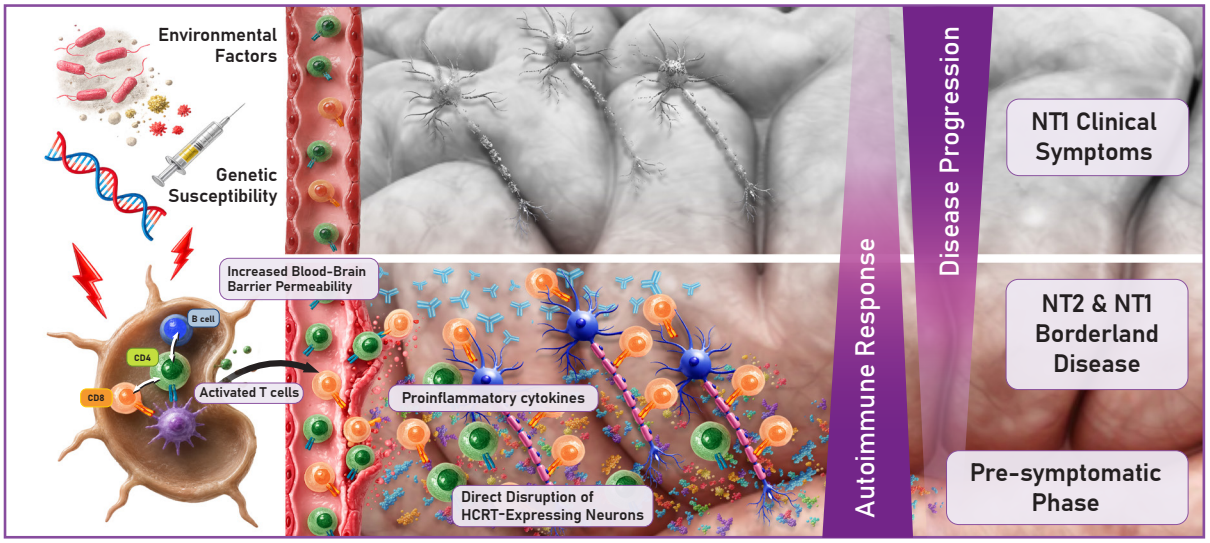
NARCOLEPSY BEYOND SLEEP

Pathophysiology and Downstream Effects

FIGURE 1: **ETIOLOGY OF NARCOLEPSY**[1]



Narcolepsy is believed to result from an autoimmune-mediated process in genetically predisposed individuals, triggered by environmental factors that lead to a selective loss of hypocretin (HCRT), also named orexin, in the lateral hypothalamus.

GENETIC PREDISPOSITION

- Up to 98.5% of patients with NT1 and 40%–60% of patients with NT2 carry the variant HLA-DQB1 *06:02 allele

AUTOANTIBODIES

- Several reports have shown the existence of autoreactive T cells directed against antigens expressed by HCRT-neurons in NT1 patients

ENVIRONMENTAL FACTORS

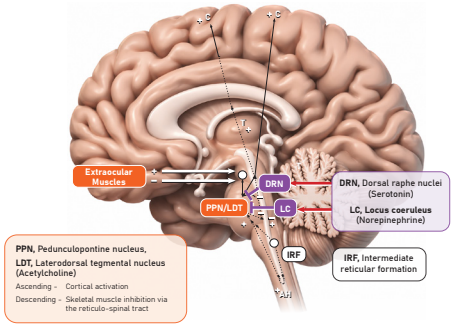
- Disease concordance rate in mono-zygotic twins is 25%–31%
- A 3-fold increase in narcolepsy incidence was found after the 2009 H1N1 influenza pandemic that affected mostly Asian countries

THE UNDERLYING CAUSE OF HUMAN NARCOLEPSY APPEARS TO BE EITHER THE AUTOIMMUNE-INDUCED LOSS OF HYPOCRETIN NEURONS OR MUTATION OF THE HYPOCRETIN GENE ITSELF.

FIGURE 2: **NARCOLEPSY AND RAPID EYE MOVEMENT (REM) NEUROPHYSIOLOGY**[2,3]

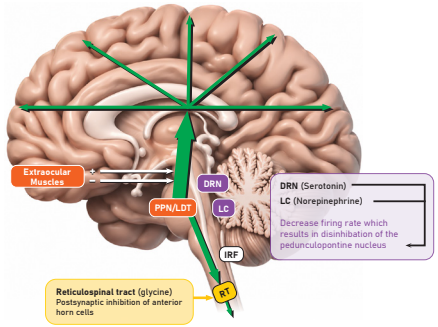
Narcolepsy involves the intrusion of REM sleep components into wakefulness, caused by the loss of hypocretin/orexin, which normally stabilizes sleep-wake boundaries.

REM-OFF



PPN is a key structure of the ascending reticular activating system. It is critical for maintaining wakefulness.

REM-ON



LC-driven disinhibition of the PPT's cholinergic neurons contributes to the onset and maintenance of REM sleep, including generating REM and suppressing muscle tone.

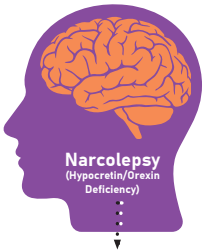
THE CORE OF THE REM-GENERATING CIRCUIT IS LOCALIZED AT THE MESOPONTINE JUNCTION, MEDIAL TO THE TRIGEMINAL MOTOR NUCLEUS AND VENTRAL TO THE LC.

FIGURE 3: **LINKS BETWEEN HYPOCRETINERGIC/OREXIN DEFICIENCY, SLEEP DISRUPTION, & CARDIOVASCULAR PATHOPHYSIOLOGY**

Multiple interrelated pathways have been suggested to contribute to downstream effects of narcolepsy, including cardiovascular and cardiometabolic risk; however, these mechanisms have not yet been clearly defined.[4,5]

AUTONOMIC DYSFUNCTION

- Alterations in nocturnal BP values
- Impaired heart rate variability
- Sympathetic overactivity and reduced parasympathetic tone



INCREASED CIRCULATING INFLAMMATORY LEUKOCYTES

- Elevated inflammatory cytokines
- Chronic low-grade inflammation
- Endothelial activation and dysfunction

INCREASED SUSCEPTIBILITY TO ATHEROSCLEROSIS AND MYOCARDIAL FIBROSIS

- Endothelial injury and impaired vascular repair
- Atherosclerotic plaque formation
- Myocardial remodeling and fibrosis

IT IS POSSIBLE THAT THE SAME BIOLOGICAL MECHANISMS RESPONSIBLE FOR NARCOLEPSY SYMPTOMS 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.

1. Latorre D, et al. *Semin Immunopathol.* 2022;44(5):611-623; 2. Fraigne JJ, et al. *Front Neurol.* 2015;6:123; 3. Lu J, et al. *Nature.* 2006;441(7093):589-594; 4. Jennum PJ, et al. *Sleep Med Rev.* 2021;58:101440; 5. Bertelotti C, Silvani A. *Clin Auton Res.* 2018.28(6);545-555.

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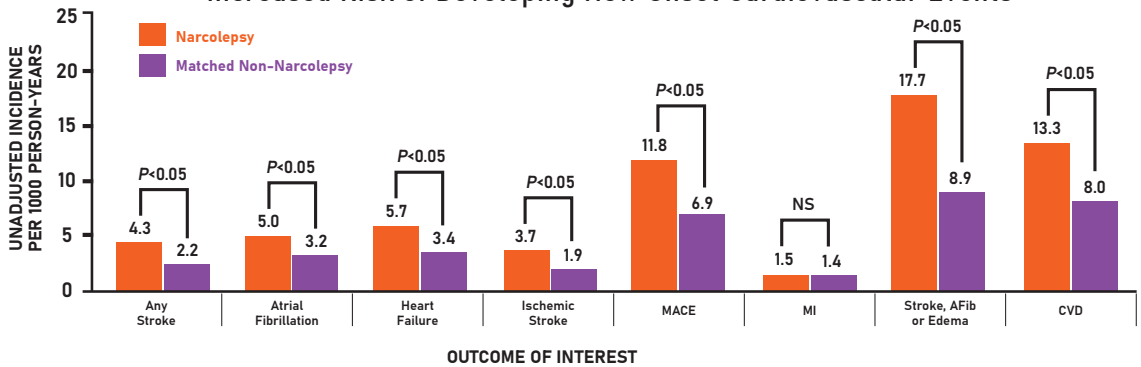
Cardiovascular and Cardiometabolic Risks

FIGURE 4: ASSOCIATED CARDIOVASCULAR EFFECTS OF NARCOLEPSY

Cardiovascular Burden of Narcolepsy Disease (CV-BOND): A Real-World Evidence Study[1]

Increased Risk of Developing New Onset Cardiovascular Events



Narcolepsy	n=12,768	12,746	12,752	12,770	12,680	12,807	12,610	12,635
Matched Non-Narcolepsy	n=38,391	38,275	38,318	38,398	38,224	38,415	38,121	38,109

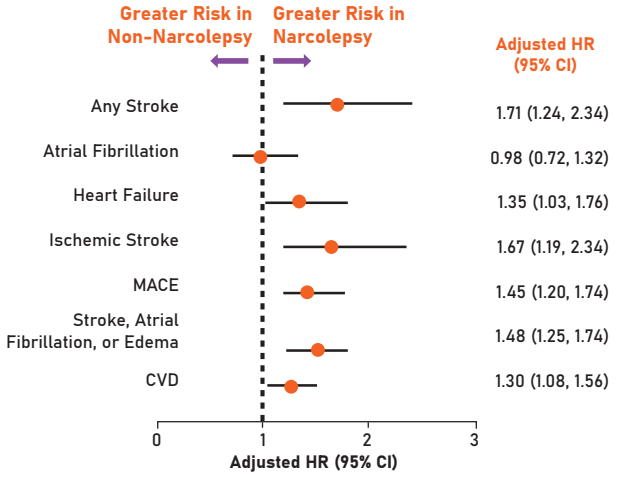


FIGURE 5: CVD RISK FACTORS AND ASSOCIATED COMORBIDITIES

Narcolepsy is associated with comorbidities that increase cardiovascular risk, including obesity, diabetes, OSA, and depression.[1]

	OSA	Mood Disorders	Anxiety Disorders	Headache/ Migraine	Diabetes or Obesity	Hyperlipidemia
PEOPLE WITH NARCOLEPSY	33.8%	25.6%	21.7%	17.3%	11%	15.4%
PEOPLE WITHOUT NARCOLEPSY	2.2%	6.2%	7.2%	4.9%	8.3%	10.6%

In patients with OSA, objective sleepiness has been associated with higher levels of the proinflammatory IL-6, which may contribute to cardiovascular risk.[2]

FIGURE 6: CARDIOVASCULAR CONSIDERATIONS IN NARCOLEPSY TREATMENT[3-9]

Modafinil	Contains a warning for increased monitoring for cardiovascular disease
Pitolisant	Contains a warning for QT interval prolongation and should be avoided in patients with history of cardiac arrhythmias
Sodium oxybate	Contains a warning for high sodium content and monitoring in patients with heart failure, hypertension, or impaired renal function
Solriamfetol	Contains a warning for increased monitoring for high blood pressure and heart rate
Methylphenidate	Contains a warning for serious cardiovascular events and for increased monitoring for blood pressure and heart rate
Amphetamines	Contains a warning for individuals with heart disease, due to potential for increased risk of cardiac events and death if history of MI or angina

AFib, atrial fibrillation; **CI**, confidence interval; **CVD**, cardiovascular disease; **EDS**, excessive daytime sleepiness; **HR**, hazard ratio; **IL**, interleukin; **MACE**, major adverse cardiac event; **MI**, myocardial infarction; **NS,** not significant; **OSA**, obstructive sleep apnea.

1. Ben-Joseph RH, et al. *Sleep.* 2023;46(10):zsad161; 2. Jennum PJ, et al. *Sleep Med Rev.* 2021;58:101440; 3. Black J, et al. *Future Cardiol.* 2025;21(6):339-348; 4. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf; 5. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211150_Orig2s000lbl.pdf; 6. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021196s042lbl.pdf; 7. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211230s009lbl.pdf; 8. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212690s000lbl.pdf; 9. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017078s042lbl.pdf.