



## Narcolepsy: A Review

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### ABSTRACT:

Narcolepsy is a lifelong sleep complaint characterized by a classic tetrad of inordinate day dizziness with infectious sleep attacks, cataplexy (unforeseen bilateral loss of muscle tone), hypnagogic daydream, and sleep palsy.<sup>[1]</sup> This Review focuses on our current understanding of how inheritable, environmental, and immune-affiliated factors contribute to a prominent (but not insulated) orexin signaling inadequacy in cases with NT1. Data supporting the view of NT1 as a hypothalamic complaint affecting not only sleep – wake but also motor, psychiatric, emotional, cognitive, metabolic, and autonomic functions are presented, along with misdoubts concerning the ‘ narcoleptic borderland ’, including narcolepsy type 2 (NT2).<sup>[2]</sup> Narcolepsy paired with cataplexy is substantiated to be an autoimmune complaint.<sup>[3]</sup> These gestures of cataplexy can be brought on by strong feelings. This article critically appraises the substantiation for determination and treatment of narcolepsy.

**KEYWORDS:** Cataplexy, Hypocretin, Drowsiness, Hypersomnia, Polysomnography.

### INTRODUCTION:

Narcolepsy is an enervating lifelong rapid-fire eye movement (REM) sleep disease. Narcolepsy is characterized by inordinate day drowsiness and cataplexy, which may be accompanied by hypnagogic or hypnopompic visions and sleep paralysis.<sup>[4]</sup> Narcolepsy happened several times each day, frequently in unusual circumstances and occasionally with little warning.<sup>[5]</sup> Narcolepsy can produce a variety of life-stuff presumably more serious and pervasive than, for case, those of epilepsy, thus emphasizing the significance of early determination and treatment.<sup>[6][7]</sup> It frequently coexists with other sleep conditions, like obstructive sleep apnea progression, periodic limb movements in sleep, REM sleep behavior complaint, and nightly eating complication.<sup>[8-12]</sup>

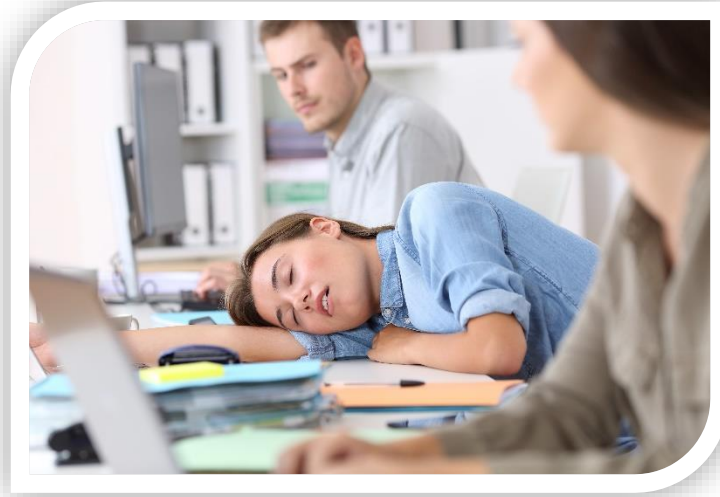


fig.1- Narcolepsy Condition

### EPIDEMIOLOGY:

The frequency of narcolepsy in European countries varies from 0.02 to 0.05.<sup>[13][14]</sup> It has been suggested that the differences in frequency may be partially related to the association between narcolepsy and the prevalence of the major leukocyte antigen (HLA) DQB1 \* 0602 phenotype.<sup>[15]</sup> The varying frequency rates may be as a result of varying disorder definitions, varying study designs, varying age group addition in studies, or an actual varying disorder prevalence due to other factors.<sup>[16][17]</sup> The group having narcolepsy without cataplexy may represent 10 – 50% of the narcolepsy population.<sup>[18]</sup> The estimated prevalence rate is 0.74/ 100,000 per year for narcolepsy with cataplexy and 1.37/ 100,000 per year for both narcolepsy with cataplexy and narcolepsy without cataplexy.<sup>[19]</sup>

### ETIOLOGY OF NARCOLEPSY:

1. Hypocretin Deficiency
2. Hypothalamic Lesions
3. Inherited Disorders (Eg. Niemann-Pick Disease Type C)
4. Brain Tumors
5. Craniocerebral Trauma
6. Cerebrovascular Disorders
7. Encephalomyelitis
8. Neurodegenerative Diseases<sup>[20]</sup>

**SYMPTOMS:**

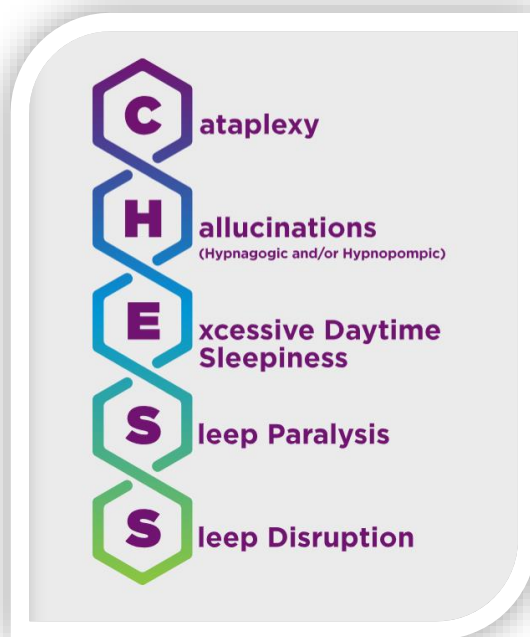


fig.2- Symptoms

**CLASSIFICATION:**

The international classification of Sleep Disorders For Narcolepsy:

Table-1

Narcolepsy With Cataplexy:
1) Inordinate day drowsiness nearly daily for at least 3 months
2) Definite history of cataplexy
3) Conclusion should be verified, whenever possible, by one of the following Polysomnography and MSLT”; mean sleep latency should be <8 minutes and at least 2 SOREMS.
4) CSF hypocretin level $\leq 110$ pg/ml or 1/3 of mean normal controls.
5) Hypersomnia is not better explained by another disorder or medication.

Table-2

Narcolepsy Without Cataplexy :
1) Extreme day drowsiness nearly daily for at least 3 months
2) Definite cataplexy isn't present.
3) Conclusion must be verified by polysomnography or MSLT Mean sleep latency should be $\leq 8$ minutes and $\geq 2$ SOREMS.
4) Hypersomnia isn't better explained by another disorder or drug

Table-3

Secondary Narcolepsy( Narcolepsy due to medical condition) :
1) Extreme day drowsiness nearly daily for at least 3 months.
2) One of the following is present definite history of cataplexy; if cataplexy isn't present.
3) Diagnosis must be verified by polysomnography and MSLT; mean sleep latency should be <8 minutes and at least 2 SOREMS; CSF hypocretin level $\leq 110$ pg/ml.
4) Underlying medical or neurological condition accounts for the sleepiness.
5) Hypersomnia is not better explained by another disorder or medication.

## PATHOPHYSIOLOGY:

The underlying pathological medium of NT1 is the loss of hypocretin signalling. The hypocretin system is made up of neurons producing hypocretin located in the hypothalamus. All narcoleptic cases are born with these neurons and the hypocretin shortage develops latterly in life. The exact medium that leads to the destruction of the hypocretin neurons in narcoleptic cases is still unknown. The only eventuality proposed thesis for the development of narcolepsy is due to a loss of immunological tolerance the autoimmune thesis. An autoimmune basis for narcolepsy has long been suspected and data from inheritable, epidemiologic and immunologic studies explosively suggest this to be the case. The development of an autoimmune condition is multifactorial and includes both bearing inheritable tendencies combined with an environmental detector.// In narcolepsy, both have been demonstrated with strong inheritable associations with HLA- DQB1 \* 0602 and other vulnerable grounded polymorphisms, as well as suggested environmental triggers including streptococcal infections, H1N1 infections and H1N1 vaccination.<sup>[21]</sup>

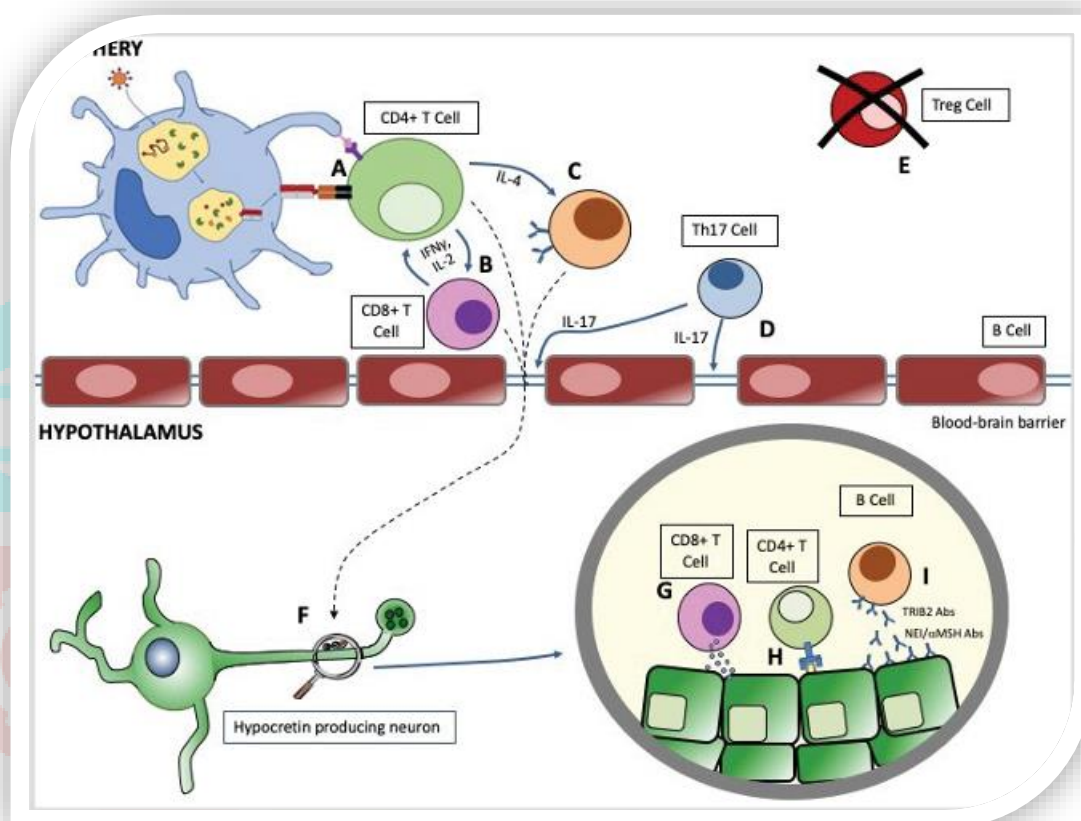


fig.3- Pathophysiology of Narcolepsy

In order to prove that a disorder or condition is the result of a loss of immunological tolerance, the presence of autoreactive vulnerable cells or autoantibodies must be demonstrated and an autoantigen correlated. Despite most years of examination, it remains unclear how the inheritable differences and environmental triggers actually contribute to the onset of this condition. As a result, veritably many studies in narcolepsy have produced confounding confirmation to establish the autoimmune pathogenesis. In 2010, two independent studies showed the presence of antibodies against tribbles homologue 2 (TRIB2)- a protein produced by numerous cells including hypocretin neurons in narcoleptic cases. These autoantibodies were firstly described in uveitis and were set up to have advanced titres in a small group of narcoleptic cases when compared to healthy controls. This was the first study to report the impact of the humoral vulnerable response in narcolepsy. The impact of TRIB2 autoantibodies is debatable and other studies have shown that the situations of these antibodies aren't increased in verified narcolepsy cases. Also, as TRIB2 is expressed on other cell populations both in the CNS and periphery, these antibodies are doubtful to have a direct part in the onset of narcolepsy.<sup>[22]</sup>

## DIAGNOSIS:

The first step in the diagnosis of narcolepsy is history- taking from the case and from mates, relatives, and buddies. Apart from atonia and areflexia in cases having active cataplexy, the physical examination should be normal. The current International category of Sleep diseases( ICSD- 2) description for narcolepsy is shown in Table 1,2 and 3. It's predicated on history, polysomnography, multiple sleep quiescence tests (MSLT), and dimension of hypocretin levels in cerebrospinal fluid. It classifies narcolepsy into three types (see Table). extreme day sleepiness is the most constant point of narcolepsy<sup>6</sup> and measuring it precisely is important. There are a number of private and objective scales to measure this.<sup>[23]</sup>

If the person is getting a minimum of six hours of sleep, the doctor will ask them to undergo the following tests:

### 1) Polysomnogram( PSG):

This is a sleep study done in a sleep clinic while a person is completely asleep. Then, doctors observe a person's sleep patterns, breathing, heart rate, and other functions to rule out other sleep diseases.

### 2) Multiple sleep latency test( MSLT):

A person will suffer an MSLT the day after the PSG. In it, a person will take four or five 20- minute naps within 2 hours. A positive test result will show a rapid-fire onset of REM sleep( in lower than 15 minutes) at least doubly during the test, and lower than eight minutes of mean sleep latency across trials.

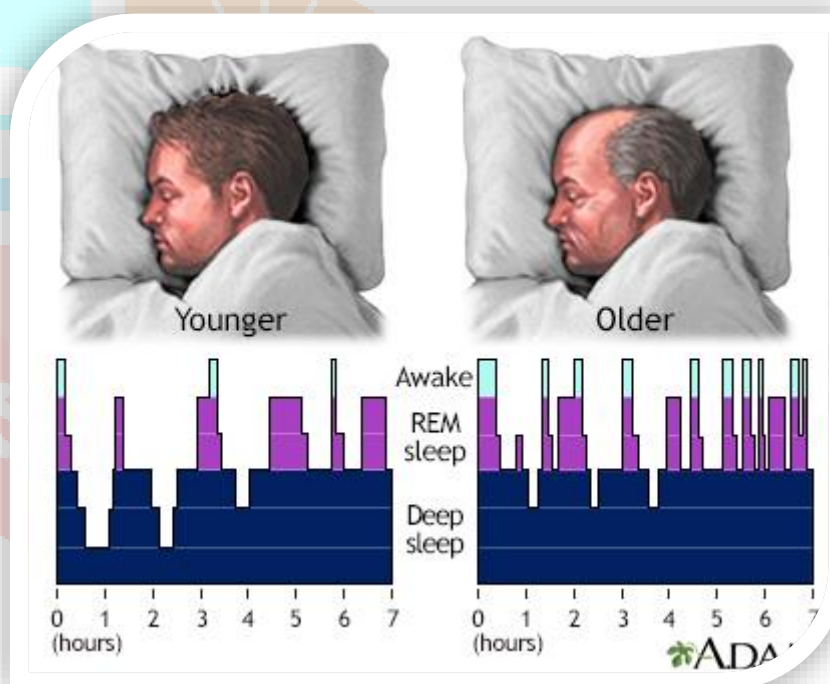


fig.4- Comparison in Younger and Older Patients

## TREATMENT:

The handling of narcoleptic cases can be achieved using both pharmacological and non- pharmacological agents. frequently a combination of both are employed in order to manage the condition. Non-pharmacological agents largely correspond of developing set behavioral strategies. Each strategy is individualized to each case and consists of avoiding sedentary conditioning, maintaining a regular night time routine and planning day naps.<sup>[24]</sup> Caffeine and energy drinks are also frequently consumed to fight bouts of inordinate day sleepiness but aren't sustainable and have been shown to have side effects which are mischievous to posterior sleep.<sup>[25]</sup> unborn treatments Introduction of hypocretin- 1 into the cerebral ventricular system was establish to be useful in mice but not in hypocretin- 2 mutated dogs. Intranasal administration is promising, as well as transplantation of neonatal hypothalamic stem cells into the brainstem.<sup>[26][27]</sup> Narcolepsy with cataplexy is highly suspected to be an autoimmune disease. still, attempts to modify vulnerable processes, including use of steroids, plasmapheresis, and intravenous immunoglobulin, have been met with limited and short- term success.<sup>[28]</sup>

Histamine 3 receptors regulate the release of histamine. Antagonism of the histamine 3 receptor enhances narcolepsy, while stimulation causes sedation. Histamine 3 receptor antagonists have been shown to be effective in dogs and mice.<sup>[29][30]</sup> Other promising new treatments include thyrotrophin-releasing hormone and the nicotine patch.

As research continues to provide insights into the mechanisms underlying narcolepsy, the development of new treatments continues to evolve, offering more options for optimising management of narcolepsy symptoms, particularly EDS and cataplexy.

## DRUGS USED IN TREATMENT OF NARCOLEPSY:

- 1) Pitolisant
- 2) Solriamfetol

- Investigational Drugs:

- 1) FT218 (controlled release sodium oxybate)
- 2) JZP-258
- 3) AXS-12 (reboxetine)
- 4) THN 102 (modafinil/ flecainide)<sup>[31]</sup>

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