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CLINICAL REVIEW

Cardiovascular disorders in narcolepsy: Review of associations and determinants

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SUMMARY

Narcolepsy type 1 (NT1) is a lifelong disorder of sleep-wake dysregulation defined by clinical symptoms, neurophysiological findings, and low hypocretin levels. Besides a role in sleep, hypocretins are also involved in regulation of heart rate and blood pressure. This literature review examines data on the autonomic effects of hypocretin deficiency and evidence about how narcolepsy is associated with multiple cardiovascular risk factors and comorbidities, including cardiovascular disease. An important impact in NT1 is lack of nocturnal blood pressure dipping, which has been associated with mortality in the general population. Hypertension is also prevalent in NT1. Furthermore, disrupted nighttime sleep and excessive daytime sleepiness, which are characteristic of narcolepsy, may increase cardiovascular risk. Patients with narcolepsy also often present with other comorbidities (eg, obesity, diabetes, depression, other sleep disorders) that may contribute to increased cardiovascular risk. Management of multimorbidity in patients with narcolepsy should include regular assessment of cardiovascular health (including ambulatory blood pressure monitoring), mitigation of cardiovascular risk factors (eg, cessation of smoking and other lifestyle changes, sleep hygiene, and pharmacotherapy), and prescription of a regimen of narcolepsy medications that balances symptomatic benefits with cardiovascular safety.

Introduction

Narcolepsy is characterized by a pentad of symptoms: excessive daytime sleepiness (EDS), cataplexy, disrupted nighttime sleep (DNS), sleep-related hallucinations (hypnagogic and hypnopompic), and sleep paralysis [1]. Narcolepsy type 1 (NT1; formerly called narcolepsy with cataplexy) is a lifelong condition that is always characterized by a low level (≤110 pg/mL) of the neuropeptide hypocretin 1 (also called orexin A) in cerebrospinal fluid and often by the presence of cataplexy [1]. In narcolepsy type 2 (NT2; formerly called narcolepsy without cataplexy), cataplexy is absent and hypocretin 1 levels in cerebrospinal fluid are >110 pg/mL [1]. NT2 is sometimes difficult to diagnose because it can present as other hypersomnolence disorders, requiring correction of the diagnosis [2]. Therefore, NT1 is generally considered to be the more severe of the two types. The global prevalence of narcolepsy has been estimated at 25–50 per 100,000 people [3]. Symptom onset typically occurs in adolescence, but diagnosis may be delayed by 10 years or more [4].

Preclinical data indicate a role for hypocretins in autonomic control [5]. Furthermore, narcolepsy in humans has been associated with hypertension and cardiovascular disease (CVD) [6,7]. Understanding the implications of linkage between hypocretins, comorbidities, and other factors associated with narcolepsy and cardiovascular health is important for long-term care of patients with narcolepsy. The purpose of this article is to synthesize the current literature to establish what is known about cardiovascular

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
ApoE	apolipoprotein E
BP	blood pressure
CVD	cardiovascular disease
CI	confidence interval
DNS	disrupted nighttime sleep
EDS	excessive daytime sleepiness
H/M ratio	heart-to-mediastinum ratio
HR	heart rate
MIBG	meta-iodobenzylguanidine
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OR	odds ratio
OSA	obstructive sleep apnea
PLMS	periodic limb movements during sleep
REM	rapid eye movement

risk in narcolepsy; describe possible factors related to increased cardiovascular risk in narcolepsy, including hypocretinergic deficiency and sleep disruption; examine cardiovascular risk associated with current narcolepsy treatments; provide recommendations for patient management; and consider future directions for research. When discussing studies relating to types of narcolepsy, we will use the terminology from the original source (NT1 vs NT2, narcolepsy with vs without cataplexy, or narcolepsy [type unspecified]), acknowledging that terminology has evolved over time. Because more information is available on NT1 than NT2, and because of the link between hypocretin deficiency and NT1, this article will focus on NT1.

Literature search

To identify peer-reviewed literature on cardiovascular comorbidities and risk of cardiovascular events associated with narcolepsy, PubMed was searched, without limits on date and in any language, for articles on narcolepsy that included the terms cardiovascular, hypertension, blood pressure, atherosclerosis, cardiomyopathy, syncope, atrial fibrillation, coronary microvascular disease, endothelial dysfunction, arrhythmia, heart failure, myocardial infarction, angina pectoris, coronary revascularization, sudden death, stroke, smoking, cholesterol, high-density and low-density lipoprotein cholesterol, dyslipidemia, obesity, diabetes, depression, or sleep apnea. Additional literature was identified from the bibliographies of articles from the initial search, as well as the collections of the authors. These literature results (Fig. 1) were also examined for information on hypocretins and narcolepsy treatments (stimulants and wake-promoting agents [eg, methylphenidate, amphetamine, modafinil, armodafinil, solriamfetol, and pitolisant], antidepressants [eg, clomipramine, venlafaxine, and protriptyline], and sodium oxybate).

Relationship of hypocretins to the pathophysiology of narcolepsy

Hypocretin deficiency is integral to the pathophysiology of NT1 [1]. Hypocretinergic cells in the tuberal region of the hypothalamus, which includes the lateral hypothalamus, project widely throughout the central nervous system, including areas involved in feeding, sleep/wake, and autonomic regulation [8]. Knockout mice lacking hypocretins ($Hcrt^{-/-}$) have a phenotype similar to NT1, including fragmentation of wakefulness by sleep attacks, reduced rapid eye movement (REM) sleep latency with sleep-onset REM periods, and cataplexy [9]. In human NT1 and NT2, autoreactive lymphocytes (CD4+/CD8+) targeting self-antigens expressed by hypocretin neurons have been detected, potentially consistent with an autoimmune etiology [10]. There is evidence for a relationship between hypocretin levels and sleep fragmentation; for example, studies have shown greater disruption of sleep architecture, including REM sleep abnormalities and REM sleep behavior disorder, in people with NT1 versus NT2 [11–14] and NT1 with low versus medium (40–50 and 110 pg/mL, respectively) hypocretin 1 levels in cerebrospinal fluid [12,14,15].

Narcolepsy, mortality, and cardiovascular risk

Evidence relating to increased mortality and cardiovascular risk with narcolepsy comes from several sources, many of which are based on chart reviews, analyses of medical claims data, or registries involving a large number of patients. These types of studies have certain limitations. For example, the diagnosis of narcolepsy was at the discretion of the treating physician versus being strictly based on a common set of criteria, as would occur in a clinical trial, and as such, it is possible that some of the patients did not actually have narcolepsy as opposed to another disorder of hypersomnolence or a different issue. Additionally, any medications being taken by the patients were not restricted or controlled. Finally, these large, registry-based studies were performed using records that did not include cerebrospinal fluid hypocretin levels, precluding analysis of any potential relationship between hypocretin deficiency and cardiovascular risk in narcolepsy. (Similarly, in most clinical laboratory studies, cerebrospinal fluid hypocretin levels were not available for all, or any, participants.)

Mortality

Narcolepsy is associated with increased mortality compared with the general population. For example, in an analysis of longitudinal claims data from 2008 to 2010 (including 59,528–77,616 people with narcolepsy and >170,000,000 people without narcolepsy), there was an approximate 1.5-fold excess all-cause mortality rate in the narcolepsy cohort compared with the non-narcolepsy cohort [16]. It is unknown whether there is a difference in mortality rates in NT1 versus NT2. Moreover, the causes of increased mortality of patients with narcolepsy were not ascertained, and in particular, the contribution of adverse cardiovascular events remains unclear.

Cardiovascular risk

Studies have examined whether people with narcolepsy are at increased risk of CVD, despite limitations due to the low population prevalence of narcolepsy [3] and the typically young age of the patient population at diagnosis [4]. The BOND study was a large-scale, retrospective analysis of five years of US medical claims data (2006–2010) for 55,871 adults ≥18 years of age with narcolepsy with or without cataplexy (n = 9312) and matched controls (n = 46,559) [6]. Risk of stroke (odds ratio, OR [95% confidence interval, CI]: 2.5 [2.3, 2.7]), myocardial infarction (OR [95% CI]: 1.6 [1.3, 1.8]), cardiac arrest (OR [95% CI]: 1.6 [1.1, 2.3]), and heart failure (OR [95% CI]: 2.6 [2.3, 2.9]) were all significantly increased in people with narcolepsy versus controls. There was also a significantly increased frequency of coronary revascularization procedures (coronary artery bypass graft or percutaneous transluminal coronary angioplasty; OR [95% CI]: 1.7 [1.4, 2.0]). A similar analysis of medical claims data for pediatric patients (<18 years of age) with

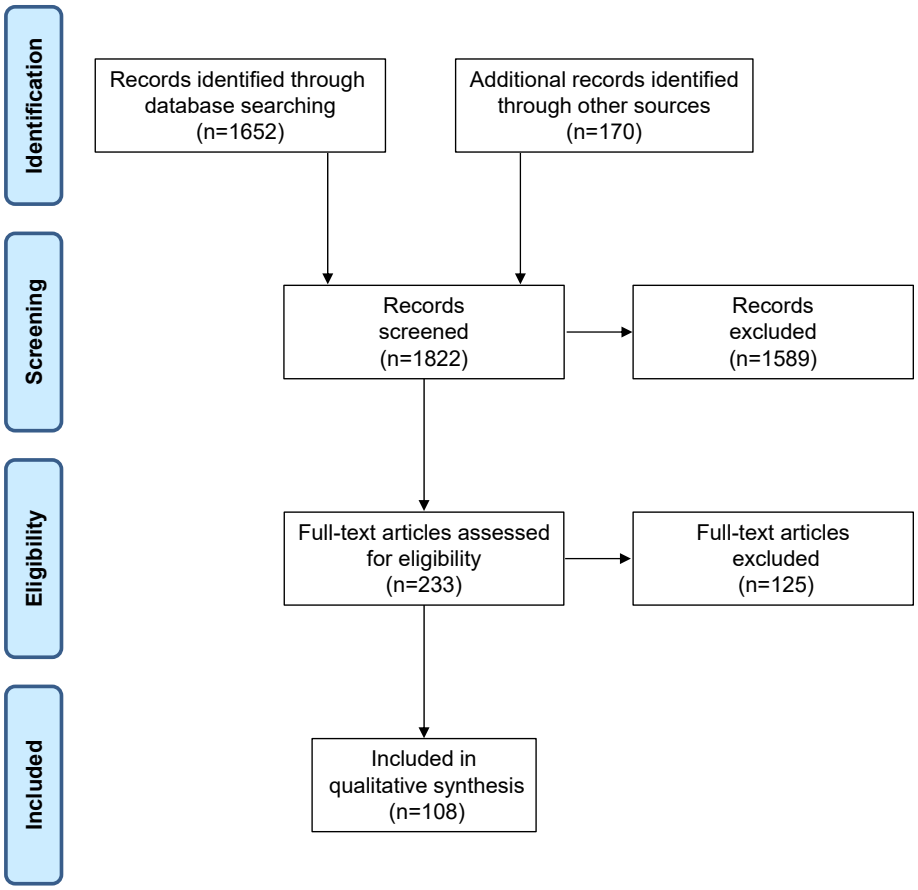

Fig. 1. Literature search results.

narcolepsy was recently published, but cardiovascular events (which are extremely rare in this age group) were not included among the selected conditions of interest [17]. In an interview-based study, heart diseases were among the conditions that were significantly more frequent among adults with narcolepsy (n = 320) compared with general population controls (n = 1464; adjusted OR [95% CI]: 2.07 [1.22, 3.51]) [7].

Key questions remaining in this area include whether certain types of CVDs or events are more prevalent than others in patients with narcolepsy, the underlying reasons for an association, and the nature or extent of the relationship in NT1 versus NT2. It is possible that the same biological mechanisms responsible for narcolepsy symptoms and signs affect the cardiovascular system via shared pathophysiology. Alternatively, it is possible that clinical features of narcolepsy, particularly sleep disruption, negatively impact the cardiovascular system through an independent mechanism. Finally, it is conceivable that both mechanisms may occur simultaneously, perhaps with additive effects.

Hypocretins and cardiovascular pathophysiology: preclinical data

Autonomic function

Hypocretinergic projections are believed to underlie state-dependent (sleep/wake) modulation of autonomic functions, and hypocretins may increase sympathetic nerve activity, heart rate (HR), and blood pressure (BP) [18]. For example, in rodents, administration of hypocretins increased BP [19], hypocretin receptor blockade decreased BP [20], and hypocretin receptor blockade reduced hypocretin-dependent increases in HR and BP [19]. Hypocretins may also impact cardiac parasympathetic control, as suggested by recent evidence in a mouse model of sudden unexpected death in epilepsy [21] and by connections of hypocretin neurons with the central autonomic network [8]. A seminal article established that sleep-related changes in BP were blunted in mice lacking hypocretinergic neurons or peptides [22], suggesting that sleep-related BP alterations in NT1 can be traced to the lack of hypocretins versus other transmitters co-released by hypocretinergic neurons. These results have been expanded in animal models of NT1 and largely translated to patients with NT1 (reviewed in Berteotti et al. [5]), as detailed below.

Endothelial function

Endothelial dysfunction, a predictive marker of cardiovascular risk [23], was induced by chronic sleep fragmentation in mice, along with structural changes in the vasculature [24]. A recent study by McAlpine and coworkers demonstrated that apolipoprotein E knockout ($ApoE^{-/-}$) mice (which are prone to atherosclerosis [25]) subjected to sleep fragmentation (which induces vascular endothelial dysfunction [24]) produced less hypocretin in the hypothalamus and developed more circulating inflammatory monocytes and neutrophils during the light (rest) period as well as larger atherosclerotic lesions, with more aortic leukocytes, compared with $ApoE^{-/-}$ mice not subjected to sleep fragmentation [26]. Peripheral hypocretin delivery to $ApoE^{-/-}$ mice subjected to sleep fragmentation led to smaller atherosclerotic lesions [26]. The

authors postulated that hypothalamic hypocretin modulates release of colony-stimulating factor 1 in bone marrow, which in turn regulates production of monocytes and atherosclerosis [26]. Sleep recovery following fragmentation restored hypothalamic hypocretin content [26]. As sleep fragmentation might have been expected to increase hypocretin production, the mechanisms that led to decreased hypocretinergic tone during sleep fragmentation remain unclear. Nevertheless, hypocretin knockout ($Hcrt^{-/-}$) mice (a model of NT1 [9]) were also found to exhibit increased circulating inflammatory lymphocytes and monocytes during the light (rest) period compared with wild-type controls. Moreover, double-knockout mice lacking both hypocretin and ApoE ($Hcrt^{-/-}$ $ApoE^{-/-}$) developed larger atherosclerotic lesions, with more aortic leukocytes, than did $ApoE^{-/-}$ controls.

Experiments in middle-aged mice lacking hypocretinergic neurons, a model of NT1, found no sign (even at the ultrastructural level) of cardiac and renal damage, despite clear blunting of sleep-related changes in BP [27]. It is worth noting that these mice had a standard (C57Bl/6J) genetic background, which lacks susceptibility to atherosclerosis [27], whereas the $Hcrt^{-/-}$ mice studied by McAlpine et al. [26] were developed from the $ApoE^{-/-}$ strain with a genetic makeup more susceptible to atherosclerosis. It is tempting to speculate that increased atherosclerosis due to hypocretin deficiency is a key factor for cardiovascular pathophysiology associated with hypocretin deficiency and NT1, with high BP during sleep as a contributing factor [28].

Myocardial function and remodeling

Hypocretins may exert protective effects at the cardiac level. Mice deficient in hypocretin receptor 2 exhibited increased cardiac dysfunction and myocardial scarring compared with wild-type mice [29]. Infusion of a hypocretin receptor 2 agonist rescued cardiac function in wild-type mice infused with neurohormones (angiotensin II and isoproterenol) that mimic heart failure [29]. Hypocretin receptor 1 and hypocretin receptor 2 are expressed throughout the rat heart [30]. Activation of hypocretin receptor 2 (but not hypocretin receptor 1) led to increased contractile shortening in isolated rat cardiomyocytes and was associated with cardioprotection (reduction of infarct size) following ischemia/reperfusion in a perfused rat heart model and an in vivo model [30].

Hypocretins and cardiovascular pathophysiology: clinical data

Autonomic function

There is some clinical evidence that hypocretin deficiency is associated with autonomic dysfunction, but also evidence to the contrary. In studies of people with narcolepsy (with and without cataplexy) [31] and in NT1 specifically [32], clinical autonomic dysfunction was noted across domains (gastrointestinal, urinary, thermoregulatory, pupillomotor, sexual, and cardiovascular), suggesting imbalance between sympathetic and parasympathetic activities.

Compared with control subjects, HR in patients with NT1 is variable during wakefulness and normal to high during sleep [5]. This is relevant because higher HR during sleep, and in particular the absence of nocturnal HR dipping, is associated with all-cause mortality [33] and subclinical cerebrovascular disease [34] in the general population. However, HR changes associated with arousals are blunted in patients with NT1 compared with controls [35]. Sorensen et al. demonstrated that HR increases in response to arousal were greatest in controls, significantly less in patients with narcolepsy without cataplexy or with normal hypocretin 1 levels, and lowest in patients with narcolepsy and cataplexy or low hypocretin 1 levels, suggesting a role for hypocretin 1 in autonomic control of the HR response [35]. Likewise, in a different study in patients with narcolepsy with cataplexy, periodic limb movements during sleep (PLMS) were associated with HR increases that were of significantly smaller magnitude compared with control subjects without narcolepsy [36]. Interestingly, in a study in three awake patients with narcolepsy with hypocretin 1 deficiency, HR decreased and systolic BP increased during induced cataplexy attacks, but diastolic BP was not significantly changed [37].

In a recent study examining cardiac sympathetic adrenergic nerve activity in people with NT1 using meta-iodobenzylguanidine (MIBG) cardiac scintigraphy, there was no difference between NT1 and controls in uptake of MIBG, a physiological norepinephrine analogue (quantified as heart-to-mediastinum [H/M] ratio) [38]. In a similar study, there was no difference in H/M ratio between participants with NT1 and comorbid REM sleep behavior disorder compared with controls [39]. In both studies, there was no association between H/M ratio and cerebrospinal fluid hypocretin levels in participants with NT1, suggesting no effect of hypocretins on cardiac adrenergic innervation and activity, at least under conditions comparable to those under which scintigraphy was performed [38–40].

People with NT1 and hypocretinergic deficiency are also at increased risk of hypertension [7,41,42], which is well known as a risk factor for CVDs. The contribution of hypocretin to hypertension is unclear, and there are a number of other possible mediators, including obesity [6,41,43,44], diabetes [6,41,43], depression [7,41,45], DNS (particularly in REM sleep) [1,46], and EDS [1].

Perhaps more important as a biomarker for cardiovascular risk are the non-dipping BP phenotype and high nocturnal BP [42]. BP normally decreases approximately 10%–20% during nighttime sleep compared with daytime waking BP, but in some individuals, nocturnal BP decreases <10%, which defines the non-dipping BP phenotype [47]. This blunted nocturnal BP dip is associated with increased cardiovascular mortality in the general population [48] and is significantly more common in people with narcolepsy with cataplexy versus healthy controls [47,49]. In one study, the difference in nocturnal BP dipping in patients with narcolepsy with cataplexy compared with controls was found despite an absence of differences in muscle and skin sympathetic nerve activity during non-REM sleep [50]. The authors hypothesized that derangement of nocturnal BP dynamics may contribute to cardiovascular risk in NT1 [47,49].

A relationship between non-dipping BP and hypocretin levels has not been definitively established. For example, in pediatric patients with NT1, alterations of BP modulation during sleep were found to be associated with lower hypocretin 1 levels in the cerebrospinal fluid compared with controls [14], whereas in adult patients with NT1, non-dipping BP was found not to be related to cerebrospinal fluid hypocretin levels [51]. However, correlations were computed between BP dipping and the residual, quite low hypocretin levels in NT1 patients, raising the possibility of a biological floor effect [14,51]. Further research is needed in this area.

Non-dipping BP may be related to sleep quality in addition to hypocretinergic deficiency. A causal relationship between non-dipping BP and impaired sleep quality is supported by data that selective slow-wave sleep deprivation was associated with attenuated nocturnal BP dipping in healthy subjects [52]. Moreover, in normotensive people without narcolepsy, those with non-dipping BP exhibited significantly poorer sleep quality than those with dipping BP [53]. People with narcolepsy and non-dipping BP exhibited increased sleep fragmentation and higher arousal index (number of arousals/hour of sleep), PLMS index (number of periodic limb movements/hour of sleep), and PLMS arousal index (number of periodic limb movements associated with arousal/hour

of sleep) compared with healthy controls [49]; similar results have been reported for people with restless legs syndrome [54]. However, as mentioned earlier, HR changes associated with arousals [35] and PLMS [36] are blunted in patients with NT1 compared with controls. It is unclear, but quite possible, that BP responses are blunted as well. Finally, mean diastolic BP dip in people with narcolepsy correlated negatively with REM sleep percentage and number of sleep-onset REM periods and positively with mean daytime sleep latency [47]. Although REM sleep represents a minor fraction of total sleep time, increases in BP during REM sleep may contribute significantly to cardiovascular risk in people with NT1. Accordingly, obstructive sleep apnea (OSA), which increases BP during sleep, may be particularly deleterious for cardiovascular health when it occurs during REM sleep [55].

Endothelial function

No difference in endothelium-dependent vasodilatation response, assessed using reactive hyperemia peripheral arterial tonometry, was observed between narcolepsy-cataplexy (drug-free) patients and controls [47]. A possible explanation for this clinical finding could have been a preserved vasomotor function in untreated (and therefore presumably sleepy) patients with narcolepsy with cataplexy, which may be related to low daytime BP findings [47,56]. Results from registry studies showed that hypertension was more common in patients with narcolepsy who were receiving treatment compared with controls [7,41]. No studies have directly addressed the issue of atherosclerosis burden in patients with narcolepsy.

Myocardial function and remodeling

Expression of hypocretin receptor 2 was increased in diseased human hearts (dilated cardiomyopathy and ischemic cardiomyopathy) compared with controls, possibly as a protective response in the setting of myocardial insult [29]. Accordingly, in humans with congestive heart failure, there was a negative correlation between hypocretin receptor 2 expression in heart tissue samples and disease severity [30]. In people with heart failure with reduced ejection fraction, higher baseline hypocretin 1 concentrations in blood were associated with significantly greater left ventricular reverse remodeling [57]. Similarly, in people with symptomatic heart failure, high baseline hypocretin 1 concentrations in blood were associated with significantly increased odds of left ventricular reverse remodeling [58]. However, these findings should be interpreted with caution for relevance to patients with narcolepsy, as measurement of hypocretin 1 in blood is not as reliable as measurement in the cerebrospinal fluid [59] due to peripheral secretion of hypocretin and binding to plasma proteins [60].

Summary of the links between hypocretins and cardiovascular pathophysiology

Converging lines of preclinical and clinical work indicate that hypocretin deficiency adversely impacts diverse pathophysiological mechanisms of CVDs. Although the underlying mechanisms are not yet defined, autonomic dysfunction with alterations in nocturnal BP values, increased circulating inflammatory leukocytes, and increased susceptibility to atherosclerosis and myocardial fibrosis appear most worthy of investigation. There is some indication that hypocretins may exert direct cardioprotective effects and directly limit atherosclerosis burden in addition to effects at the level of the central nervous system, although the evidence is only preclinical at this stage. Therefore, it is conceivable that increased cardiovascular risk in people with narcolepsy may be related to reduction of peripheral hypocretinergic tone in addition to loss of hypothalamic neurons, although there is no direct evidence to support this.

Other risk factors for CVD in patients with narcolepsy

Narcolepsy comorbidities

Narcolepsy is associated with comorbidities that increase cardiovascular risk, including obesity [6,41,43,44], diabetes [6,41,43], and depression [7,41,45]. Additionally, there is a markedly increased prevalence of precocious puberty in children with NT1 compared with the general population and age-matched obese controls [44]. Precocious puberty is associated with increased risk of CVD and mortality in adulthood [61]. Smoking is more prevalent among patients with narcolepsy compared with healthy controls [47,62]. Finally, there is evidence that people with narcolepsy are at increased risk of comorbid OSA and PLMS [6,41,43], which are also associated with increased risk of CVD, hypertension, and mortality [63–65]. In the case of OSA, the contributory role of disordered breathing related to symptoms associated with narcolepsy (DNS and EDS [66]) is likely to be underestimated, particularly in middle-aged people with established disease. It has been estimated that OSA is found in 24%–40% of adult patients with narcolepsy [67–69]; however, EDS was similar regardless of comorbid OSA in all studies [67–69]. It is unknown whether cardiovascular risk is increased by comorbid OSA in people with narcolepsy. The interrelationship between narcolepsy, other sleep disorders, and cardiovascular risk may vary based on population (adult versus pediatric), and may be difficult to disentangle [54,70].

DNS and EDS

DNS and EDS, both cardinal features of narcolepsy [1], may contribute to cardiovascular risk. It is well established that sleep disturbance is associated with increased cardiovascular risk in the general population; this is particularly true for sleep duration [71]. In narcolepsy, sleep duration does not seem to be impacted, but other sleep characteristics are.

Estimates of the prevalence of DNS in narcolepsy range widely (from 30% to 95% [46]), whereas EDS is exhibited by all people with narcolepsy [1]. DNS is described by patients as difficulty staying asleep (frequent awakenings), and is objectively measured using techniques such as polysomnography and actigraphy, which assess aspects such as abnormal transitions between sleep stages, including frequent shifts to REM sleep [46]. Whether DNS as defined subjectively or objectively is a risk factor for CVD in patients with narcolepsy remains to be determined. DNS and EDS are not specific to narcolepsy; for example, they are also seen in the elderly [72] and with other sleep disorders. DNS may independently predict CVD in patients with insomnia [73]. Studies have also found a link between DNS and increased risk of CVD events and related conditions in the general population. For example, in an analysis of 2006 data from the Behavioral Risk Factor Surveillance System for 138,201 adults in the United States, subjectively reported sleep disturbance ("trouble falling asleep or staying asleep or sleeping too much" on $\geq$6 days in a two-week period) was associated with significantly increased risk of coronary artery disease and myocardial infarction [74].

In a recent study, cerebrospinal fluid hypocretin levels in people with hypersomnolence were dose-dependently associated with markers of nocturnal sleep stability [75]. Specifically, in people with vs without hypocretin deficiency (cerebrospinal fluid hypocretin $\leq$110 pg/mL), there were significantly more wake bouts and sleep bouts, lower percentage of short wake bouts (<30 s) and higher percentage of long wake bouts ($\geq$1.5 min), and higher percentage of

short sleep bouts (≤14 min) and lower percentage of long sleep bouts (>32.5 min). These results suggest a relationship between hypocretin and sleep stability/DNS in disorders of hypersomnolence, including narcolepsy.

EDS is also associated with increased cardiovascular risk and risk of cardiovascular mortality in the general population, particularly in the elderly, for whom EDS is a frequent complaint [72]. In the Three City Study, a French population-based prospective study, elderly (≥65 years of age) people with no history of coronary heart disease or stroke (N = 7007) who reported experiencing EDS frequently had an increased risk of coronary heart disease and stroke over a median follow-up of 5.1 years compared with people who reported never experiencing EDS [76]. In the same study, regular or frequent EDS was associated with a significantly increased risk of cardiovascular mortality but not cancer-related mortality over six years of follow-up, after adjusting for a number of risk factors [77]. In a different study, the relationship between EDS and increased cardiovascular risk was independent of any history of CVD [73]. Results of studies of EDS that included younger adult participants have generally been consistent with those in elderly people, demonstrating increased risk of vascular death, ischemic stroke, and myocardial infarction [78]; ischemic heart disease [79]; and incident stroke and incident coronary heart disease [80]. However, in a large (N = 84,003) study of registered nurses (25–42 years of age), the relationship between EDS and risk of CVD was diminished after controlling for other sleep-related variables (eg, sleep duration) and cardiometabolic risk factors (eg, diabetes) [81]. The mechanisms whereby EDS increases cardiovascular risk are unclear, and the applicability of conclusions from other populations to patients with narcolepsy is tentative because EDS is, by definition, an inherent aspect of hypersomnolence disorders. By contrast, in patients with OSA, objective but not subjective sleepiness has been associated with higher levels of the proinflammatory cytokine interleukin 6 [82], which may contribute to cardiovascular risk.

Narcolepsy treatment and cardiovascular health

Some medications used to treat symptoms of narcolepsy may have potential negative effects on cardiovascular health. In NT1, these medications are typically used long term, which may exacerbate cardiovascular risk. However, long-term data on cardiovascular outcomes associated with narcolepsy treatments are generally lacking.

Wake-promoting agents used for the treatment of sleepiness in narcolepsy include modafinil, armodafinil, solriamfetol, and pitolisant, as well as traditional stimulants such as methylphenidate and amphetamine [83]. The stimulant mazindol was previously used but was potentially associated with safety concerns and is no longer available [84]. The use of modafinil is associated with greater usage of antihypertensive medications [85]. Solriamfetol (Sunosi™), which is indicated to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA, was associated with small mean increases in HR (2–4 beats per minute) and systolic and diastolic BP (1–2 mm Hg) at doses of 150 and 300 mg, compared with changes of <1 mm Hg or beats per minute for placebo, in a phase three trial with 236 participants with narcolepsy [86,87]. The increases in BP were transient over the day [88]; however, two participants had a treatment-emergent adverse event of BP increase (1 in the 150-mg group and 1 in the 300-mg group) [86,87]. Solriamfetol is currently approved in the United States and European Union; the recommended starting dose is 75 mg once daily and the maximum dose is 150 mg once daily for people with narcolepsy [86,89]. The concurrent use of modafinil and solriamfetol is contraindicated in patients with unstable cardiovascular disease, serious heart arrhythmias, and other serious heart problems [86,89]. Pitolisant (Wakix™) is a histamine-3 receptor antagonist/inverse agonist that is indicated for the treatment of EDS or cataplexy in adult patients with narcolepsy; at doses up to 40 mg/day in a one-year open-label study, there may have been an association with slight QT interval prolongation (from 409 ± 25 ms to 416 ± 25 ms at doses up to 40 mg) but without clinically meaningful cardiovascular changes [90–93]. Methylphenidate (indicated for attention-deficit/hyperactivity disorder [ADHD]) is associated with increased BP, increased HR, and cardiac arrhythmias [94], including in most studies of adults with ADHD [95]. Similarly, in a study involving 160 patients with NT1, patients treated with stimulants exhibited higher 24-h, daytime, and nighttime diastolic BP or HR compared with untreated patients [96]. Furthermore, hypertension was diagnosed in 57.6% of treated patients versus 40.6% of untreated patients. However, there was no difference in endothelial function between the treated (stimulants) and untreated patients with NT1 [96]. With stimulants, the dose level may influence the level of cardiovascular risk; in one study in patients with narcolepsy or idiopathic hypersomnia, tachycardia was more frequent in patients who received high-dose stimulants compared with standard-dose stimulants [97].

Many antidepressant drugs prescribed off-label for the treatment of cataplexy in narcolepsy have potential cardiovascular safety concerns, including clomipramine, venlafaxine, and protriptyline [98]. Clomipramine is associated with decreases in orthostatic BP, tachycardia, and electrocardiographic abnormalities [99], venlafaxine with increased BP [100], and protriptyline with myocardial infarction, stroke, heart block, arrhythmias, hypotension, hypertension, tachycardia, palpitation, and weight gain [101].

Sodium oxybate (Xyrem™) is indicated in Europe for adults with narcolepsy with cataplexy and in the United States for the treatment of EDS or cataplexy in patients seven years of age and older with narcolepsy [102,103]. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate; at the recommended dosage range for adults (6–9 g per night), patients taking sodium oxybate ingest up to 1640 mg sodium nightly, in addition to dietary sodium [103]. Sodium intake increases BP as well as risk for cardiovascular events (particularly stroke), independent of baseline BP in the general population [104]. Therefore, high sodium–containing drugs may increase BP and risk for cardiovascular events [105]. Sodium oxybate prescribing information recommends monitoring patients who are sensitive to high sodium intake (eg, those with heart failure, hypertension, or impaired renal function) [103]. A lower-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates; Xywav™) was approved in July 2020 in the United States for the treatment of EDS or cataplexy in patients seven years of age and older with narcolepsy [106].

Discussion

The interrelations of hypocretin deficiency, DNS/EDS, comorbidities, and other factors with cardiovascular risk in people with narcolepsy are complex and multifaceted (Fig. 2). Further research is needed to provide clarity on these issues. Hypocretinergic deficiency is a candidate for increasing cardiovascular risk; however, it is unclear whether the loss of hypocretins might impact cardiovascular health directly and/or indirectly (eg, via disruption of sleep and EDS). Clinical research has been challenging because narcolepsy is a rare disease. Some studies have relied on retrospective review of medical records, which may lack data on hypocretin

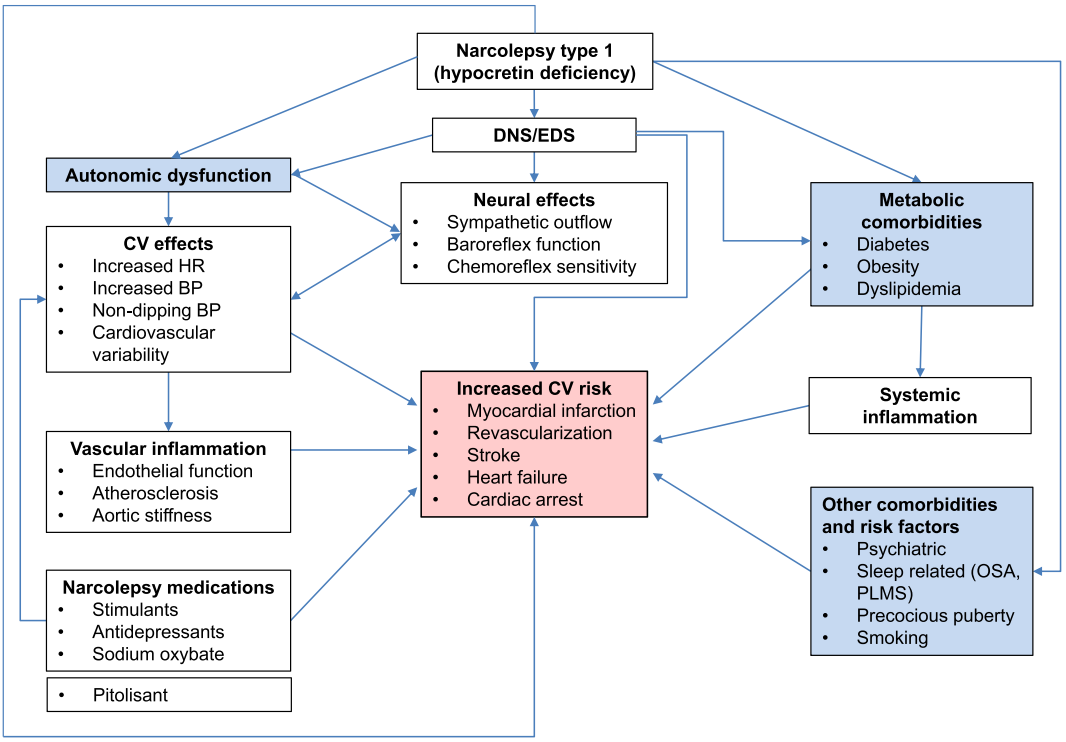

Fig. 2. A hypothetical conceptual framework for relationships between narcolepsy type 1, hypertension, and cardiovascular risk. BP, blood pressure; CV, cardiovascular; DNS, disrupted nighttime sleep; EDS, excessive daytime sleepiness; HR, heart rate; OSA, obstructive sleep apnea; PLMS, period limb movements during sleep; WPA, wake-promoting agent.

levels or sufficient information to differentiate NT1 from NT2, and patients with varying hypocretin levels in the cerebrospinal fluid may be combined into a single group to achieve sufficient power for analysis. Echoing the obstacles to analyses of hypocretins and subjective vs objective sleep disturbances, the frequent presence of multimorbidity, including other sleep disorders and conditions that are themselves associated with sleep dysregulation and/or increased cardiovascular risk, is a significant confounding factor for understanding the origins of cardiovascular risk in narcolepsy.

Data on life expectancy and the incidence and nature of cardiovascular risk in NT1 versus NT2 are lacking. For example, BP dipping has not been studied in patients with NT2 as a separate population. If cardiovascular comorbidity is unique to NT1 or more common in NT1 compared with NT2, this could shed light on whether hypocretin deficiency has a pivotal role in promoting CVD. Elevated cardiovascular risk in NT2 relative to the general population would suggest a mechanism other than hypocretin deficiency. However, it is unclear whether mild reductions in hypocretin levels, well above the accepted threshold for NT1, entail greater cardiovascular risk. Sleep issues are related to cardiovascular risk in the general population, in whom hypocretin deficiency is not expected. It is, therefore, conceivable that a hypocretin-independent mechanism of sleep disruption in NT2, similar to what is observed in other sleep disorders (and for which differential diagnosis can be difficult), might be a source of negative impact on cardiovascular health. Both EDS and DNS occur in NT1 and NT2, although it is unclear whether these symptoms are similarly severe. With regard to DNS, sleep disruption/fragmentation, particularly during REM sleep stages, might be more important than sleep duration.

No guidelines specific to assessment of cardiovascular risk in patients with narcolepsy exist, but general recommendations for broader populations may be applied. The European Society of Cardiology SCORE charts are a useful tool to estimate cardiovascular risk (specifically, 10-year mortality attributable to CVD) based on age, sex, systolic BP, total cholesterol, and smoking status using data from the general population [107]. However, the charts do not describe risk for those <40 or >65 years of age, and considering the evidence for increased cardiovascular risk in narcolepsy and the need for lifelong treatment, it could be argued that cardiovascular risk should be assessed even in younger patients with narcolepsy. European Society of Cardiology/European Society of Hypertension guidelines include additional cardiovascular risk factors in the context of a general population with hypertension, among them diabetes, overweight or obesity, family history, HR >80 beats/minute, hypertension-mediated organ damage, and established CVD or renal disease [108]. We may propose that sleep (ie, DNS, EDS, and sleep duration) should be included in the predefined cardiovascular risks. The Hygia Project (N = 18,158) identified systolic BP while asleep as the best BP measurement to estimate risk of CVD in a general population of adults with hypertension [42]. The European Society of Cardiology/European Society of Hypertension guidelines recommend ambulatory BP monitoring if nocturnal hypertension is suspected [108]. This recommendation may thus apply also to patients with narcolepsy, and particularly to those with NT1.

In conclusion, narcolepsy is associated with multiple cardiovascular risk factors and comorbidities, including CVDs. Management of multimorbidity in patients with narcolepsy should include regular assessment of cardiovascular health, mitigation of cardiovascular risk factors, and prescription of a regimen of narcolepsy medications that balances symptomatic benefits with cardiovascular safety.

Practice points

Management of patients with narcolepsy with respect to cardiovascular risk may be based on multiple considerations:

1. The calculus of needs and the benefit/risk ratio for each patient should consider the type and dose of narcolepsy drugs, the influence of concomitant medications, other medical history, and the expectation that treatment will be long term;
2. Because it is currently unclear whether cardiovascular risk differs between NT1 and NT2, the type of narcolepsy is not informative when considering the cardiovascular implications of management;
3. Special attention should be given to older patients because of the age-related increase in risk of CVD;
4. Cardiovascular risk in patients treated with stimulant medications may be limited by assessment of history of CVD, monitoring of HR and BP prior to and during treatment, lifestyle changes, and sleep hygiene;
5. Dose adjustment of stimulant medication, drug holiday, or addition of an antihypertensive agent may be necessary in the event of sustained BP elevation;
6. Behavior modification can be recommended as a way to minimize cardiovascular risk and may also have benefits for alleviating narcolepsy symptoms;
7. When substantial concern about cardiovascular risk remains, follow-up may be warranted, recommending 24-h ambulatory BP monitoring to allow the assessment of nocturnal BP values and BP dipping status.

Research agenda

Future research could address the following questions regarding cardiovascular risk in narcolepsy:

1. Whether specific cardiovascular outcomes contribute to the overall increased mortality, if confirmed, in people with narcolepsy;
2. Whether cardiovascular risk in people with narcolepsy is related to hypocretin deficiency, DNS/EDS, PLMS, apnea-hypopnea index, comorbidities, other factors, or a combination of these;
3. Whether NT1 and NT2 differ in terms of cardiovascular comorbidity;
4. Whether there is a relationship between specific aspects of sleep architecture (eg, non-REM and REM stages) and sleep disturbances (including sleep duration) and cardiovascular risk;
5. Whether narcolepsy treatments that have a beneficial effect on DNS also mitigate cardiovascular risk;
6. Whether there is hypertensive organ damage in patients with NT1, particularly those who are older, using markers such as left ventricular hypertrophy, estimated glomerular filtration rate, proteinuria, and atherosclerosis burden.

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Conflicts of interest

PJ Jennum has participated in advisory boards for UCB Europe, Bioprojet, and Jazz Pharmaceuticals.

G Plazzi is a consultant and has participated in advisory boards for UCB Pharma, Bioprojet, Idorsia, Jazz Pharmaceuticals, and Takeda.

A Silvani reports no conflicts of interest.

LA Surkin has participated in advisory boards for Jazz Pharmaceuticals.

Y Dauvilliers is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals, UCB Pharma, Flamel Technologies, Idorsia, Theranexus, and Bioprojet.

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