



Narcolepsy

Type 1 (NT1)

Narcolepsy is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles

Narcolepsy type 1 (NT1) is a sleep disorder characterized by an overwhelming tendency for excessive daytime sleepiness (EDS), episodes of cataplexy and abnormalities in rapid eye movement sleep

Hallmark symptom of NT1: Cataplexy



1 Prevalence

2 Understanding Narcolepsy Type 1

3 Pathophysiology and Neurobiology

4 Comorbidities & Diagnosis

5 Treatment Options & Future Directions

A significant challenge in the epidemiology of NT1 is the long delay between symptom onset and definitive diagnosis

Global Prevalence

- The prevalence of NT1 falls between 25 - 50 per 100,000 people
- Incidence: The annual incidence is very low, ranging from 0.64 to 1.37 per 100,000 people (rare disease)
- Age of onset: 10-30
- A bimodal distribution with the first peak at around 15 years and the second peak at about 35 years



Prevalence of NT1 in North America, Europe and South Korea



Prevalence: Overall, the prevalence of NT1 was estimated to be 19.1/100,000 people



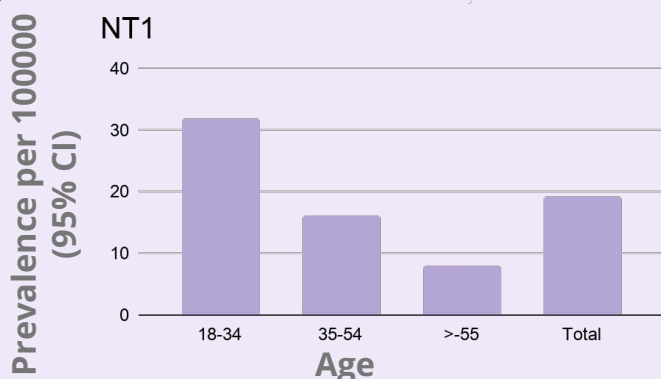
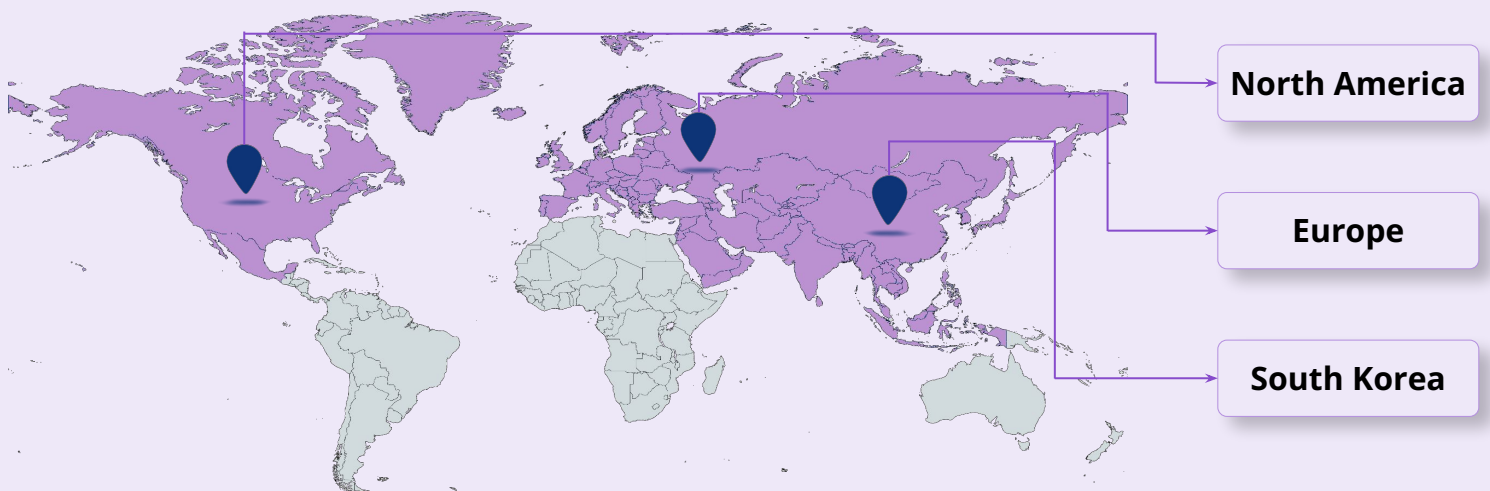
The highest prevalence was among participants aged 35 years or younger for NT1



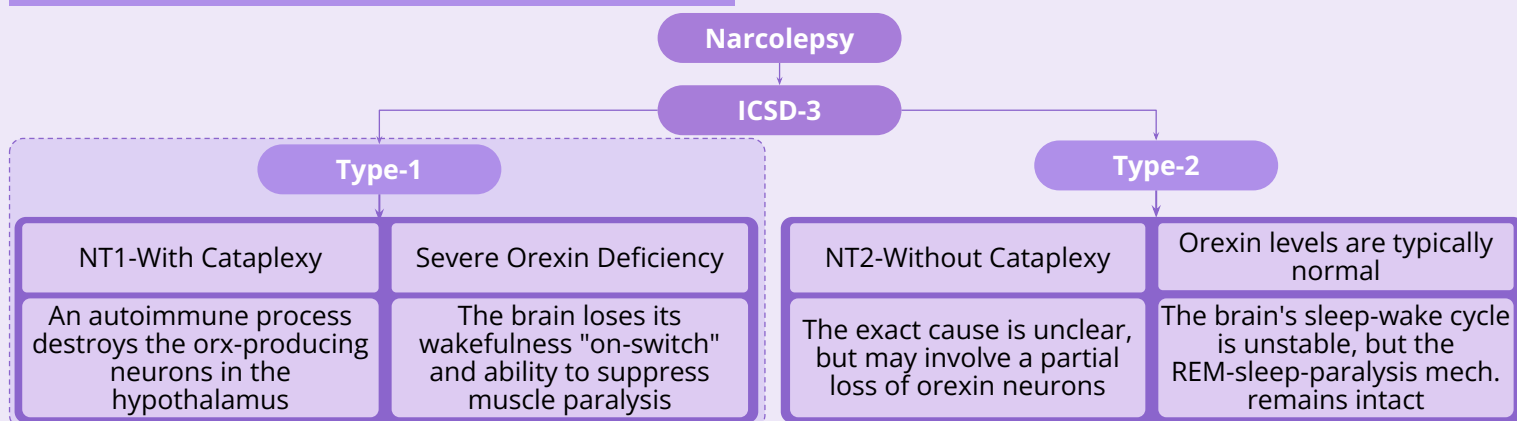
The prevalence of NT1 was similar between countries and between men and women



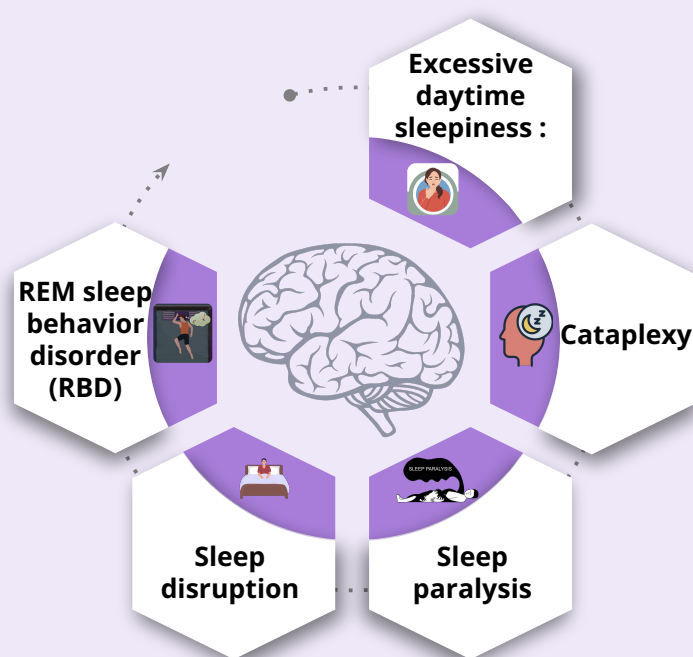
Age: The disorder affects men and women about equally



Types of Narcolepsy



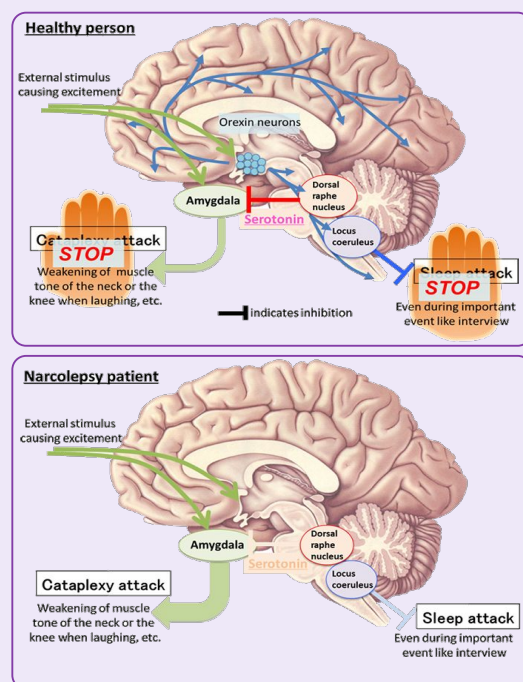
Symptoms of Narcolepsy Type 1



- 1 Excessive daytime sleepiness (EDS):**
EDS is a universal symptom of NT1 and NT2, but its severity varies; The sleepiness in NT1 and NT2 often manifests as "sleep attacks"
- 2 Cataplexy**
Cataplexy is a sudden, emotion-triggered loss of muscle tone that occurs in individuals with NT1
- 3 Sleep paralysis**
Sleep paralysis causes temporary inability to move or speak when falling asleep or waking up, often with vivid hallucinations
- 4 Sleep disruption**
Difficulties staying asleep at night
- 5 REM sleep behavior disorder (RBD)**
RBD is a condition in which individuals physically act out their dreams

Etiology & risk factor

Genetic predisposition	>95% of NT1 patients carry the HLA-DQB1*06:02 allele
Environmental triggers	Infections: H1N1 influenza, streptococcal, or general upper respiratory infections Vaccines: AS03-adjuvanted H1N1 vaccine (Pandemrix)
Family History	A family history of NT1 increases the risk
Puberty/Hormonal changes	Peak onset occurs during adolescence/puberty
Other Physical Triggers	Family history, head trauma/injury, severe physical/psychological stress, sarcoidosis, or stroke



The pathophysiology of NT1 is an autoimmune disorder characterized by the selective destruction of orexin-producing neurons in the hypothalamus of the brain

T cell-mediated autoimmunity (autoreactive CD4+ and CD8+ T cells)

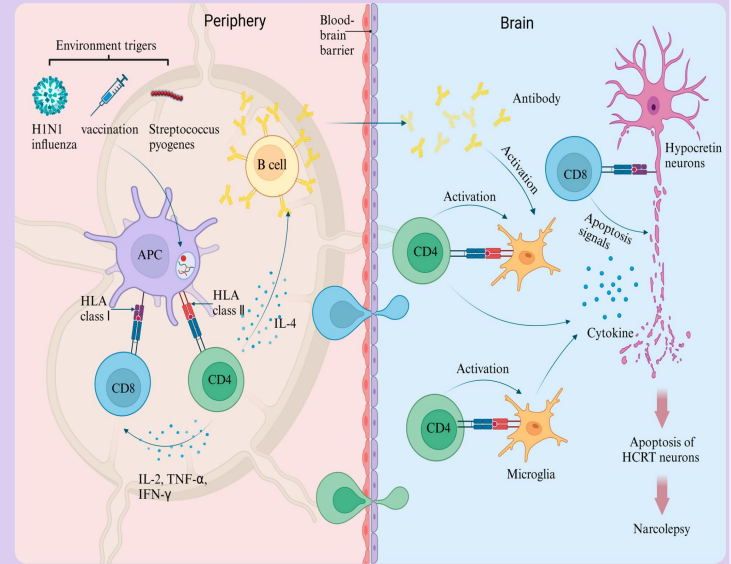
Key components: T cells, microglia and antibodies

Antigen-presenting cells (APCs) initially capture pathogens and present peptide fragments derived from these pathogens to naive T cells

Subsequently, B cells receive activation signals from these T cells, leading to their differentiation into plasma cells that produce antibodies

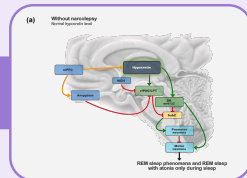
Activated T cells are capable of inducing inflammatory responses and secreting cytokines & chemokines, which can compromise the integrity of the BBB, facilitating the infiltration of lymphocytes & antibodies into the CNS within the brain

HLA-II is expressed only by microglia, while HLA-I is found in neurons. CD8+T cells can destroy hypocretin-producing neurons, and T cells and antibodies can activate microglia, whose inflammatory signals recruit immune cells and exacerbate damage to hypocretin neurons



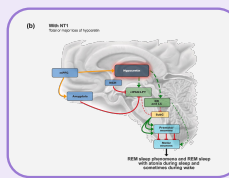
NT1 is a neurodegenerative condition involving specific dysfunction in the hypothalamus, REM-sleep regulation circuits and neurotransmitter systems

Normal REM Sleep Paralysis



- During REM sleep, your brain actively suppresses muscle tone to prevent you from acting out your dreams. This happens through a coordinated effort of several brain regions
- The Locus Coeruleus (LC), a brainstem nucleus that normally maintains muscle tone by releasing **norepinephrine** onto motoneurons, is inhibited
- Simultaneously, a region called the subcoeruleus (SubC) becomes active
- The SubC excites neurons in the **medial medulla** that release the inhibitory neurotransmitters **GABA and glycine**, which then directly inhibit motoneurons
- The combination of the LC's reduced activity and the SubC's active inhibition is what causes the complete loss of muscle tone during REM sleep

Narcolepsy Type 1 (NT1) and Cataplexy



- NT1 is characterized by a **lack of hypocretin neurons**. These neurons are crucial for stabilizing wakefulness and keeping the LC active
- In a healthy brain, hypocretin neurons are maximally active during positive emotions, which helps **maintain LC activity** and **muscle tone**
- In NT1, the **absence of hypocretin** makes the **LC's activity unstable during wakefulness**
- When a person with NT1 experiences strong emotions (like laughter or joy), a pathway from the **mPFC to the amygdala** is activated. The **amygdala then disinhibits the SubC region**
- This emotional activation of the **SubC**, combined with the **unstable LC activity**, triggers the same **muscle-paralyzing pathway** that normally occurs during **REM sleep**

Symptom overlap with psychiatric and other sleep disorders, along with a high prevalence of comorbidities, increases the disease burden

01

Eating disorders

- Narcolepsy is strongly linked to obesity, caused by a lower metabolism and reduced physical activity due to constant sleepiness
- There is an increased risk for binge eating, driven by intense food cravings rather than body image concerns

02

Sleep disorders

- Narcolepsy is frequently accompanied by other sleep disorders like sleep apnea, RLS/PLMS, RBD and insomnia, with adults having a 45.6% higher prevalence of sleep apnea. This comorbidity is also common in pediatric patients

03

Anxiety

- Anxiety disorders, including panic attacks and social phobias, affect up to 53% of narcolepsy patients
- This anxiety is often triggered by the unpredictability of cataplexy and the disorienting effects of hallucinations, creating a fear of losing control

04

Depression

- Depression affects over 57% of narcolepsy patients, and overlapping symptoms can complicate diagnosis
- The chronic burden of narcolepsy can lead to depression, but a shared hypocretin deficiency may also be a direct cause

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ADHD

- Mental fogging and excessive sleepiness of narcolepsy can be mistaken for inattention and hyperactivity of ADHD
- The hyperactivity can even be a compensatory response to being under-aroused

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Schizophrenia

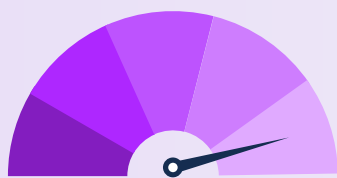
- Narcolepsy and schizophrenia share symptoms like hallucinations, sleep fragmentation, and psychosis
- Narcolepsy typically causes visual hallucinations, while schizophrenia causes auditory ones

Diagnosing Narcolepsy Type 1

Diagnosis is based on clinical symptoms, PSG, MSLT and sometimes CSF hypocretin levels

Epworth Sleepiness Scale (ESS):

- ESS is a self-assessment questionnaire designed to measure a person's general level of daytime sleepiness
- The total score - 0 to 24



0-5 6-10 11-12 13-15 16-24

Lower Normal Higher Normal Mild Normal Moderate Normal Severe excessive

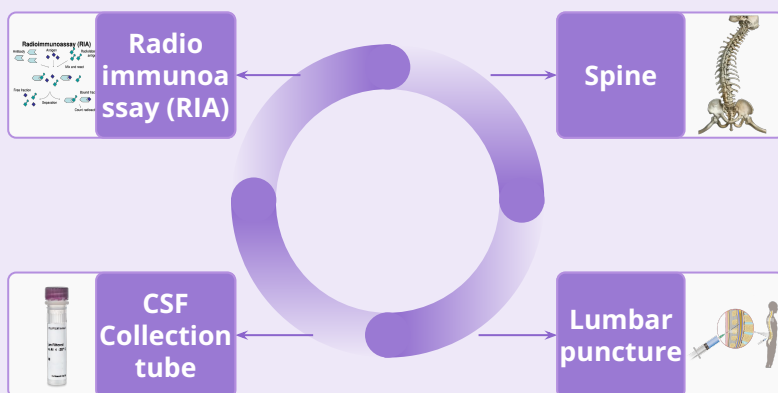
Polysomnography (PSG):

- The overnight test to rule out other sleep disorders like sleep apnea
- NT1 presents with a unique set of PSG findings that are linked to the dysregulation of REM sleep

Multiple Sleep Latency Test (MSLT)

- The primary data points measured are sleep latency (the time it takes to fall asleep) and the occurrence of Sleep-Onset REM Periods (SOREMPs)
- The entire trial is 20 min long from the start of sleep onset
- A positive result has: mean sleep latency of ≤ 8 min & ≥ 2 SOREMPs

The Biological Confirmation



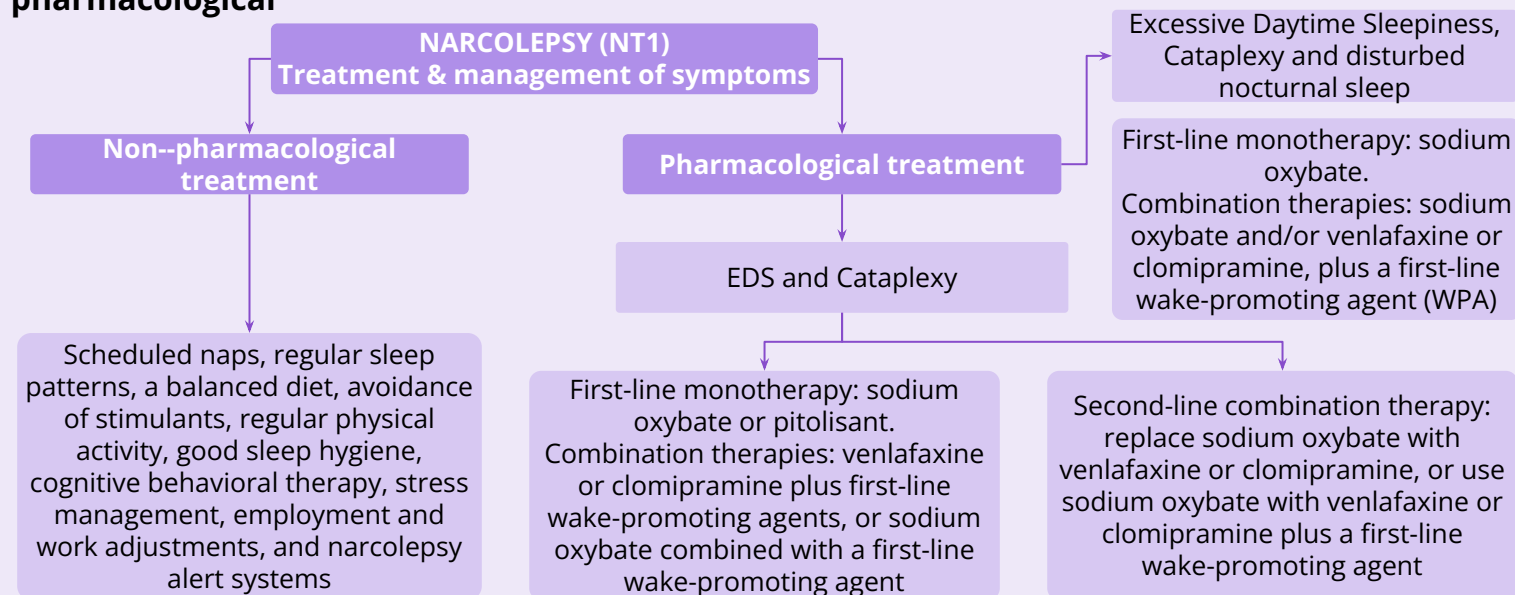
Cerebrospinal Fluid (CSF) Hypocretin-1 Measurement

- The diagnosis can be confirmed if a lumbar puncture (spinal tap) reveals a low concentration of hypocretin-1 (or orexin) in the CSF, specifically ≤ 110 pg/mL

HLA Typing

- While not a primary diagnostic tool, genetic testing for the HLA-DQB1*06:02 allele can provide supportive evidence

The treatment of narcolepsy is divided into two categories: Non-pharmacological and pharmacological

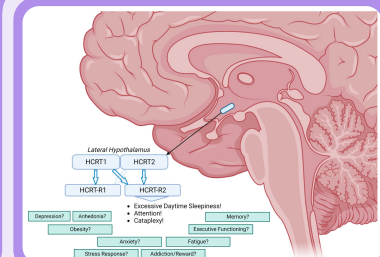


Currently FDA-Approved Treatments for NT1

COMPANY NAME	BRAND NAME	MOA	ROA	DOSE	Common AE
	ORZEFUL	ORX2 agonist		1 mg and 2 mg(BID)	Insomnia, pollakiuria, micturition urgency & salivary hypersecretion
	XYREM/XYWAV	GABAb agonist		4.5g - 9g (BID)	Anxiety, decreased appetite, diarrhea, dizziness, headache, hyperhidrosis, parasomnias
	LUMRYZ	GABAb agonist		4.5 g - 9 g (QD)	Reduced appetite, dizziness and nausea
	WAKIX	H3 receptor antagonist/inverse agonist		8.9-35.6 g	Anxiety, insomnia and nausea
	SUNOSI	DNRI		75-150 mg	Anxiety, insomnia, nausea, decreased appetite and headache
	RITALIN	DNRI		Varies	Dry mouth, loss of appetite, weight loss, headache, dizziness, tremors, tachycardia, elevated blood pressure, insomnia
	PROVIGIL	DNRI		100-200 mg	Anxiety, back pain, diarrhea, dizziness, dyspepsia, headache, insomnia & nausea
	NUVIGIL	DNRI		50-250 mg	Anxiety, back pain, diarrhea, dizziness, dyspepsia, headache, insomnia & nausea

Address the root cause, dual function and potential for broader effects

- Hypocretin deficiency results in a wide range of symptoms, including classic sleep-related symptoms and various non-sleep-related issues (e.g., mood disturbance, obesity, pain)
- The emergence of selective HCRT-2 agonists presents an exciting opportunity to treat the full spectrum of NT1 symptoms
- It remains to be determined if selective HCRT-2 agonists will be the "long-awaited holy grail" for NT1 treatment or just a "crucial stepping stone" to more advanced therapies





Contact us:

 sales@vyuhpharma.com

 Henderson, Nevada, USA - 89014

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