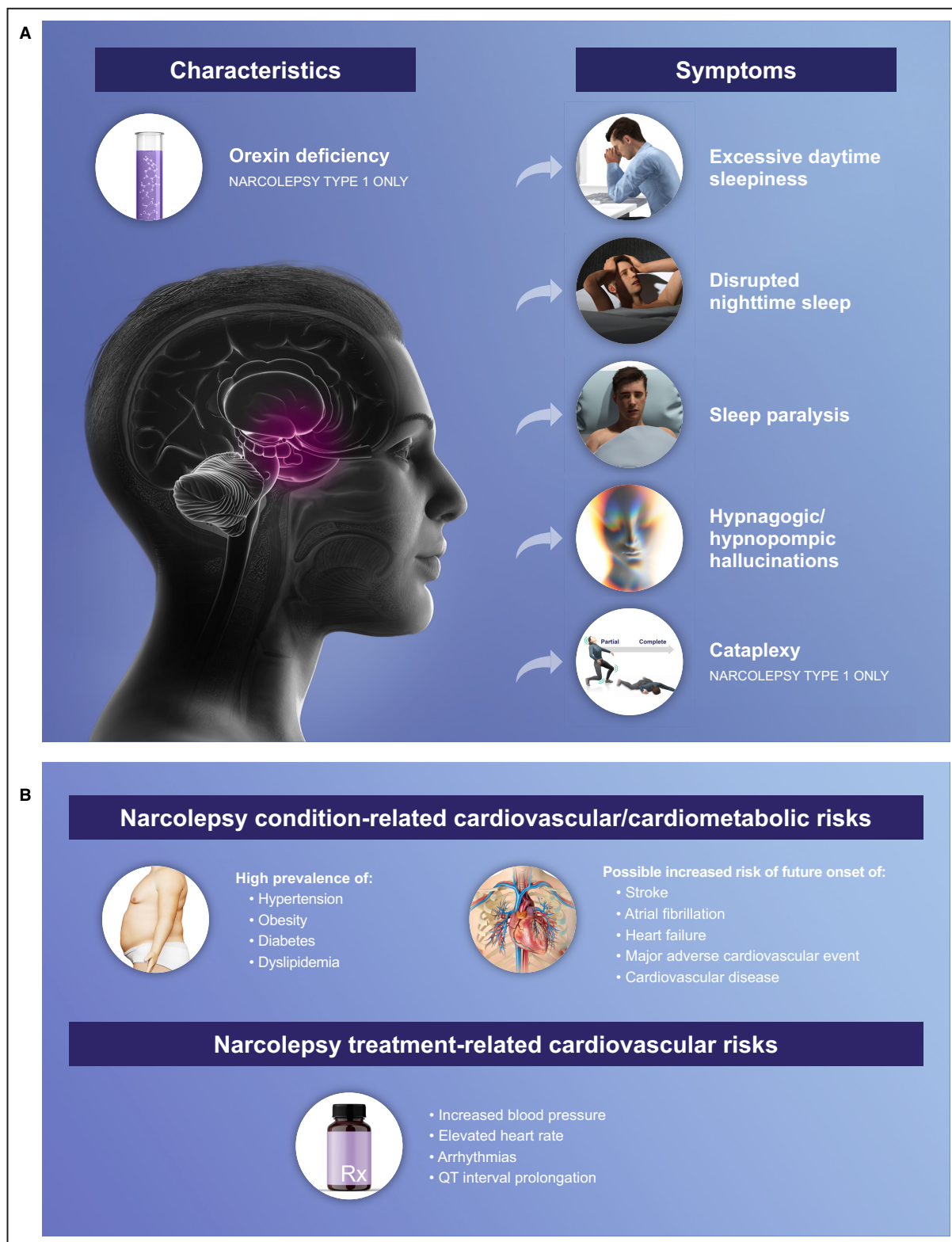
serotonin–norepinephrine reuptake inhibitors,<sup>10,11</sup> which can be associated with cardiac arrhythmias and increased BP.<sup>12–15</sup> Many patients are treated with oxybates, and most formulations (except for low-sodium oxybate<sup>16–18</sup>) contain large amounts of sodium, which may increase cardiovascular risks.<sup>19,20</sup> Because narcolepsy usually develops in teens and young adults,<sup>21</sup> people with narcolepsy have potentially more years of exposure to adverse risk factors (eg, younger-onset obesity and elevated BP<sup>4,22</sup>), which may contribute to a greater lifetime risk of cardiovascular disease compared with people without narcolepsy.

Thus, an expert consensus panel was formed to review the existing evidence and establish agreement on the risk of hypertension and cardiovascular/cardiometabolic disease in people with narcolepsy and to develop strategies to mitigate these risks.

## Possible Mechanisms Underlying a Link Between Narcolepsy and Cardiovascular/ Cardiometabolic Risks

The mechanisms by which any potential cardiovascular/cardiometabolic risks are increased in people with narcolepsy are not well understood. NT1 is caused by orexin deficiency, yet in addition to promoting the waking state, stimulation of orexigenic pathways also increases heart rate, BP, and possibly metabolic rate.<sup>23,24</sup> For example, injection of orexin-A into the dorsomedial hypothalamus increases BP and heart rate, and these responses are attenuated by pretreatment with an orexin receptor 1 antagonist.<sup>24</sup> Similarly, in a recent phase 2 controlled trial, administration of an orexin receptor 2 agonist to patients with NT1 increased BP in 3 of 56 patients, and 24-hour mean heart rate was increased in the higher-dose groups on 2 separate days of treatment.<sup>25</sup> Thus, if orexins increase BP and heart rate, one might expect the opposite effect (ie, reduced cardiovascular/cardiometabolic risk) in people with NT1 who have large reductions in orexin.

However, reduced orexin signaling may indirectly increase BP by fragmenting sleep. People with narcolepsy often have disrupted nighttime sleep, with frequent spontaneous awakenings, as well as a higher prevalence of obstructive sleep apnea (OSA).<sup>3,26</sup> This sleep disruption may increase sympathetic tone, which could result in a nondipping BP pattern at night (defined as a BP decrease of <10% compared with daytime BP),<sup>27</sup> and in the long term contribute to hypertension.<sup>28</sup> Nocturnal nondipping is also associated with greatly increased risk of cardiovascular death.<sup>27,29,30</sup> Increased nighttime arousals have been associated with autonomic dysfunction and hypertension in healthy adult men.<sup>31–33</sup> In addition, preclinical data suggest that sleep fragmentation can worsen atherosclerotic burden. Repeated awakenings in



**Figure 1.** Overview of narcolepsy characteristics/symptoms (A) and potential cardiovascular/cardiometabolic risk factors associated with narcolepsy and narcolepsy treatments (B).

mice resulted in increased food intake, elevated BP, increased infiltration of inflammatory cells in the aortic wall, disruption of elastic fibers in the aorta, and

altered endothelial function.<sup>34</sup> In mice with a genetic predisposition for atherosclerosis, sleep fragmentation increased the size of their atherosclerotic lesions.<sup>35</sup>

Narcolepsy often develops in children and adolescents, though there is often a lag of several years between the appearance of symptoms and diagnosis.<sup>21</sup> When NT1 develops in childhood, rapid weight gain is common, and in adults with NT1, body mass index is 10% to 20% higher than in those without NT1.<sup>22,36</sup> Possible causes of this weight gain include reduced sympathetic tone and a lower metabolic rate, both of which are increased with orexin<sup>23</sup>; but as of yet, there is no clear evidence for reduced sympathetic tone or metabolic rate, or changes in food intake or physical activity in children with NT1.<sup>22</sup> In a mouse model, central administration of orexin-A stimulated food intake<sup>37</sup> whereas an orexin receptor 1 antagonist reduced feeding.<sup>38</sup> However, because orexin increases time awake, the increased food intake could have been in part related to being awake for longer.

Finally, it is possible that cardiovascular/cardiometabolic risks in people with narcolepsy could be elevated by indirect mechanisms, such as lifestyle factors (eg, lack of exercise or poor food choices). Some people with narcolepsy may be too sleepy or fatigued to exercise.<sup>39</sup> Lack of quality sleep has been associated with suboptimal food choices (such as fast food and high-calorie items), although dietary data for people with narcolepsy are sparse.<sup>40,41</sup> Comorbid conditions that are associated with narcolepsy may also increase cardiovascular/cardiometabolic risk. OSA and restless legs syndrome are more prevalent in people with narcolepsy than in those without narcolepsy, per US claims analysis,<sup>3</sup> which may themselves be associated with greater cardiovascular/cardiometabolic risk.<sup>42,43</sup> Psychiatric disorders, such as depression and anxiety, have been reported to have greater prevalence in people with narcolepsy when compared with age- and sex-matched controls from the general population<sup>44,45</sup> or with patients without narcolepsy.<sup>46</sup> Such psychiatric disorders themselves may be associated with an increased risk of cardiovascular disease (CVD).<sup>47,48</sup> A cross-sectional analysis of data from the Behavioral Risk Factor Surveillance System from 2017 to 2020 found that people with depression had 2.3 times higher odds of having CVD, and those without CVD were more likely to have suboptimal cardiovascular health.<sup>49</sup>

## METHODS

The authors declare that all supporting data are available within the article.

### Expert Panel Selection and Meeting Preparation

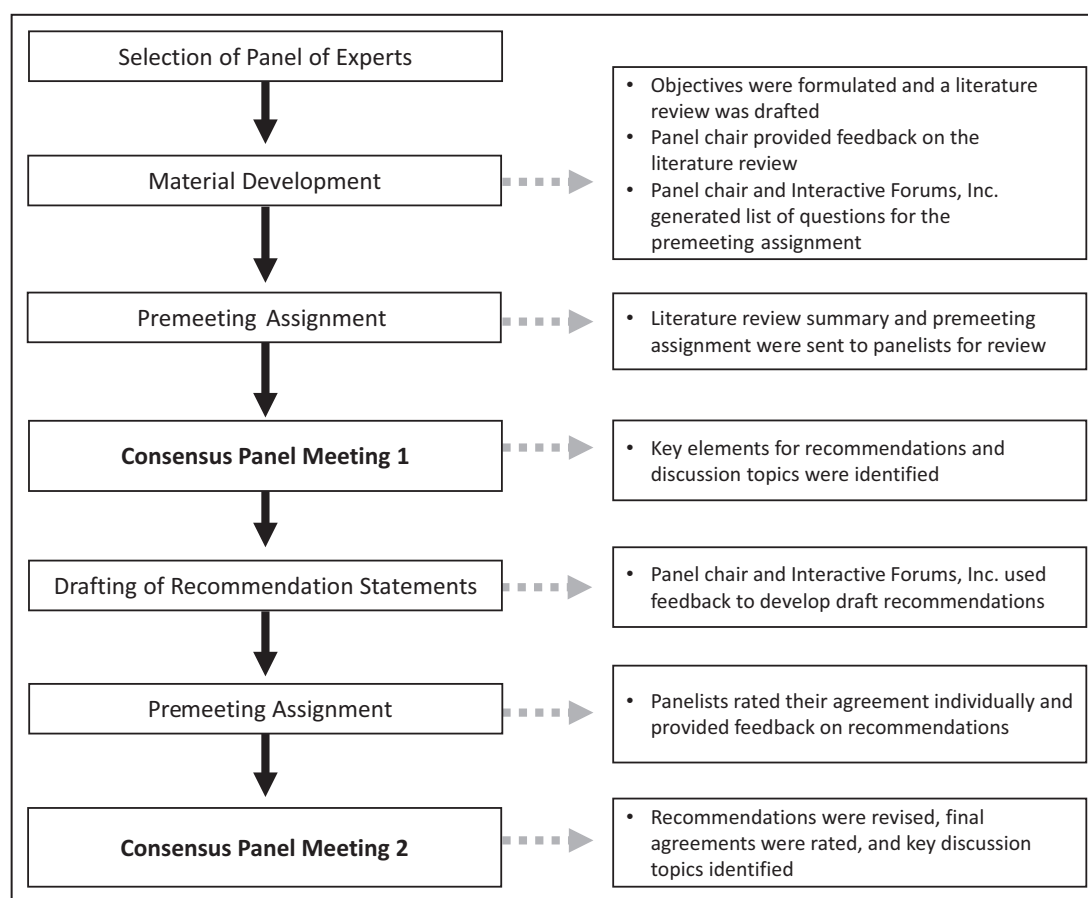
Interactive Forums, Inc., provided centralized oversight of invitations to potential panelists. A total of 14

experts were invited via email, with 8 acceptances (Figure 2). The consensus panel consisted of 4 cardiologists with clinical or research expertise in sleep medicine and 4 sleep medicine specialists with significant interest in cardiology. One was chosen to serve as the panel chair. Selection criteria included publications and congress activity in both cardiology and sleep medicine. Other considerations for panelist selection included recommendations by the panel chair and other panelists and previous advisory board engagement. After approval of each potential panelist for invitation by the panel chair, Interactive Forums, Inc., sent email invitations on the chair's behalf to request panel participation, assess panelists' availability, and determine dates for the consensus panel meetings. Institutional review board approval was not required for this study.

A modified Delphi panel method was used to systematically and quantitatively combine expert opinion and evidence by asking panelists to rate, comment, discuss, revise, and then rerate the panel recommendations over the course of 2 premeeting assignments and 2 meetings. Under the guidance and direction from the panel chair, Interactive Forums, Inc., conducted a narrative literature review to summarize published literature on the risk of developing hypertension and cardiovascular/cardiometabolic disease in people with narcolepsy and potential strategies for risk mitigation. Of note, the initial literature review included the risk of cardiovascular/cardiometabolic disease in people with idiopathic hypersomnia; however, due to the paucity of available evidence in this patient population, consensus recommendation statements were developed only for narcolepsy. The literature review summary and a premeeting assignment were sent to panelists to obtain feedback about their impressions of the strength of published evidence (on a scale from 0 [not at all strong] to 4 [very strong]) and their recommendations to provide guidance to clinicians treating patients with narcolepsy. The survey responses were then collected, reviewed, and organized for presentation at Consensus Panel Meeting 1.

### Development of Recommendation Statements

During Consensus Panel Meeting 1, which was held on February 10, 2023, panelists (n=8) identified key elements for recommendations related to the risk of developing hypertension and cardiovascular/cardiometabolic disease in people with narcolepsy and potential strategies for risk mitigation. These recommendations were condensed into a series of statements that were distributed to the panel in a premeeting assignment before Consensus Panel Meeting



**Figure 2. Flowchart of consensus panel process.**

2. Panelists were asked to rate their level of agreement with each statement on a scale from 0 (not at all) to 4 (very much) and to provide their suggestions to improve the draft recommendation statements. During Consensus Panel Meeting 2, which was held on March 13, 2023, panelists (n=6) discussed and further revised the set of recommendation statements. The panelists also generated ancillary discussion topics of low, medium, and high priority for each recommendation, and all expressed interest in disseminating the recommendations in the form of a published manuscript on reducing the risk of hypertension and cardiovascular/cardiometabolic disease in narcolepsy.

The recommendation statements were made entirely by the expert panel; the panel sponsor (Jazz Pharmaceuticals) was involved only in reviewing each statement to ensure that the guidance provided was consistent with US Food and Drug Administration prescribing information. The consensus protocol was not prospectively registered.

### Strength of Evidence Ratings

The highest level of evidence in support of each statement was rated using the following scale:

A: high-quality evidence from >1 randomized controlled trial (RCT); meta-analyses of high-quality RCTs; ≥1 RCTs corroborated by high-quality registry studies.

B-R (randomized): moderate-quality evidence from ≥1 RCTs; meta-analyses of moderate-quality RCTs.

B-NR (nonrandomized): moderate-quality evidence from ≥1 well-designed, well-executed nonrandomized studies, observational studies, or registry studies; meta-analyses of such studies.

C-LD (limited evidence): randomized or nonrandomized observational or registry studies with limitations of design or execution; meta-analyses of such studies; physiological or mechanistic studies in human subjects.

C-EO (expert opinion): consensus of expert opinion based on clinical experience.<sup>50</sup>

## RESULTS

The agreement rating of all experts for all revised recommendation statements was 4.0 (very much agree) (Table 1). The level of evidence in support of each recommendation statement is shown in Table 2.<sup>51–58</sup>

**Table 1. Consensus Agreement on Recommendation Statements**

Statement number	Recommendation statement	Mean agreement rating*
		Initial, final
1	Recognize the risk of hypertension and cardiovascular/cardiometabolic disease in patients with narcolepsy	3.3, 4.0
2	Reduce the risk of hypertension and cardiovascular/cardiometabolic disease in patients with narcolepsy	3.8, 4.0
3	Reduce sodium intake to lower the risk of hypertension and cardiovascular disease in patients with narcolepsy	3.6, 4.0

\*The experts rated their agreement with each recommendation statement on a scale from 0 (not at all agree) to 4 (very much agree).

## Recommendation 1: Recognize the Risk of Hypertension and Cardiovascular/ Cardiometabolic Disease in Patients With Narcolepsy

### Statement 1a: Consider That Narcolepsy Has Been Linked to Increased Cardiovascular/ Cardiometabolic Risk

Observational and retrospective studies have suggested that patients with narcolepsy may have a greater prevalence of cardiovascular/cardiometabolic comorbidities than those without narcolepsy. A retrospective analysis of a large US insurance claims database from 2006 to 2010 evaluated incidence rates of cardiovascular/cardiometabolic comorbidities for 9312 adults with narcolepsy (NT1 or NT2) and 46559 controls without narcolepsy randomly selected on a 5:1 basis to match patients with narcolepsy by age, sex, geographic region, and payer type (private or Medicare).<sup>3</sup> In this cohort, comorbid hypertension was present in 44% of patients with narcolepsy versus 31% of controls. Patients with narcolepsy also had increased rates of obesity (odds ratio, 2.3 [95% CI, 2.2–2.5] and diabetes (odds ratio, 1.8 [95% CI, 1.7–1.8]). A second analysis of the administrative claims database including 54 million patients in the United States from 2014 to 2019 found that patients with narcolepsy (n=12816) had higher incidence rates of new-onset cardiovascular comorbidities or events compared with controls without narcolepsy (n=38441) matched 3:1 by calendar date of cohort entry, age, sex, US geographic region, and payer type (commercial or Medicare).<sup>5</sup> It is important to note that insurance claim analyses are subject to limitations, such as not capturing data from patients who are uninsured or otherwise lack access to health care, or those who live outside the United States. Additionally, the studies cited here were limited by possible confounding variables, such as disease duration, body mass index, and treatment history, among many

clinical features not captured by this type of database, which may affect the results and conclusions.<sup>59</sup>

Beyond claims analyses, a systematic review and meta-analysis of observational studies of the metabolic profile in people with narcolepsy versus controls found a higher prevalence of hypertension and dyslipidemia in people with narcolepsy.<sup>4</sup> Additionally, a recent Mendelian randomization study (that used variations in single-nucleotide polymorphism data from 460913 individuals from a UK Biobank genome-wide association study) found that narcolepsy was associated with increased risk of heart failure (odds ratio, 1.7 [95% CI, 1.0–2.9];  $P=0.037$ ) and coronary artery disease (odds ratio, 1.7 [95% CI, 1.0–2.9];  $P=0.045$ ).<sup>60</sup>

Still, not all studies support this perspective. In a study of 19 people with NT1, patients with narcolepsy had lower BP and heart rate compared with 19 sex- and age-matched controls.<sup>61</sup> In these patients, heart rate, but not BP, was correlated with cerebrospinal fluid orexin levels; although those with virtually no cerebrospinal fluid orexin had the lowest BP compared with those with the highest orexin levels. Akin to the above, in a clinical study of 50 individuals with NT1, participants had lower daytime diastolic BP, although a greater percentage showed a nondipping BP phenotype at night, compared with 42 healthy controls.<sup>62</sup>

### Statement 1b: Recognize That Patients With Narcolepsy May Have Other Sleep Disorders, Which May Also Increase Cardiovascular/ Cardiometabolic Risk

People with narcolepsy have a higher prevalence of OSA and restless legs syndrome than those without narcolepsy, per US claims analyses.<sup>3</sup> A 2021 scientific statement from the American Heart Association (AHA) established that OSA is associated with increased risk of stroke, heart failure, coronary artery disease, atrial fibrillation, and other arrhythmias.<sup>42</sup> The evidence for the association of restless legs syndrome with increased CVD risk is mixed; some cross-sectional and longitudinal studies demonstrate an increased risk, but others show no increased risk.<sup>43</sup>

### Statement 1c: In Patients With Narcolepsy Without Existing Cardiovascular/ Cardiometabolic Disease, Annually Monitor BP, Weight, and Waist Circumference

Increases in BP may signal developing hypertension. Increased weight or waist circumference may be associated with metabolic syndrome, a constellation of interrelated metabolic risk factors including atherogenic dyslipidemia, elevated BP, and elevated plasma glucose that predisposes patients to the risk of developing atherosclerotic CVD.<sup>51</sup>

**Table 2. Ratings of the Strength of Evidence in Support of Each Recommendation Statement**

Statement number	Statement	Evidence sources	Highest level of evidence*
1a	Consider that narcolepsy has been linked to increased cardiovascular/cardiometabolic risk	Black et al, 2017 <sup>3</sup> Mohammadi et al, 2021 <sup>4</sup> Ben-Joseph et al, 2023 <sup>5</sup>	B-NR
1b	Recognize that patients with narcolepsy may have other sleep disorders, which may also increase cardiovascular/cardiometabolic risk	Black et al, 2017 <sup>3</sup>	B-NR
1c	In patients with narcolepsy without existing cardiovascular/cardiometabolic disease, annually monitor BP, weight, and waist circumference	Grundy et al, 2005 <sup>51</sup>	A
1d	Implement guideline recommendations for screening lipids and glycated hemoglobin A <sub>1c</sub>	US Preventive Services Task Force, 2001 US Preventive Services Task Force, 2021 <sup>52,53</sup>	A
1e	In the setting of conditions such as hypertension, family history of premature cardiovascular disease, diabetes, glucose intolerance, obesity, metabolic syndrome, and OSA, initiate earlier or more frequent monitoring as clinically indicated		C-EO
2a	Educate patients on the association between narcolepsy and cardiovascular/cardiometabolic comorbidities	Black et al, 2017 <sup>3</sup> Mohammadi et al, 2021 <sup>4</sup> Ben-Joseph et al, 2023 <sup>5</sup>	B-NR
2b	Counsel and monitor patients on the AHA's "Life's Essential 8" to obtain optimal sleep duration and quality and implement other lifestyle changes (eg, regular exercise, better food choices, timing of meals, reduced sodium intake, cessation of smoking) to decrease the risk for cardiovascular/cardiometabolic disease	Lloyd-Jones et al, 2022 <sup>54</sup>	A
2c	Sleep clinicians should evaluate for and treat comorbid cardiovascular/cardiometabolic risk factors and conditions in collaboration with primary care, cardiology, endocrinology, sleep medicine, and other relevant specialties		C-EO
2d	Evaluate for and treat comorbid OSA		C-EO
2e	Tailor narcolepsy drug therapy based on the risk for hypertension and cardiovascular disease		C-EO
3a	Educate patients that high sodium intake from diet or medications can increase the risk of hypertension and cardiovascular disease	Wang et al, 2020 <sup>19</sup>	B-NR
3b	Advise patients that reductions in sodium intake may lower their BP and cardiovascular risk	Filippini et al, 2021 <sup>55</sup> Cook et al, 2007 <sup>56</sup> Yin et al, 2022 <sup>57</sup>	A
3c	Provide dietary educational materials (eg, AHA guidelines, DASH diet, WHO recommendations) to aid in reducing sodium intake		C-EO
3d	Advise patients to use a salt substitute (if not contraindicated) and implement a low-sodium diet	Neal et al, 2021 <sup>58</sup>	B-R

AHA indicates American Heart Association; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; OSA, obstructive sleep apnea; RCT, randomized controlled trial; and WHO, World Health Organization.

\*Consensus statements were assigned the highest level of evidence available on the basis of the systematic review. Levels of evidence are defined as follows: A, high-quality evidence from >1 RCT, meta-analyses of high-quality RCTs, ≥1 RCTs corroborated by high-quality registry studies; B-R (randomized), moderate-quality evidence from ≥1 RCTs, meta-analyses of moderate-quality RCTs; B-NR (nonrandomized), moderate-quality evidence from ≥1 well-designed, well-executed nonrandomized studies, observational studies, or registry studies; meta-analyses of such studies; C-LD (limited evidence), randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subjects; C-EO (expert opinion), consensus of expert opinion based on clinical experience.

### **Statement 1d: Implement Guideline Recommendations for Screening Lipids and Glycated Hemoglobin A<sub>1c</sub>**

The US Preventive Services Task Force recommends that men aged >35 years and women aged >45 years undergo routine lipid screening, which should include total cholesterol and high-density lipoprotein cholesterol.<sup>52</sup> For adults under these ages who have other risk factors for coronary heart disease, routine lipid screening is also recommended. The US Preventive Services Task Force also recommends that adults aged 35 to 70 years who are overweight or obese (without diabetes) be screened for prediabetes and

type 2 diabetes by means of measuring fasting plasma glucose or hemoglobin A<sub>1c</sub> levels, or an oral glucose tolerance test.<sup>53</sup>

### **Statement 1e: In the Setting of Conditions Such as Hypertension, Family History of Premature Cardiovascular Disease, Diabetes, Glucose Intolerance, Obesity, Metabolic Syndrome, and OSA, Initiate Earlier or More Frequent Monitoring as Clinically Indicated**

For individuals with these conditions, annual visits to a primary care provider should include monitoring

of modifiable risk factors (eg, smoking, exercise, diet), BP, lipid panel, and resting ECG. Close monitoring for cardiovascular risks may include 24-hour BP monitoring and coronary artery calcium scores. Metabolic syndrome is strongly associated with increased cardiovascular/cardiometabolic disease.<sup>63,64</sup> In addition to hypertension and waist circumference, diagnostic criteria for metabolic syndrome include elevated triglycerides, elevated fasting glucose, and reduced high-density lipoprotein cholesterol.<sup>51</sup> Assessment of these markers may be important to monitoring ongoing risk of CVD in patients with narcolepsy.

Data on elevated cardiovascular/cardiometabolic risk in narcolepsy are mainly from studies in adults; evidence in younger patients is needed to guide cardiovascular risk and narcolepsy management. Patient advocacy groups for people with narcolepsy (Table 3) may provide educational programs that raise awareness about increased cardiovascular/cardiometabolic risks in people with narcolepsy.

## **Recommendation 2: Reduce the Risk of Hypertension and Cardiovascular/ Cardiometabolic Disease in Patients With Narcolepsy**

### **Statement 2a: Educate Patients on the Association Between Narcolepsy and Cardiovascular/Cardiometabolic Comorbidities**

As reviewed in Statement 1a, several analyses of large populations of patients with narcolepsy support the increased prevalence of cardiovascular/cardiometabolic disease compared with people who do not have narcolepsy.<sup>3,4</sup> While these studies have their limitations, and further studies are needed, the association of cardiovascular/cardiometabolic disease in the narcolepsy population should be noted.

### **Statement 2b: Counsel and Monitor Patients on the AHA's "Life's Essential 8" to Obtain Optimal Sleep Duration and Quality and Implement Other Lifestyle Changes (eg, Regular Exercise, Better Food Choices, Timing of Meals, Reduced Sodium Intake, Cessation of Smoking) to Decrease the Risk for Cardiovascular/ Cardiometabolic Disease**

In 2022, the AHA updated "Life's Simple 7" (a construct identifying 7 key components for cardiovascular health) and called this "Life's Essential 8" on the basis of additional knowledge gained during the years since the initial construct.<sup>54</sup> Getting the proper amount of sleep at night is now recognized as an essential component of cardiovascular health.<sup>65</sup> Even relatively small increases in sleep duration can improve health

**Table 3. Advocacy Groups for People With Narcolepsy**

Organization Name	Websites
Project Sleep	<a href="http://project-sleep.com">project-sleep.com</a>
Wake Up Narcolepsy (United States and Canada)	<a href="http://www.wakeupnarcolepsy.org">www.wakeupnarcolepsy.org</a>
Hypersomnia Foundation	<a href="http://www.hypersomniafoundation.org">www.hypersomniafoundation.org</a>
Narcolepsy Network (United States)	<a href="http://www.narcolepsynetwork.org">www.narcolepsynetwork.org</a>
Narcolepsy UK	<a href="http://www.narcolepsy.org.uk">www.narcolepsy.org.uk</a>
European Narcolepsy Network	<a href="http://www.eu-nn.com">www.eu-nn.com</a>
Sleep Disorders Australia	<a href="http://www.sleepoz.org.au">www.sleepoz.org.au</a>

factors related to cardiovascular/cardiometabolic risk. For example, in a study of 22 people with pre-hypertension or hypertension type 1, sleeping for an additional 30 minutes per night was associated with significant reductions in BP.<sup>66</sup> A randomized clinical trial of 80 nonobese individuals showed that extending sleep duration by an average of 1.2 hours per night significantly reduced daily caloric intake compared with those who maintained their usual sleep duration.<sup>67</sup> In a study of 42 people with narcolepsy, cardiopulmonary fitness in an exercise stress test was lower than that of age- and sex-matched controls and was inversely related to sleepiness and cataplexy frequency.<sup>68</sup> Given the importance of lifestyle change as a whole, clinicians should counsel patients with narcolepsy on healthy lifestyle to improve their CV risk profile beyond focusing on pharmacological therapy for narcolepsy.

Nevertheless, from the perspective of medications and sleep, it should be recognized that narcolepsy therapy with stimulants may cause insomnia or difficulty sleeping,<sup>8,9,69</sup> and some oxybate medications may require patients to wake from sleep in the early morning for repeat dosing.<sup>70,71</sup> Both sodium oxybate and low-sodium oxybate require awakening from sleep for the second dose, disrupting sleep in people whose disorder is associated with sleep disruption.<sup>26</sup> In this context, the US Food and Drug Administration recently approved a single-dose, extended-release sodium oxybate for treatment of narcolepsy<sup>72</sup>; this medication has high sodium content similar to conventional, twice-nightly sodium oxybate, but the single dose has the advantage of not requiring a second awakening. People with narcolepsy treated with oxybate have been reported to experience ~42 to 53 arousals and 9 to 38 awakenings each night.<sup>26</sup> Although no studies have directly compared the effects of twice-nightly sodium oxybate or low-sodium oxybate<sup>70,71</sup> with extended-release sodium oxybate,<sup>72</sup> clinical trial data from the individual clinical development programs demonstrate that once-nightly and twice-nightly oxybate regimens are associated with similar improvements in sleep

architecture, stage shifts, arousals or awakenings, and patient-reported sleep quality.<sup>26</sup>

**Statement 2c: Clinicians Should Evaluate for and Treat Comorbid Cardiovascular/ Cardiometabolic Risk Factors and Conditions in Collaboration With Primary Care, Cardiology, Endocrinology, and Other Relevant Specialties**

An interdisciplinary approach to reducing cardiovascular risk could include non-sleep specialists such as nutritionists, nurse practitioners, pharmacists, and other health care providers, in addition to the patient's primary physician. Both the European Society of Cardiology and American College of Cardiology/AHA guidelines on cardiovascular disease prevention emphasize the importance of team-based, patient- and family-centered interventions across several areas of expertise to address key aspects of CVD prevention, including social determinants and risk factor treatment.<sup>73,74</sup> Team-based care has been associated with lower CVD risk in people with hypertension, diabetes, and dyslipidemia.<sup>74</sup>

**Statement 2d: Evaluate for and Treat Comorbid OSA**

Diagnostic testing for OSA typically involves assessing respiratory parameters during sleep in a laboratory equipped for polysomnography or with an at-home testing device.<sup>75</sup> Treatment for OSA can include behavioral measures (eg, weight loss, exercise, avoiding sleeping supine, alcohol abstinence), positive airway pressure, mandibular repositioning devices, and surgery (eg, otolaryngologic or bariatric surgery).<sup>75</sup>

**Statement 2e: Tailor Narcolepsy Pharmacotherapy on the Basis of the Risk for Hypertension and Cardiovascular Disease**

For patients with cardiovascular/cardiometabolic comorbidities, narcolepsy treatment should be selected carefully to avoid further increased cardiovascular risk. The following considerations are important to balancing the risks and benefits of treatment options that may be associated with greater cardiovascular risk.

Stimulants such as methylphenidate and dextro-amphetamine that are commonly prescribed to treat narcolepsy are associated with cardiovascular risks and are accompanied by warnings against use in patients with known cardiac disorders.<sup>8,9</sup> Accordingly, the American College of Cardiology issued a statement in 2015 cautioning against the use of stimulants in patients with arrhythmia and advising that, for patients whose condition may warrant treatment with stimulants, a careful weighing of benefits and risks should

be performed.<sup>76</sup> ECGs are not routinely performed before prescribing stimulants; however, for patients with suspected cardiac disease, obtaining a cardiologist's opinion before prescribing stimulants may be recommended. A 2023 case-control study of individuals with attention deficit/hyperactivity disorder found that longer cumulative duration of methylphenidate use was associated with increased risk of CVD.<sup>77</sup> However, a meta-analysis of observational studies of methylphenidate found no increased risk of stroke, myocardial infarction, or all-cause death, but did find an increased risk of sudden death/arrhythmia (risk ratio, 1.5 [95% CI, 1.0–2.1]; from 6 studies and 1.5 million individuals).<sup>78</sup> Importantly, patients with narcolepsy may be taking stimulants for an extended period because narcolepsy symptoms usually begin in childhood or adolescence and require ongoing management throughout adulthood.<sup>21</sup> Thus, patients should be educated on the cardiovascular risks associated with stimulant treatments. Future longitudinal studies should examine whether patients with narcolepsy taking stimulants for years have an increased risk of CVD.

Pitolisant is a histamine-3 receptor antagonist/inverse agonist used for treating excessive daytime sleepiness and cataplexy in adults with narcolepsy.<sup>79</sup> Although considered generally safe for people with narcolepsy,<sup>80</sup> pitolisant should not be combined with other drugs that may increase the QT interval.<sup>79,81</sup>

Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline, citalopram) and serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine) are used off-label as second-line treatments for cataplexy.<sup>10,11</sup> Some cardiovascular events, including arrhythmias (eg, QT interval prolongation, torsade de pointes), have been observed in people taking selective serotonin reuptake inhibitors.<sup>12–14</sup> Venlafaxine can increase BP.<sup>15</sup>

For some patients, the cardiovascular risks linked to some narcolepsy medications (eg, stimulants and other wake-promoting agents) may be counterbalanced by improving sleep hygiene, which can positively impact cardiovascular health. In addition, improvement in excessive daytime sleepiness brought about by treatment with a stimulant or wake-promoting agent may be associated with a reduction in cardiovascular risk factors that counteracts the inherent cardiovascular risks of the medication. For example, although the wake-promoting agent modafinil has been associated with increased heart rate and BP in healthy adults,<sup>82</sup> a meta-analysis of 6 randomized, placebo-controlled clinical trials of modafinil for the treatment of excessive daytime sleepiness in people with narcolepsy, OSA, and shift-work sleep disorder found no significant changes in these parameters from baseline to final study visit among patients treated with modafinil.<sup>83</sup> Improved sleep from effective narcolepsy treatment may also help restore nocturnal BP dipping.<sup>29,30</sup>

### Recommendation 3: Reduce Sodium Intake to Lower the Risk of Hypertension and Cardiovascular Disease in Patients With Narcolepsy

#### Statement 3a: Educate Patients That High Sodium Intake from Diet or Medications Can Increase the Risk of Hypertension and Cardiovascular Disease

In the general population, sodium intake (such as from sodium chloride [salt]) has been associated with cardiovascular risk. For example, a dose–response meta-analysis of 20 cohort studies found that the risk of CVD increased by 6% for each 1 g of sodium consumed and indicated a linear relationship.<sup>19</sup> According to the US Department of Agriculture *Dietary Guidelines for Americans, 2020 to 2025*, the recommended daily allowance of sodium intake for adults is 2.3 g/day, or 5.75 g of salt (sodium chloride).<sup>84</sup> The AHA further recommends that adults with hypertension and those at increased risk of hypertension should consume no more than 1.5 g of sodium per day.<sup>85</sup> These recommendations may be especially important for patients with narcolepsy on the basis of the increased prevalence of hypertension reported in narcolepsy.<sup>3,4</sup> The average daily sodium intake of people aged >1 year in the United States is 3.3 g (ranging from 2 to 5 g).<sup>84</sup> In 2023, the World Health Organization published a “Global Report on Sodium Intake Reduction” and stated that the target of 30% reduction in global sodium consumption would not likely be reached by 2025, as originally planned.<sup>86</sup> The average daily salt intake worldwide has been estimated at 10.8 g.<sup>86</sup>

In addition to dietary sodium, people with narcolepsy may need to consider the sodium content of their medication. While many medications commonly prescribed for people with narcolepsy do not significantly contribute to daily sodium intake, some sodium oxybate formulations contain large amounts of sodium (Table 4).<sup>70,72</sup>

No studies have yet compared oxybate medications containing high versus low amounts of sodium in terms of cardiovascular/cardiometabolic risks. A literature review concluded that treatment with sodium

oxybate does not confer additional cardiovascular risk in patients with narcolepsy on the basis of its sodium content and the clinical evidence through June 2020.<sup>87</sup> However, the authors acknowledged that the short duration of some pivotal studies may be insufficient to assess cardiovascular risk, and the effects of sodium oxybate treatment on cardiovascular outcomes have not been examined prospectively, nor have they been evaluated in patients predisposed to higher cardiovascular risk.<sup>87</sup> In contrast to the conclusions of the earlier review, a later retrospective analysis of claims data from patients who are normotensive with narcolepsy reported those who initiated treatment with sodium oxybate had an increased risk (odds ratio, 1.81 [95% CI, 0.73–4.46]) of new-onset hypertension compared with patients who did not start sodium oxybate treatment (1:2 propensity score matched on clinical and demographic characteristics).<sup>88</sup> Conversely, several studies have reported no effects of low-sodium oxybate on BP. In a post hoc analysis of phase 3 studies of oxybate-naïve patients with narcolepsy or idiopathic hypersomnia, open-label, low-sodium oxybate treatment for 10 to 14 weeks was not associated with changes in systolic BP.<sup>89</sup> In a real-world study of patients transitioning from sodium oxybate to low-sodium oxybate, among the 18 patients with comorbid hypertension at baseline who completed the study, 10 (56%) reported an improvement in hypertension, 8 (44%) reported no change, and none reported worsening.<sup>90</sup> A clinical trial is currently underway to assess 24-hour BP in patients before and after they switch treatment from sodium oxybate to low-sodium oxybate ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05869773), NCT05869773). Regardless of whether sodium oxybate is associated with a greater risk of hypertension due to its high sodium content, it is noteworthy that both pediatric and adult patients with NT1 have lost weight when treated with sodium oxybate,<sup>91–94</sup> as have adult patients with NT1 when treated with low-sodium oxybate.<sup>95</sup> By decreasing body weight, it is conceivable that oxybate treatments could reduce BP and other cardiovascular risk factors that are associated with overweight in certain people.<sup>96</sup>

Among people who are salt sensitive, increased salt intake is associated with increased BP,<sup>97</sup> and salt sensitivity tends to increase with advancing age.<sup>97</sup> A recent prospective study of 213 community-based middle-aged to elderly participants (normotensive or with treated or untreated hypertension) who completed both high- and low-sodium diets found that 46% of participants were salt sensitive (defined as showing a  $\geq 5$  mmHg decline in mean arterial pressure between the high- and low-sodium diet).<sup>98</sup> Even in individuals who are not salt sensitive, however, reducing sodium intake can lower cardiovascular/cardiometabolic risk. For example, excess sodium intake has been associated with arterial stiffness and

**Table 4. Sodium Content in Oxybate Medications\***

Medication	Sodium content per maximum recommended dose
Sodium oxybate, oral solution (Xyrem)	1640 mg
Sodium oxybate, for extended-release oral suspension (Lumryz)	1640 mg
Calcium, magnesium, potassium, and sodium oxybates, oral solution (Xywav)	131 mg

\*No other commonly prescribed narcolepsy medications include sodium content in the prescribing information; labeling of the quantitative sodium content is not required by the US Food and Drug Administration if a maximum dose of the drug contains <5 mg.<sup>18</sup>

increased left ventricular wall thickness and mass, independent of BP.<sup>99,100</sup> Among adults with normal kidney function, higher salt intake is a predictor of future kidney dysfunction independent of its effects on BP.<sup>101</sup> High sodium intake (>3.6g/day) is also associated with increased incidence of dialysis initiation.<sup>102</sup> Sodium intake may also elevate cardiovascular risk through effects on the renal system, as chronic kidney disease is associated with increased risk of cardiovascular events and death.<sup>103,104</sup>

Younger patients with comorbidities should be aware of potentially increased risk of cardiovascular disease and consequences of higher sodium intake, even in the absence of current hypertension. In an analysis of 12 249 children and adolescents (aged 8–17 years) who participated in the National Health and Nutrition Examination Survey 2003 to 2016, after adjusting for age, sex, race, weight status, and energy intake, an additional 1000mg of daily usual sodium consumption was associated with 39% higher odds of developing elevated BP or hypertension ( $P=0.012$ ).<sup>105</sup> Higher sodium intake was also significantly associated with obesity in 4033 children aged 6 to 11 years who participated in the National Health and Nutrition Examination Survey 2009 to 2016.<sup>106</sup> Despite a lack of evidence on risk of hypertension and CVD in pediatric narcolepsy, it is never too early to develop healthy habits.

### **Statement 3b: Advise Patients That Reductions in Sodium Intake May Lower Their BP and Cardiovascular Risk**

Notably for patients with narcolepsy who do not demonstrate risk factors for cardiovascular/cardiometabolic disease, reductions in sodium intake have been associated with improvements in BP even in individuals who are normotensive or with baseline sodium intake <2.5g/day (ie, approaching or below US Department of Agriculture recommended daily intake of <2.3g/day). In the aforementioned analysis of 213 participants who completed both high- and low-salt diets, the observed BP response to dietary salt content was similar between individuals with normotension and hypertension (controlled, uncontrolled, and untreated).<sup>98</sup> A dose–response meta-analysis of 85 clinical trials (encompassing >10000 participants collectively) demonstrated a near-linear association between changes in sodium excretion and changes in BP across a wide variance of sodium intake.<sup>55</sup> In an observational follow-up analysis of 2415 participants from the randomized TOHP (Trials of Hypertension Prevention) studies (13–16 years after the studies ended), participants who had been assigned to a sodium reduction group showed a 25% reduction in relative risk of CVD compared with participants in control groups who maintained their usual diet with no specific sodium reduction strategies.<sup>56</sup> A meta-analysis of randomized studies

(including the SSaSS [Salt Substitute and Stroke Study], the largest trial of potassium-enriched salt substitute to date) found that participants who used a salt substitute had significantly reduced risk of all-cause death (5 studies), cardiovascular death (3 studies), and major adverse cardiovascular events (2 studies).<sup>57</sup> Participants who used a salt substitute also had a significant reduction in BP (19 studies).

### **Statement 3c: Provide Dietary Educational Materials (eg, AHA Guidelines, Dietary Approaches to Stop Hypertension Diet, World Health Organization Recommendations) to Aid in Reducing Sodium Intake**

Education about total sodium consumption is important for people with narcolepsy and should include dietary information as well as other sources of sodium intake. Health and nutrition education can be highly effective in reducing daily sodium intake.<sup>107</sup> The Centers for Disease Control and Prevention and World Health Organization provide practical tips for reducing sodium that are easy to implement.<sup>108,109</sup> For example, the Dietary Approaches to Stop Hypertension diet plan can be an effective way to control sodium intake and is well studied.<sup>110,111</sup>

### **Statement 3d: Advise Patients to Use a Salt Substitute (If Not Contraindicated) and Implement a Low-Sodium Diet**

People with narcolepsy and particularly those taking medications high in sodium may consider offsetting their sodium intake through dietary modifications. The SSaSS found that use of a salt substitute (75% sodium chloride and 25% potassium chloride by mass) led to a reduction in the rates of stroke, major cardiovascular events, and death among people with hypertension.<sup>58</sup> Potassium-enriched salt substitutes contain potassium chloride and are generally safe for healthy adults with normal kidney function.<sup>112</sup> However, for individuals with chronic kidney disease or diabetes (which is linked to hyperkalemia through its association with hyporeninemic hypoaldosteronism) or those who are taking medications that may impair potassium excretion such as renin–angiotensin–aldosterone system inhibitors (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics),<sup>113</sup> increasing potassium levels may increase the risk of hyperkalemia.<sup>112</sup>

## **DISCUSSION**

This consensus panel made 3 recommendations: (1) recognize the risk of hypertension and cardiovascular/cardiometabolic disease in patients with narcolepsy;

(2) reduce the risk of hypertension and cardiovascular/cardiometabolic disease in patients with narcolepsy; and (3) reduce sodium intake to lower the risk of hypertension and cardiovascular disease in patients with narcolepsy. A strength of these consensus panel recommendations is that full agreement was obtained on all final statements. However, the consensus was achieved on the basis of the expert opinions guided by the limited body of evidence. The panel recognized that there are several key knowledge gaps that limit the current breadth of understanding of any potential cardiovascular/cardiometabolic risks in the narcolepsy population, including whether people with narcolepsy truly have higher rates of CVD and stroke, the cardiovascular risks in pediatric patients with narcolepsy, long-term cardiovascular risks in patients who take stimulants for the treatment of narcolepsy symptoms over many years, and the role of sodium reduction in decreasing cardiovascular/cardiometabolic risks in patients with narcolepsy.

The development of these consensus recommendations has highlighted key areas that will be critical to investigate in future research. Defining cardiovascular/cardiometabolic risks and comorbidities directly attributable to narcolepsy (both in the overall narcolepsy population and in NT1 and NT2 subgroups, which differ in terms of the presence or absence of orexin deficiency) could help to identify the mechanisms by which people with narcolepsy develop elevated cardiovascular/cardiometabolic risks. Profiling cardiovascular/cardiometabolic risks in the pediatric narcolepsy population may assist with offsetting cardiovascular/cardiometabolic risks and comorbidities in these patients later in life. Conducting longitudinal analyses may aid in understanding the time course of cardiovascular comorbidity development in patients with narcolepsy. Testing the effect of reducing sodium intake on cardiovascular/cardiometabolic risk in people with narcolepsy in clinical studies may aid in patient education and testing the effect of once-nightly versus twice-nightly oxybate dosing and resulting differences in sleep quality, BP dipping, pharmacokinetic parameters, and cardiovascular/cardiometabolic risks may help inform treatment recommendations.

Conducting studies on cardiovascular/cardiometabolic risks and comorbidities in people with other hypersomnia spectrum conditions, such as idiopathic hypersomnia, for whom data are extremely limited, would also be of interest. Idiopathic hypersomnia shares with narcolepsy the common symptom of excessive daytime sleepiness but is a distinct disorder that may include symptoms such as sleep inertia, long and unrefreshing naps, and long sleep time (>11 hours in a 24-hour period).<sup>1</sup> One small study of 57 subjects reported that 32% of those with idiopathic hypersomnia had hypertension, which was lower than that in

94 patients with NT1 (49%) but greater than that in 83 patients with NT2 (27%).<sup>114</sup> A retrospective analysis of administrative claims data from 11 412 people with idiopathic hypersomnia and 57 058 controls matched for age, sex, geographic region, insurance type, and cohort entry date found that idiopathic hypersomnia was associated with more than double the odds of CVD, major adverse cardiovascular event, stroke, and hypertension diagnosis or use of antihypertensives.<sup>115</sup> A full report of this finding has not yet been published.

These consensus recommendations will help increase awareness of potential cardiovascular/cardiometabolic risks in patients with narcolepsy among both sleep specialists and non-sleep specialists. Early monitoring for, and prevention of, cardiovascular risks in this population is critical, especially as narcolepsy usually develops in adolescents and young adults who will be exposed to adverse effects of the disease and potential adverse effects of its treatment for decades.

## ARTICLE INFORMATION

Received February 23, 2024; accepted June 18, 2024.

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### Acknowledgments

The authors thank Stephen D. Lande, PhD, of Interactive Forums, Inc., and Robin L. Stromberg, PhD, consultant to Interactive Forums, Inc., for their contributions to the consensus panel process. Under the direction of the authors, Emily C. Bruggeman, PhD, and Emilie Croisier, PhD (employees of Peloton Advantage, LLC, an OPEN Health company), provided medical writing and editorial support.

### Sources of Funding

The study was sponsored by Jazz Pharmaceuticals. Jazz Pharmaceuticals provided funding to Peloton Advantage for medical writing and editorial support. Jazz Pharmaceuticals did not conduct a review of the manuscript.

### Disclosures

Dr Kwon has consulted for Jazz Pharmaceuticals and Caretaker Medical and has received funding from the National Institutes of Health, Department of Defense, and ResMed Foundation. Dr Gami has consulted for Jazz Pharmaceuticals. Dr Javaheri has received payment from Jazz Pharmaceuticals for presentation and for participation in the consensus panel that developed these recommendations, is on the speakers bureau of Avadel and Idorsia Pharmaceuticals, has received payment from Eli Lilly and Company for consultation, and is a consultant to Zoll-Respicardia. Dr Pressman has participated in the Cardiometabolic Health Congress, a division of Tarsus Medical. Dr Scammell has consulted for Avadel, Axsome, Consynance, Eisai, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Merck, Paladin Labs, Orion Pharma, Takeda, Tris Pharmaceuticals, Vertex Pharmaceuticals, and Woolsey Pharmaceuticals; and has received research grants from the National Institutes of Health, Avadel, Merck, Harmony Biosciences, Jazz, and Takeda. Dr Surkin has participated in advisory boards for Jazz Pharmaceuticals, Takeda Pharmaceuticals, and Alkermes Inc. Dr Zee serves on scientific advisory boards for Jazz, Eisai, and Harmony Biosciences; serves as a consultant for CVS Caremark; and owns stock in Teva.

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