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Review Article

Narcolepsy – A review

Narcolepsy - Clinical Characteristics, Aetiopathophysiology, Diagnosis and Treatment- A Global Review

Naga Prashant Koppuravuri[1]*, Sangeetha N [2], Thasvin U R [2], T Y Pasha [1], Rajesh Venkataraman V [2] and V Siva Ganesh [3]

[1]Dept. of Pharmaceutical Chemistry, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G.Nagara, Karnataka, India.

[2]Dept. of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G.Nagara, Karnataka, India

[3]Dept. of Pharmacology, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G.Nagara, Karnataka, India

Abstract: Narcolepsy is a rare chronic, debilitating sleep disease that is currently categorized as different types of CNS hypersomnia in narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2). Narcolepsy type 1 (NT1) is narcolepsy with cataplexy caused by a selective loss of hypothalamic neurons that produce hypocretin, while NT2 is narcolepsy without cataplexy and normal hypocretin levels. Hypocretin is a neurotransmitter that regulates sleep, body homeostasis, emotions, and behavior and has extensive projections to a variety of brain locations, including the locus coeruleus (norepinephrine neurons), tuberomammillary nucleus, raphe nucleus (serotonergic neurons), and dopaminergic neurons (ventral tegmental areas). Hypocretin is a neurotransmitter that not only excites the central nervous system, but also affects serotonin and histamine levels. Hypocretin is a neurotransmitter that regulates the activity of serotonin, histamine, dopamine, acetylcholine, GABA, and glutamate in the central nervous system. It is now understood to be a separate condition with its own pathogenesis and neurochemical abnormalities. Narcolepsy affects men and women equally and has a prevalence of 20–60 cases per 100,000. The highest rate is found in Japan, while the lowest is found in Israel. There is no cure for narcolepsy, despite a reliable pathophysiological hypothesis linking NT1 to an autoimmune process that damages hypocretin-producing cells. Because current symptomatic pharmaceutical treatments are not 100% effective for all symptoms, behavioral therapies play a synergistic role in the disease treatment. We examine the narcolepsy diagnostic and treatment options, including symptomatic pharmacological treatments as well as behavioral and psychological measures that may help doctors to improve narcoleptic patients' quality of life.

Keywords: Narcolepsy, Cataplexy, Orexin, SOREMs, EDS

***Corresponding Author**

Naga Prashant Koppuravuri , Department of Pharmaceutical Chemistry, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G.Nagara, Karnataka, India

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1. INTRODUCTION

Extreme daytime sleepiness (EDS) is a symptom of narcolepsy, which is a chronic, disabling sleep disorder. Narcolepsy is categorized as Narcolepsy type 1(NT1) and Narcolepsy type 2(NT2) a unique central nervous system hypersomnia according to the ICSD-III (International classification of sleep disorders). Narcolepsy type 1 (NT1) is narcolepsy with cataplexy caused by a selective loss of hypothalamic neurons that produce hypocretin, while NT2 is narcolepsy without cataplexy and normal hypocretin levels[1]. Hypocretin is a neurotransmitter that regulates sleep, body homeostasis, emotions, and behavior[2] and has extensive projections to a variety of brain locations, including the locus coeruleus (norepinephrine neurons), tuberomammillary nucleus, raphe nucleus (serotonergic neurons), and dopaminergic neurons [3](ventral tegmental areas). Hypocretin is a neurotransmitter that not only excites the central nervous system but also affects serotonin and histamine levels. Hypocretin is a neurotransmitter that regulates the activity of serotonin, histamine, dopamine, acetylcholine, GABA, and glutamate in the central nervous system [4]. Hypocretin deficiency can result in aberrant sleep regulation systems, which can lead to EDS and other REM manifestations such as hypnagogic or hypnopompic hallucinations[5]. Diagnosis of narcolepsy is based upon the Patient history, symptoms and with the help of diagnostic tools that includes multiple sleep latency test, video polysomnography, orexin levels, and neuroimaging. There is no cure for narcolepsy, and the therapeutic approach to treat narcolepsy includes cognitive therapy, psychological counseling, pharmacological therapy. Behavioral therapy plays a synergistic role in disease treatment. Nonpharmacological treatment includes dietary stimulants such as tea, coffee, mate, etc. as they have the advantage of not being considered as drugs and therefore, they have different psychological input. These beverages should be prepared in a consistent manner and drunk at scheduled times. The caffeine content of six cups of strong coffee has about the same stimulant effect as 5mg of dextromethorphan. The aim of this review is to provide complete and detailed information about narcolepsy as the currently available reviews are focusing on either of the one topics such as etiology, diagnosis, treatment methods etc. As this review provides complete information, which includes aetiopathogenesis, clinical manifestations, diagnostic tests and treatment options which is easy to understand and helpful for further research.

2. EPIDEMIOLOGY

Narcolepsy has an incidence of 20 to 60 occurrences per 100,000 [4]. Japan has the highest rate[6], while Israel[7] has the lowest. It's possible that the wide variation is due to variances in diagnostic criteria. In more than 80% of cases, the earliest symptoms appear between the ages of 15 and 35[8]. The life expectancy is average. Excessive drowsiness and spontaneous sleep episodes are the most common early symptoms. Complete remissions have not been reported, despite partial remissions being observed. It affects men and women equally, but in some cases, narcolepsy affected more men than women[9]. Environmental and genetic factors are most likely to blame. The evidence that narcolepsy patients have a higher mortality rate is still inconclusive [10]Narcolepsy typically begins in adolescence, with a slight second peak beginning around the age of 35. Narcolepsy affects 10-15% of patients before the age ten[11]. Prior to the twenty first century, however, narcolepsy in children had been examined infrequently[12]. Narcolepsy progress quickly, with symptoms appearing days or weeks after a triggering event, such as immunization, stress or head trauma, a long-term course with unpredictable symptom onset or a gradual course with years, if not decades, between the onset of distinct symptoms[13]. Different pathophysiological factors are most likely to be blamed for these diverse presentations[13]. In a study of 1,099 people with narcolepsy, Gianina Luca has discovered that, cataplexy occurs most frequently in the middle of the night. 49 percent of the cohort individuals developed concurrently with EDS, and the remaining 43 percent developed after EDS[14]. Only 8% of people have cataplexy before developing EDS. The time interval between the onset of EDS and the commencement of cataplexy is usually 2–3 years, but this might vary, it can last for up to 40-50 years[14]. Patients with narcolepsy without cataplexy may experience remission[15]. Narcolepsy without cataplexy, on the other hand, seldom remits (although it has been observed). Only one case has been recorded (in a patient who got immunotherapy soon after the commencement of the disease)[16]. Furthermore, narcoleptic symptoms usually improve with time, and the severity of EDS and cataplexy usually diminishes as people get older, as a result of coping mechanisms[17]. A study which was conducted in Finland in twins, born before 1958 and 30-60 years of age including 11, 354 individual's prevalence of NT1 was found to be 26 per 1,00,000 individuals[18].

3. ETIOLOGY

In the early 1980s, evidence reported that , narcolepsy was associated with the human leukocyte antigens (HLA)system and suggested the involvement of the immune system in its pathogenesis[19]. The demonstration of low CSF levels of orexin-A (and shortly thereafter of the selective loss of orexin neurons in the lateral hypothalamus) in patients with narcolepsy raised the possibility that , these cells were the target of such a process[20]. Orexin A and B are tiny neuropeptides that activate target neurons via type 1 and type 2 orexin receptors, respectively[21]. The loss of this critical system causes narcolepsy symptoms by disrupting the functioning of various frontal, limbic, diencephalic, and brainstem networks[22]. This dysfunction has been defined as a state of instability or lack of boundary control manifested by an inability to stay in sleep or waking states for the proper amount of time, as well as the occurrence of sleep events during wakefulness and vice versa[23]. As a result, narcolepsy sufferers have short periods of both waking and sleeping. REM sleep aberrant muscular relaxation (atonia) happens during wakefulness (cataplexy), and dreaming can happen at sleep–wake and wake–sleep transitions (hypnagogic or hypnopompic hallucinations). The presence of patients with narcolepsy with and without cataplexy who have normal levels of orexin in their CSF, as well as patients with low or absent orexin levels in their CSF secondary to hypothalamic damage who do not have narcolepsy or cataplexy symptoms, raises the possibility that a deficiency in orexin production is neither (always) necessary nor (always) sufficient to cause narcolepsy in humans[24]. Today, narcolepsy is considered to arise from multiple hits: the co-occurrence of genetic predisposition, environmental factors and triggering events eventually leads to the selective, immune-mediated destruction, dysfunction or silencing of orexin- producing neurons. It was reported the presence of autoreactive CD8+ and CD4+ T cells in NT1 and NT2[25], which provide further support to the hypothesis of a pivotal role of specific T cells in the neuronal damage seen in human narcolepsy[26].

4. GENETIC FACTORS

Narcolepsy is thought to affect people with a genetic susceptibility that predisposes to immune system activation when they are subjected to unknown environmental stimuli. Monozygotic twins are 25–30% concordant for narcolepsy with cataplexy[27], a level of agreement that suggests both a genetic predisposition and a role for environmental factors in narcolepsy. Despite the fact that just 1–2% of first-degree relatives have been diagnosed with narcolepsy, this suggests a 10–40x increase in risk when compared to the general population[27]. To date, the genes that encode the major histocompatibility complex (MHC) protein have been identified as the principal genetic risk factors for narcolepsy. HLA genes code for molecules that transmit antigen fragments to T-cell receptors, directing an immunological response to a specific antigen. HLA class II polymorphisms in the closely connected loci DQB1*06:02 and DQA1*01:02, which together produce the DQ0602 heterodimer, are strongly linked to type I narcolepsy (NT1). DQB1*06:02 is carried by almost all patients with narcolepsy and cataplexy (82–99%), although only 12–38% of non-narcoleptic individuals have this allele[27]. DQB1*06:02 is thought to be a susceptibility factor for the illness; homozygous DQB1*06:02 carriers have a two-fold increased risk of narcolepsy compared to heterozygous carriers. DRB1*03-DQB1*02, DRB1*1301-DQB1*0603, DQB1*05:01, DQB1*06:09, and DQB1*02, however are assumed to be strongly protective for the development of narcolepsy in Europeans[28] and HLA-DPA1(*)01:03-DPB1(*)04:02 and HLA- HLA class I alleles have also been linked to an increased risk of narcolepsy as well as protection from it[29]. Associations with a variation in the T-cell receptor alpha and beta genes, whose products identify antigens presented by HLA molecules, and Cathepsin H, which prepares antigens for presentation, are also predisposing factors for narcolepsy[30]. Rare missense mutations in the gene encoding the purinergic receptor subtype P2RY11, which is expressed in both cytotoxic lymphocytes and the brain, have been linked to narcolepsy and have resulted in functional changes. Both the calcium ion and the cyclic adenosine 3′ , 5′ -monophosphate (cAMP) pathways have abnormalities in P2RY11 signaling [30].

5. ENVIRONMENTAL FACTORS

The low occurrence of narcolepsy and cataplexy in monozygotic twins suggests that environmental factors play a role[31]. In some but not all studies, the season of birth was linked to the incidence of narcolepsy, suggesting that, early exposure to viruses, bacteria, or toxins may affect the development of the brain. Individuals with a weakened immune system are more likely to develop narcolepsy[32]. Environmental variables (such as infections) may reactivate or initiate an immunological response that results in the development of the disease. Orexin neurons are destroyed. The influenza A virus subtype H1N1 has the most significant link to infection. In 2009-2010, after immunization in Finland and other northern European nations where the Pandemrix vaccine had been used against pandemic H1N1 influenza, a statistically significant sixfold to ninefold increase in the risk of narcolepsy was documented[33]. Differences in vaccine content may explain why no other influenza vaccines demonstrated this association[34]. An immunological study released in 2019 reveals that orexin may be the target of an autoimmune reaction. This is triggered by molecular mimicry of a specific component of the influenza haemagglutinin protein[35]. Other immunizations have also been linked to narcolepsy, although these relationships could be coincidental[36]. Finally, narcolepsy has occasionally been reported to occur after traumatic brain injury (trauma to the brain)[37]. In the sera of narcolepsy patients, a few forms of autoantibodies have been detected[38]. On the other hand, sera from individuals with various sleep disorders and healthy controls were also found. Moreover, passive transfer experiments in animal models involving these autoantibodies didn't reproduce narcolepsy. The finding that narcolepsy occasionally occurs in combination with paraneoplastic syndromes and other autoimmune disorders, which includes multiple sclerosis, celiac disease, and systemic lupus erythematosus, provides indirect evidence of an autoimmune pathophysiology of narcolepsy[39]. In addition, some narcolepsy patients react to immunomodulatory therapy[40]. Although there are evidence of inflammation in the CSF, and a lack of disease-specific antibodies (pleocytosis and oligoclonal bands) was observed on rare occasions[41]. Increased levels of some cytokines (TNF and IFN), as well as CD4+ and CD8+ T cell activation, have also been observed in serum (and to some extent in CSF)[42]. Some authors identified autoreactive CD4+ and CD8+ T cells in individuals with NT1and NT2 that specifically target antigens expressed by orexin neurons in 2018. In accordance with this observation, two subsequent papers similarly reported the presence of autoreactive CD8+ and CD4+T cells in patients with NT1 [25,26,35].

6. CLINICAL MANIFESTATIONS

6.1 Excessive Daytime Sleepiness (EDS)

EDS is the most common (and disabling) symptom of narcolepsy, and it commonly manifests as an inability to stay awake, although it can also manifest as a subjective experience of sleepiness followed by focus difficulties. EDS is more commonly present in the morning hours and is usually irresistible, with fast sleep changes (so-called sleep attacks). Involuntary napping was observed by 80 percent of 1,079 patients in major European research[43], and bouts might range anywhere from a few seconds to 30 minutes[44]. These episodes are most common in routine conditions, but they can also happen while patients are active. Naps are usually (15–20 minutes) brief, restorative, and connected with oneiric (dreaming) experiences[45]. Patients can acquire so-called automatic behaviors, which are anomalous waking activities such as adding salt in coffee, writing beyond the edge of a piece of paper, or driving to the wrong destination[46], for which they can be amnesiac, resulting in blackouts. Individuals with narcolepsy who resist sleep are more likely to engage in such behaviors, but nonspecific symptoms such as headache, visual or sensory abnormalities, and hypoacusis can also occur (hearing loss). EDS must be separated from fatigue. Up to 60% of narcolepsy patients suffer fatigue, which is more resistant to treatment than EDS[47]

6.2 Cataplexy

The only specific symptom of narcolepsy that can be identified is cataplexy. In the presence of a normal state of consciousness, this term refers to brief episodes of bilateral decrease of muscular tone produced by unexpected emotions[45]. Unless the trigger is still present, partial attacks are very brief (2–10 seconds). Face drooping, eyelid closure, sagging of the jaw, dysarthria, passive tongue protrusion, and bilateral lack of motor control of the limbs are all symptoms of decreased muscle tone. The Babinski sign (a type of toe

reflex) appears briefly, and Parkinson's disease-related tremor may remain[48]. A few patients were completely unable to move (termed cataplectic immobility). One-third of patient's report falling, but injuries are uncommon. Partial attacks can progress over seconds to complete attacks with a length of less than 2 minutes; a duration of more than 5 minutes is infrequent and generally associated with the discontinuation of anticataleptic medicines[49]. Attacks using single muscles are unusual, and unilateral dominance is unusual[50]. Excessive movement in the form of phasic (facial muscle twitching), tonic (tongue protrusion, grimacing, or neck extension), and repetitive motor activities can be superimposed on muscular atonia, leading to a misdiagnosis of epilepsy or a movement disorder[50]. Positive motor phenomena may be more prevalent in youngsters and at the outset of disease [45,51]. The number of attacks per day varies from dozens to a few per year[52]. The most common cause is laughter; 50 percent of patients develop cataplexy while being tickled[44]. Cataplexy is more frequent during sports, hunting, playing games, and sexual intercourse (when it is called orgasmolepsia)[53]. Sudden or unexpected triumphant emotions (and, less commonly, aggressive emotions) favor cataplexy and explain its appearance during sports, hunting, playing games, and sexual intercourse (when it is called orgasmolepsia). Cataplexy is rarely triggered by negative emotions such as anger, fear, shame, suffering, or sorrow[45,54]. During cataplexy bouts, consciousness, ocular movement, and breathing are normally intact, however some patients describe blurred vision and a feeling of suffocation.

6.3 *Sleep Paralysis and Hallucinations*

When falling asleep (hypnagogic) or waking up, paralysis is defined as a complete inability to move (hypnopompic). The patients appear to be fully conscious, yet they are unable to move. Sleep paralysis is similar to cataplectic attacks in that it lasts longer (up to 10 minutes), occurs less frequently, and is not usually triggered by emotions. It is accompanied with vivid hallucinations in more than half of the patients[55], which can also occur on their own. Visual hallucinations are the most common, with auditory and tactile hallucinations being rare. Olfactory and gustatory hallucinations are rare. In 20-30% of narcoleptic individuals experiences all four symptoms of the narcoleptic tetrad[56]. The presence of another individual and attack scenarios has been reported on occasion. Hallucinations can be terrifying, and they can make you afraid of falling asleep. Patients usually know right away that, the sensations aren't or can't be real, although narcolepsy-related hallucinations can be strong enough to lead to a misdiagnosis of schizophrenia[57]. Dream delusions occur when patients with narcolepsy act in accordance with prior dreams that aren't necessarily hypnagogic hallucinations[58].

6.4 *Cognitive Disturbances*

Patients with narcolepsy have attention deficit hyperactivity disorder (ADHD), impaired cognitive performance, altered executive functioning, trouble sustaining attention, and decision-making issues[59]. EDS is thought to be the primary cause of these cognitive abnormalities[60].

6.5 *Metabolic Disturbances*

In the early 1920, overweight was first identified in people with narcolepsy and cataplexy[61]. Individuals with narcolepsy have a higher BMI (up to 10-20%) than the normal population [11,62]. Despite a higher frequency of diabetic mellitus, patients with narcolepsy have a decreased rate of lipolysis and remain insulin sensitive, which is likely due to their higher BMI. Some studies[11,63] found lower metabolic rates, decreased motor activity, and aberrant eating habits. These alterations are assumed to be the result of underlying hypothalamic-pituitary dysfunction, which could also explain why people with narcolepsy have a higher rate of precocious puberty [11,63].

Fig 1: Major Narcolepsy Symptoms[64]

6.6 *Fragmented Nocturnal Sleep*

Nocturnal waking spells, which occur in 60–80% of all narcoleptic patients, are typically brief and rarely last more than an hour[65]. Despite the irregular night sleep, the total sleep time in narcolepsy appears to be normal. There is also no evidence of changed non-REM sleep (NREM)[1], and nocturnal awakening and daytime sleep attacks appear to be unconnected[66]. Furthermore, sleep-onset insomnia is uncommon in narcolepsy patients. Patients with narcolepsy, on the other hand, occasionally appear with long and unbroken sleep periods, sleep inertia, or sleep drunkenness (especially at the outset of the condition and in childhood)[67]. Only a weak link exists between nocturnal sleep disruption and EDS[68].

Periodic limb movements are associated with the severity of EDS and orexin insufficiency in non-REM and REM sleep, as well as waking[69]. Patients with narcolepsy may be more prone to restless legs (or limbs) syndrome[70]. Dreams are frequently described as vivid, with archaic or bizarre as well as delusional components. Narcolepsy sufferers are more likely than the general population to have nightmares and lucid dreams[71].

6.7 Autonomic Disturbances

Fainting spells, erectile dysfunction, night sweats, stomach/intestinal disorders, hypotension, dryness of mouth, palpitations, altered skin temperature profiles, and abnormal pupillary function have all been reported in conjunction with narcolepsy but have not been explored in depth[72]. Finally, narcolepsy sufferers are more likely to experience olfactory impairment, headaches, and chronic lower back pain. At this time, the origin and significance of these characteristics in the diagnosis of narcolepsy are unknown (Cohen et al., 2018).

6.8 Psychiatric and Emotional Disturbances

In the context of psychoanalytic ideas of dreams, a mental etiology for narcolepsy was preferred until the 1950s[74]. Several studies have linked narcolepsy to psychiatric disorders. First, narcolepsy can be triggered by stressful life experiences[75]. Second, psychiatric disorders are more common in people with narcolepsy than in the general population; for example, 20–30% of narcolepsy patients experience depression and anxiety (Droogleever Fortuyn et al., 2011). Third, patients with schizophrenia and other psychiatric illnesses have been observed to experience narcolepsy-like symptoms[22]. Patients with cataplexy can develop functional impairments linked with pseudo cataplectic events, complicating treatment options[77]. Furthermore, observations in humans and animal models support the theory that narcolepsy is caused by a basic malfunction of reward and emotional processing networks. Narcolepsy is linked to a lower quality of life, as well as a higher chance of car accidents, injuries, and other health issues (Ohayon et al., 2014).

7. PATHOPHYSIOLOGY

Normal sleep is divided into two types: REM (rapid eye movement) and non-REM (non-rapid eye movement) sleep[79]. NREM phases S1 to S4 are followed by REM sleep, which lasts about 90 minutes and is repeated 4 to 5 times per night[79,80]. REM during the start of sleep or within10 minute of falling asleep, Sleep onset REM periods (SOREM) is the most common symptom of narcolepsy[81]. The mechanisms of narcolepsy have evolved over time in the last 40 to 50 years. In the1960s, it was identified that several of its features were connected to REM sleep dysregulation; for example, when falling asleep, people with narcolepsy entered REM sleep faster than those without. This is known as a sleep onset REM period or a decreased REM sleep latency (SOREMP). This transition to REM sleep can occur at any time. Without ever entering NREM sleep, right after falling asleep[80]. Narcolepsy is characterized by cataplexy, sleep paralysis, and hypnagogic hallucinations. All of this could be due to the effect of REM sleep intruding into waking life. It should be highlighted, however, that cataplexy is pathognomonic for narcolepsy[80]. Except for the ocular and breathing muscles, severe bouts might result in full paralysis. Narcoleptic symptoms are most likely caused by changes in the brain's chemistry, according to pathophysiological characteristics. Several lines of evidence link narcolepsy to cholinergic dysfunction and mechanisms involving monoaminergic neurotransmitters, which are important in the regulation of proper sleep[82]. In the amygdala, globus pallidus, putamen, and nucleus caudates, altered alpha-1and alpha 2 receptor binding have been seen. Increased rates of particular monoaminergic metabolites, are also linked to changed monoaminergic functioning in narcolepsy[83]. Narcolepsy symptoms have also been linked to the cholinergic and dopaminergic systems. M2 stimulation of the cholinergic system, which increases cataplexy, and M2 and D2/D3 receptor abnormalities in the pons have been shown in animal models[84]. The concentration of dopamine and its metabolites in CSF is reduced in narcoleptic patients[85]; In D1-and D2-receptor the data for binding in the basal ganglia and amygdala have been inconsistent[86,87]. In 1998, two groups of researchers independently found a novel hypothalamic peptide neurotransmitter, named orexin and hypocretin[88]. In the lateral hypothalamus hypocretins 1 and 2 are produced by a group of thousands of neurons[89]. Investigations in dogs with sporadic autosomal recessive narcolepsy found evidence of a Hcrtr-2 mutation[90]. To date, three distinct hcrtr-2 mutations have been identified, all of which result in a total loss of function while the hcrt-1 mechanisms remain intact[91]. In mice, knocking down pre hypocretin resulted in a narcolepsy-like phenotype[92]. Except in one example, no evidence of hcrt-1, hcrt-2, hcrtr-1, or hcrtr-2 mutations has been found in people[93]. However, Nishino and colleagues found low hcrt-1 levels in the CSF in seven out of nine narcoleptic patients, and post-mortem examinations revealed a substantial loss of hypocretin-containing neurons in narcoleptic patients' hypothalamus[93]. According to a study, narcolepsy has the strongest link to HLA*0602, which is found in 95% of narcoleptic patients with cataplexy and 41% of narcoleptic patients without cataplexy, but only 18% to 35% of the general population[80]. Low levels of hypocretin in the central nervous system (CNS) are currently used to aid in the diagnosis of narcolepsy[94]. Hypocretin-1 levels in the CSF that are less than 110 ng/L have a strong positive predictive value. Hypocretin-1 concentrations in the CSF were almost always greater than 200 ng/L in controls and people with various sleep and neurologic problems (Dauvilliers et al., 2007). Low CSF hypocretin concentrations in the absence of narcolepsy have been linked to Guillain-Barre syndrome subtypes, brain tumors, vascular disorders, and head trauma in rare cases[89]. These findings, coupled with other evidence, show that hypocretin insufficiency is to blame for the majority of narcolepsy cases accompanied by cataplexy, while the source of hypocretin cell loss remains unknown. There is also no evidence that an immunological reaction plays a role in the death of hypocretin neurons[89].

Table 1. Narcolepsy Symptoms and Associated Features[17]

Symptoms	Associated features
Leading symptoms	Excessive day time sleepiness
Associated sleep wake symptoms	Fatigue, sleep paralysis, hallucinations, frequent dreams, Nightmares, lucid dreams and enacted dreams, Disturbed night sleep, restless legs syndrome,

	Parasomnias.
Other associated manifestations	overweight, autonomic disturbances, anxiety, Depression, ADHD, headache, olfactory dysfunction, Digestive disturbances, decreased quality of life.
Ancillary findings	short sleep latencies and disturbed vigilance Sleep-onset rapid eye movement episodes HLA-DQB1*06:02 positivity Sleep-disordered breathing REM sleep behavior disorder Periodic limb movements Loss of REM sleep atonia

Histaminergic system: Histaminergic neuronal activity and release are at their peak during wakefulness, but can be reduced if histaminergic neurons are destroyed or histamine signaling is inhibited. In some studies, found that patients with NT1 or NT2, histamine levels in CSF have been linked to sleepiness and hypocretin 1 levels, with mixed results. There were no differences detected, for example, changes the levels of histamine or its metabolite tele methylhistamine in patients with NT1 and other central nervous system disorders. This indicates that patients with NT1, an increased number of histaminergic neurons in the brain, the level of histamine or its metabolite in the CSF are not useful for the diagnosis of narcolepsy[18]. Hypocretin deficiency: In the human lateroposterior hypothalamus, there are approximately 70,000 hypocretin-producing neurons, which project to almost the whole neuraxis. Other indicators of hypocretin-producing neurons (besides hypocretin) are also lacking in the brains of NT1 patients, thus it's a prevalent misconception that hypocretin neurons as a whole are destroyed[18].

8. DIAGNOSIS

In large-scale European research, the mean time between symptom start and diagnosis was shown to be as long as 14 years[14]. Diagnosis of narcolepsy is often particularly difficult and delayed in children, in part because of their sometime unusual presentations of EDS and cataplexy. Furthermore, there is no normative data for multiple sleep latency test (MSLT) findings in children, and there is little experience with CSF orexin measures in children under the age of six.

8.1 Narcolepsy Type 1

Type 1 narcolepsy (NT1) is defined by the current international classification of sleep disorders as the presence of EDS for more than three months in conjunction with either CSF orexin levels of less than 110 pg/ml (measured using a method that has not been validated internationally) or cataplexy and a mean sleep latency of less than 8 minutes on the MSLT and at least two SOREMPs (sleep onset REM periods) during the MSLT and/or night-time polysomnography. Type 1 Narcolepsy is most frequent and well-understood type of narcolepsy. A positive diagnosis of narcolepsy type 1 (NT1) can be made on clinical grounds (TABLE 1). EDS is frequently the first symptom, but only cataplexy is associated with it. Although EDS is frequently the first symptom, only cataplexy is pathognomonic for narcolepsy. As a result, determining the cause of cataplexy is critical. Cataplexy, on the other hand, is uncommon and must be diagnosed based on the patient's medical history; no validated methods exist; however, a standardized trigger test might be useful[95]. Only a few studies back up the value of videographic and neurophysiological recordings of cataplexy[51]

8.2 Narcolepsy Type 2

In the current international classification of sleep disorders, NT2 is defined as the presence of EDS for more than three months without cataplexy, but with a mean sleep latency on the MSLT of less than eight minutes and two SOREMPs on the MSLT and/or nocturnal polysomnography, as well as CSF orexin levels greater than 110 pg/ml (or not measured). The diagnosis of NT2 must be altered to NT1 if cataplexy develops over time or CSF orexin levels fall below 110 pg/ml. In comparison to NT1 patients, NT2 patients have less severe EDS and a lower frequency of REM sleep-related symptoms such as sleep paralysis, hallucinations, and RBD (rapid eye movement sleep behavior disorder)[96]. Despite this, NT2 is remains a controversial entity. This uncertainty persists in part because NT2 is a diagnosis of exclusion, which means that auxiliary tests must rule out alternative causes of the patient's symptoms (such as chronic sleep loss or deprivation, sleep apnea, circadian rhythm abnormalities, and medication and/or substance addiction). Several observations, however, suggest the existence of NT2. First, in people with initially isolated EDS, cataplexy usually develops after a few weeks, though the interval can span several decades. Second, people with narcolepsy who do not experience cataplexy show some orexin loss in their brains[97]. Third, partial orexin depletion causes EDS but not cataplexy in animal models[98].

8.3 Drawbacks of Current Criteria

The current international classification criteria have been criticized because they overemphasize the value of ancillary findings that are either nonspecific (SOREMPs) or not sufficiently validated. Although orexin deficiency is a well-validated biomarker of narcolepsy, current tools for measuring CSF orexin levels exhibit some methodological issues[99]and may also detect inauthentic orexin metabolites[100]. Furthermore, they do not provide verified (operational) standards for cataplexy diagnosis and do not account for the existence of various narcolepsy phenotypes and etiologies. HLA-DQB1*06:02 positivity, SOREMPs and decreased CSF orexin levels can also be found in patients with partial or atypical or even without any clinical features of narcolepsy[101].

8.4 Narcolepsy Phenotypes.

From a clinical standpoint, several possible phenotypes of narcolepsy can be identified: Narcolepsy with typical (unequivocal) cataplexy and with all biological indicators (namely, HLA- DQB1*06:02positivity, sleep-onset REM episodes and decreased or absence of orexin A); narcolepsy with typical cataplexy but without any biological markers; narcolepsy without cataplexy but with some biological markers; and the presence of some biomarkers in the absence of narcolepsy symptoms[15,97]. Narcolepsy with typical

cataplexy and all standard biological indicators can present as narcolepsy without cataplexy and normal orexin A levels in the CSF at first. As a result, current diagnostic criteria do not recognize this disease entity as a kind of narcolepsy or distinguish it from idiopathic hypersomnia (except for one subtype of idiopathic hypersomnia linked with prolonged sleep time and 'sleep drunkenness')[102].

8.5 Narcolepsy Etiologies.

Four types of narcolepsies can be distinguished based on their etiology: sporadic idiopathic narcolepsy, familial narcolepsy, sporadic secondary narcolepsy (due to brain injury and other diseases)[24], and hereditary secondary narcolepsy (narcolepsy-plus syndromes)[103]. Focused lesions in the hypothalamus (for example, in neurosarcoidosis or neuromyelitis Optica) and brainstem are the most common causes of sporadic secondary narcolepsy [103]. In hereditary Narcolepsy, which is linked to neurological impairments or disorders such as deafness, cerebellar ataxia, and polyneuropathy in inherited narcolepsy syndromes [103]. There has also been evidence of a link between narcolepsy and multifocal brain illnesses (such as traumatic brain injury or multiple sclerosis) [39,104].

9. DIAGNOSTIC TESTS

To confirm the diagnosis of narcolepsy as defined by current international criteria, US guidelines proposes sleep questionnaires, video polysomnography, MSLTs, and orexin measures. However, the sensitivity and specificity of several of these tests are limited. HLA-DQB1*06:02 Positive genetic testing adds nothing to the certainty of an NT1 diagnosis; however, its absence makes an NT1 diagnosis extremely unlikely. Genetic testing is therefore beneficial in patients with ambiguous clinical findings.

9.1 Questionnaires

On the generic Epworth tiredness scale, patients with narcolepsy typically score 18 (range 14–20 out of a potential 24) points[102]. In three different populations, the Swiss Narcolepsy Scale was found to have the best sensitivity and specificity (both > 90%) for the diagnosis of narcolepsy with cataplexy, and it was also superior to the Ullanlinna Narcolepsy Scale[61,105].

9.2 Multiple sleep latency test

Multiple sleep latency tests were performed. The sensitivity and specificity of typical short sleep latency and SOREMP findings are approximately 70–80 percent for NT1 and (as defined) 100 percent for NT2.The MSLT revealed that patients with NT2 had longer non-REM and REM sleep latency lengths than those with NT1[96]. Age, shift work, sleep deprivation, and medication, on the other hand, have an impact on MSLT results[101]. The MSLT detects more than two SOREMPs in 4–13% of the general population's healthy people, and 3–6% of this group meets the MSLT criteria for narcolepsy diagnosis [101,106]. The sequencing of sleep stages may be a stronger indicator of EDS etiology than sleep delay duration[107]. In patients with NT1, typical MSLT findings are also present at follow-up examinations, whereas in individuals without cataplexy, the MSLT findings frequently improve or SOREMPs disappear over time[108].

9.3 Video polysomnography

During nocturnal video polysomnography, SOREMPs can be detected in 50% of NT1 patients[109], and this test appears to be more specific but less sensitive than the MSLT for narcolepsy diagnosis. Other findings on video polysomnography in patients with narcolepsy include awakenings and/or arousals after sleep onset, an increased amount of stage 1 sleep, frequent shifts to N1 sleep or waking from deeper stages of sleep, insufficient non-REM sleep density, increased frequency of sleep-disordered breathing, minor motor events during REM sleep, RBD and periodic limb movements in sleep[69]. For the detection of EDS and SOREMPs in toddlers and preschool children, continuous 24h polysomnographic recordings are preferred to nocturnal polysomnography and MSLT.

9.4 Orexin levels

CSF levels of orexin A are either greatly decreased (<110 pg/ml) or undetectable in 95% of patients with NT1. Although the radioimmunoassay currently used to evaluate orexin A levels yields only relative values, cannot quantify tiny changes, and may also detect inauthentic orexin metabolites[100], this is the most sensitive and specific diagnostic test for NT1. CSF orexin levels are frequently normal in patients who do not have cataplexy (so-called NT2). However, some of these individuals (10–25 percent in big series; range 0–40 percent) have CSF orexin A values 110pg/ml and are thus identified with NT[99]. Patients with familial and secondary narcolepsy, as well as HLA-DQB1*06:02-negative patients, have normal orexin levels in their CSF[99].

9.5 Neuroimaging

A variety of neuroimaging studies have been performed in patients with narcolepsy in the past 20 years. Older structural imaging modalities showed normal findings; however, reports published in the past 3–4 years, which used more-advanced techniques, suggest that the frequency of brain abnormalities (such as demyelinating and vascular changes) might have been underestimated[39]. The number of quantitative morphological, spectroscopic and metabolic imaging studies is limited, and their results often could not be replicated[110]. By showing changed patterns of activity in the hypothalamus, corticolimbic, and brainstem reward circuits with laughter, functional MRI investigations have revealed fresh insights into the neural networks underlying human cataplexy[111]. Patients with narcolepsy have been shown to have impairments in reward and affective processing, which could explain why they sleep so much.

9.6 Diagnostic delay

Because of the long time between onset of symptoms and diagnosis, many narcolepsy patients go undetected or are misdiagnosed, resulting in a higher prevalence of narcolepsy and a barrier to patient care. Although the lack of a simple, accurate diagnostic test for narcolepsy may play a role in the diagnostic lag, since these symptoms could be a sign of something else for which there is a higher level of awareness. Cataplexy should not be ignored, can be used as the only factor for identifying whether or not someone has narcolepsy. In addition, all patients with EDS should include narcolepsy on their differential diagnosis list because the two disorders can occur at the same time. There is a need for educational programs to raise knowledge of narcolepsy symptoms and the proper diagnosis procedures. Such activities should target a

variety of people involving both health-care providers, the general public, Teachers, school counsellors, school psychologists, and nurses are all examples of people who work in schools. Educational efforts should not just focus on symptom descriptions, but also on the psychological impact that these symptoms may have on individuals, because the impact, at least in some patients, may be more easily identified than the symptoms themselves. The importance of being referred to a qualified specialist should also be stressed, because early referral combined with increased symptom awareness may have a positive effect. Synergistically, they help to shorten the time between the development of symptoms[112].

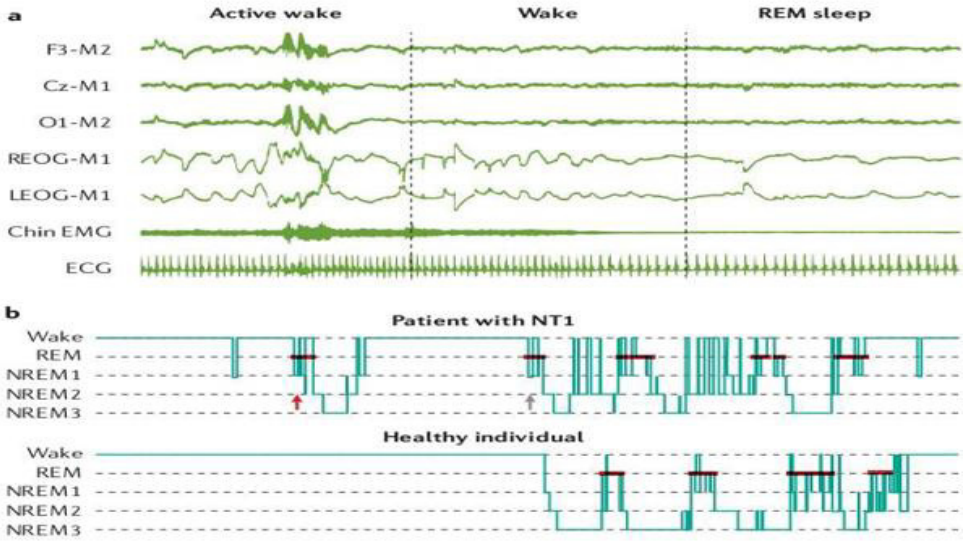

Fig 2: Electrophysiological Hallmarks of NT1[18].

a) During a patient's second multiple sleep latency test nap, three consecutive epochs with a direct transition between epochs of awake and an epoch of rapid eye movement (REM) sleep with type 1 narcolepsy (NT1). A total loss of muscular tone is noted as part of the transition in the electromyography (EMG) channel, whereas electroencephalography (EEG) (F3M2, CzM1, and O1M2) shows theta activity is identical to that of wake channels, and the electrooculography (EOG) channel shows eye movement. b) A hypnogram of a patient with NT1 recorded during a continuous polysomnographic recording. During a spontaneous daytime nap, sleep-onset REM periods (SOREMPs) can be observed (red arrow) as well as during nocturnal sleep (grey arrow). It is possible to witness frequent awakenings compared to a healthy individual subject. ECG; electrocardiography; LEOG-M1, left eye EOG; NREM, non-REM; REOG-M1; right eye EOG[18].

10. TREATMENT

There is no cure for narcolepsy, and the treatment methods that are currently available are not entirely effective for all symptoms. In this context, behavioral therapies play a synergistic role in the disease management.

10.1 Non-Pharmacological Treatment

Narcolepsy has been linked to serious and significant psychosocial costs[113]: for example, narcolepsy has been linked to a higher risk of work- and traffic-related accidents[114], sexual dysfunctions[115], neuropsychological changes[116], and a significant reduction in overall life quality[117], and a considerable reduction in overall life quality Clinical guidelines in several countries (UK and European Association of Neurology for Europe, and American Academy of Sleep Medicine consensus for North America) [118,119] encourage the use of cognitive and behavioral actions, such as nap scheduling, as complementary therapies to reduce the risk of sleep disorders. The UK consensus recommendations[118] propose a symptomatologic approach to managing narcoleptic symptoms, including increased patient knowledge of the disease, scheduled naps, nocturnal sleep length, job planning assistance, and psychosocial support. On the contrary, guidelines proposed by the American Academy of sleep Medicine[119]do not describe any behavioral measures, although the need to improve the quality of life of patients with narcolepsy is identified.

10.2 Behavioral Treatment for EDS

The best strategy to improve daytime sleepiness is to plan daytime naps, according to several research[118]. Naps of 15 to 20 minutes, scheduled two or three times per day, are especially useful in alleviating EDS and increasing alertness. Naps should not last longer than 30 minutes, as they may be unrefreshing and produce increasing drowsiness. Short naps helped some patients [120], but long naps helped others sleep better at night[120]. Because some people need to stay concentrated on their jobs for a period of time during the day, planned naps may prove to be an impractical solution. In addition, it has been suggested that sleep extension sessions be done for the treatment of EDS. The sleep satiation strategy is based on the sleep homeostasis theory and involves extending nocturnal sleep for two weeks (nocturnal sleep period: 10:00 pm to 6:00 a.m.)[121]. Sleep satiation is a technique that involves detecting the frequency of a behavior in order to evaluate the degree of drowsiness and keeping a sleep diary to track the number of sessions. Then, continuous 1-day episodes are scheduled without light dark cues. This behavioral disposition can clarify the benefits of naps and scheduled nocturnal sleep extension.

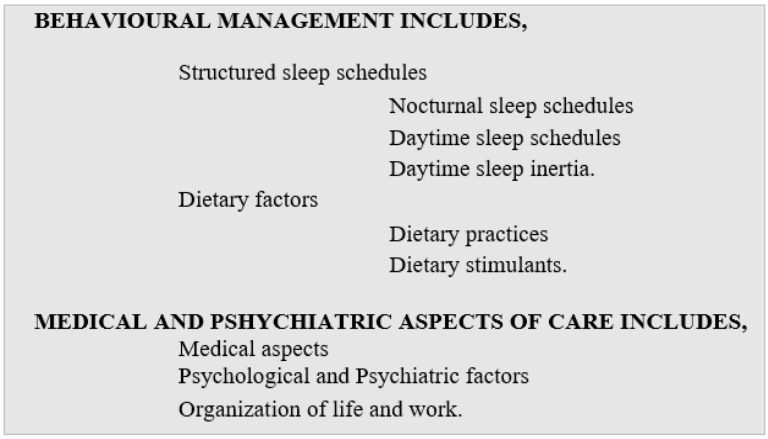

Fig 3: Behavioral Management

10.3 Cognitive Therapy

Since 2001, many studies have established the effectiveness of cognitive behavioral treatment (CBT) for narcolepsy. The goal of this technique is to discover and maybe modify the patient's dysfunctional cognitions and treatment adherence, as well as to identify patients who are taking multiple medications. Taking drugs at the right times, practicing excellent sleep hygiene, and taking scheduled naps are all recommended[122]. The influence of narcolepsy symptoms on the patient's quality of life, emotions, and other functional domains is highlighted in therapy[123]. The first randomized study[115] used self-report measures (such as the Epworth Sleepiness Scale, Ullanlinna Narcolepsy Scale, and SF 36) to see if a multicomponent (sleep satiation, nap training, cognitive restructuring, and problem-solving techniques) treatment outperformed standard treatments (control group, 6 months and 1 year of treatment). The therapy group, in particular, showed a significant improvement. Not only in terms of quality of life (physical function, social function, vitality, and emotional role), but also in terms of subjective EDS reports have improved. A different study[124] attempted to determine the efficacy of cognitive interventions in the treatment of narcolepsy. It was hypothesized that interventions such as cognitive restructuring and intervention will reduce the problem-maintaining safety behaviors. Researchers analyzed the patients' overall quality of life and gave them a questionnaire on their beliefs and attitudes toward narcolepsy before starting CBT. The CBT group had considerably higher post-treatment assessment scores ($p > 0.005$) than the control and drug treatment groups.

10.4 Physical Activities

Physical activity is recommended on a regular basis. Indeed, some studies have shown that it has a good effect on drowsiness, and it could be helpful in tracking the weight gain that often occurs with the commencement of NT1. In an animal investigation, wheel running increased wakefulness in hypocretin knockout mice. Cataplexy, on the other hand, increased [92]. According to an actigraphy study in NT1 children and adolescents[125], regular physical activity is associated with significant changes in children's sleepiness and sleep/awake profiles (fewer daily NAPs and less time asleep thought the day) and does not provoke cataplexy.

10.5 Cataplexy

Various symptomatic techniques, already utilized. to treat other types of diseases where the emotional or physiological component was central, were offered as part of the CBT approach. One of these symptomatic methods for cataplexy is systematic desensitization. The CBT method is based on a gradual approximation of conditions in which the frequency and severity of psychological dysfunctions rise. In the treatment of cataplexy, CBT appears to be a good place to start in order to help the patient cope with his emotions. Researchers hierarchically organize unpleasant visual stimuli that the patient previously defined as events that elicit cataplexy using a systematic desensitization strategy. The technique begins with both the therapist and the patient operating a mental illustration of events that the patient fears (details are carefully stated). The clinician next instructs his patient, who is now thoroughly relaxed, to picture these pictures in his mind. Anxiety-related triggers in the various situations gradually become more intense. In the treatment of cataplexy, another CBT strategy known as stimulus satiation has been used. The doctor keeps what encourages the patient's cataplectic behavior until it no longer has an effect[115].

10.6 Counseling

Both the patient and the parents have benefited from psychological counselling. To achieve appropriate symptom management and treatment, the patient should be properly educated, especially if he or she has recently been diagnosed. Explaining narcolepsy symptoms and how they might develop, vary, and affect relationships, job, and other relevant domains; current accessible pharmacologic and behavioral therapy (e.g., excellent sleep hygiene) and their effects; and finally, additional lifestyle factors that may affect the symptoms (e.g., the influence of alcohol on EDS)[126]. Peer support is a type of psychosocial support that can improve the patient's knowledge and confidence in dealing with the disorder. It is defined as assistance provided by a person with experiential knowledge of the stressors and behaviors similar to the target population[126]. Indeed, both people with disabilities and their families can benefit from the support that comes from sharing experiences with others. Families and children may never have the opportunity to seek psychosocial support if the condition is extremely infrequent[127].

10.7 Pharmacological Treatment

10.7.1 First line treatment for EDS

Modafinil selectively stimulates wake-generating sets in the hypothalamus by increasing dopamine in the extracellular concentration, but the exact mechanism of action is

unknown[128]. Modafinil reduces EDS, improves subjective sense of improvement on the Clinical Global Improvement of Change (CGI-C), and increases average sleep latencies on the Maintenance of Wakefulness Test (MWT) at doses of 200–400 mg/day[129]. Modafinil is usually started with 100 mg (in the morning) and gradually increased to a split dosing (100 + 100) in the morning (after breakfast) and at lunch. It can be gradually increased up to 200 + 200[129] after a few weeks. When compared with other stimulants, modafinil has lower abuse/addiction potential and is generally well tolerated. Headaches, nausea, tension/anxiety, and insomnia are common adverse effects[130]. It is vital to remember that modafinil reduces the effectiveness of oral contraceptives; therefore, greater ethinylestradiol or other contraceptive methods are recommended. The FDA and EMA have approved modafinil for the treatment of both NT1 and NT2 patients in adults [122].

10.7.2 *Armodafinil*

Drug Armodinafil is a partial agonist of the D2 receptor and is an R-enantiomer of modafinil with a specific target. According to clinical recommendations, armodafinil should be taken as a single dose in the morning, starting at 100 mg and increasing to a maximum of 250 mg per day. Subjective drowsiness (as evaluated by the SF-36) decreased from 16.9 to 12.6[122] after 12 months of therapy. The FDA has approved armodafinil for the treatment of both NT1 and NT2 patients in adults[131].

10.7.3 *Pitolisant*

Pitolisant [132], a first-in-class H3R antagonist/inverse agonist with anticataleptic and wake-promoting effects, is an N-piperidyl derivative. Pitolisant is approved in the European Union (EU) for the treatment of narcolepsy in adults with or without cataplexy, with a dosage range of 4.5–36 mg/day [133]. The US Food and Drug Administration (FDA) approved pitolisant in August 2019 for the treatment of EDS in adult narcolepsy patients; the suggested dose range is 17.8–35.6 mg/day [134]. Note that European studies (and EU labelling) used a different method for determining pitolisant dosing than those used in the United States; as a result, doses of 4.5, 9, 18, and 36 mg in European research/labelling are comparable to doses of 4.45, 8.9, 17.8, and 35.6 mg in the United States. Pitolisant's main actions are thought to be mediated pre-synoptically via histaminergic neurons in the brain. Pitolisant reduces the inhibitory effect of histamine (or H3R agonists) on endogenous histamine release and promotes histamine release throughout the central nervous system (CNS) as an H3R competitive antagonist and inverse agonist [132]. Pitolisant also affects other neurotransmitter systems, causing an increase in acetylcholine and dopamine release in the cerebral cortex but not in the striatal complex [135]. The recommended maximum dose for patients with moderate-to-severe renal impairment is 17.8 mg/day, but pitolisant is not recommended in patients with end-stage renal disease (ESRD) [133]. Pitolisant exposure (maximum plasma concentration [Cmax], AUC) increased in stage 2–4 renal failure, but t12 was unaffected. Child-Pugh A had no effect on pitolisant PKs, but severe hepatic impairment (Child-Pugh B) was associated with a 2.4-fold increase in AUC and a doubling of t1/2 [6]. Pitolisant dose modifications aren't needed in mild hepatic impairment; the highest recommended dose in moderate hepatic impairment is 17.8 mg/day; and pitolisant isn't recommended in sepsis. According to Pitolisant product literature, patients taking hormonal contraceptives should be recommended to adopt an alternative, non-hormonal method of contraception during treatment and for 21 days after discontinuing pitolisant[138]. A study in healthy volunteers demonstrated that pitolisant had no effect on PK profiles of sodium oxybate or modafinil and that sodium oxybate has no clinically relevant effect on pitolisant PKs; modafinil decreases pitolisant exposure, though dose adjustment is not required [136]. Pitolisant should be taken in the morning with breakfast, at a single dose ranging from 9 mg to 36 mg per day over a few weeks, according to prescription guidelines. The amount of 36 mg/day appears to be the most beneficial, according to experts. In most cases, the intended impact is achieved within a few weeks. There is no evidence of clinical long-term efficacy to yet. Pitolisant does not appear to be a drug that may be abused and is well tolerated. Headaches, sleeplessness, and nausea are all common adverse effects. Symptoms such as headache and nausea are common at the start of treatment [137]. Other contraceptive techniques should be suggested because of the potential interaction with oral contraceptives. Pitolisant is licensed by the European Medicines Agency (EMA) for both NT1 and NT2 patients in adults [138]. Gamma hydroxybutyrate or sodium oxybate in the central nervous system, sodium oxybate is a gamma-hydroxybutyric acid B-subtype (GABAb) receptor agonist, notably distributed in the hypothalamus and basal ganglia. The specific mechanism of sodium oxybates effect is unknown. It has been linked to an increase in slow-wave sleep, a reduction in the number of awakenings, a shorter REM sleep period, and significant increases in sleep efficiency [139]. Sodium oxybate helps with cataplexy, EDS, and other narcolepsy symptoms, particularly disturbed nocturnal sleep, which shows the most improvement. EDS recovery is not as quick as it is with stimulant medicines; it takes weeks or months to see results, in part because the correct therapeutic dosage must be determined for each individual patient[140]. In several studies, a relationship between reduced EDS and increased attentiveness has been discovered in several studies. Another retrospective study [141] discovered that combining modafinil with sodium oxybate significantly reduced subjective somnolence (Epworth Sleepiness Scale) (ESS). The mean MWT sleep delay in NT1 and NT2 patients was compared to sodium oxybate + placebo. Despite this, clinical evidence suggests that sodium oxybate is less effective at alerting than modafinil [142]. Sodium oxybate is now only accessible in liquid form and should be taken twice a night. A patient should be awakened during the night to take the second dose (a clock may be helpful). The recommended starting dose is 4.5 g each night, divided into two 2.25 g doses, the first given immediately before bedtime and the second given shortly after bedtime.

The initial starting dose should be gradually increased by 1.5 g/night every week. After 4–8 weeks of therapy (6–9 g/night), results should be visible. Nausea, dizziness/confusion, weight loss, enuresis, anxiety, and depressed symptoms are the most common adverse effects [122]. The drug may be too salty for certain people. In this scenario, doctors recommend flavoring the water or lowering the recommended amount to avoid nausea. If nausea is severe, a 5-HydoxyTryptamine-3 antagonist, such as ondansetron, may be prescribed [10]. Sodium oxybate in adults for the treatment of cataplexy and EDS in both NT1 and NT2 patients was approved by the FDA [22]. For NT1 only sodium oxybate was approved by the EMA.

10.8 Second-Line Treatments

10.8.1 Methylphenidate

Methylphenidate increases the dopamine and norepinephrine

transmission. It is typically used when other drugs have proven to be ineffective. Only a few studies [143] found substantial variations in narcoleptic patients' ability to stay awake and active when compared to control volunteers. The effect on sleepiness is remarkable, manifesting within days even at the lowest dose (10 mg); nevertheless, a greater dose of up to 60 mg can be used to get a clinically relevant response [118]. Tachycardia, hypertension, sweating, palpitations, irritability, hyperactivity, mood fluctuations, weight loss, anorexia, and insomnia are all common methylphenidate adverse effects. The prescription prescribes taking 10–20 mg of methylphenidate with breakfast in the morning and another 10–20 mg at lunch. The maximum suggested dose is 60 mg, which is frequently divided into 2–4 doses throughout the day. In adults, methylphenidate for the treatment of EDS in both NT1 and NT2 patients was approved by the EMA (but not all EU countries) and FDA [122].

10.9 Third-Line Treatments

10.9.1 Amphetamines and Other Therapeutic Options

Amphetamines are unquestionably one of the most affordable medications [118]. Nonetheless, it is generally known that these medicines carry several hazards, including a significant propensity for misuse, which can result in cardiovascular side effects (selegiline; reboxetine; ephedrine, pemoline, L-carnitine. Dextroamphetamine), a kind of amphetamine, is allowed for treating EDS in various European countries, with a beginning dose of 5 mg and a maximum of 60 mg per day [144]. Mazindol was available in France for the treatment of EDS in narcolepsy, with therapeutic doses ranging from 1 to 4 mg per day until 2016. This medicine has been linked to hepatotoxicity [145], and fresh data on the risk-benefit ratio in narcolepsy is needed. Finally, the FDA recently approved two alternative admixtures: the first (AdderallTM) combines amphetamine and dextroamphetamine, while the second (EvekeoTM) contains amphetamine sulfate as the major active ingredient [122].

10.9.2 Solriamfetol

Solriamfetol (75-150 mg/day) is a new brand medicine that hit the market in 2019. It is a specific inhibitor of dopamine and norepinephrine reuptake, which distinguishes it from other wake-promoting drugs. Furthermore, unlike amphetamine stimulants, it does not induce the release of monoamines. In phase 3 controlled clinical investigations, solriamfetol reduced patient-reported EDS as measured by the ESS and improved wakefulness as indicated by the objective MWT in adult narcolepsy patients[146]. Headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety are all common side effects of solriamfetol. The FDA has approved solriamfetol for the treatment of EDS in adults[147].

10.10 Cataplexy Pharmacological Treatment

Gamma hydroxybutyrate or sodium oxybate Sodium oxybate therapy decreases the number of cataplectic attacks and cataplexy intensity in NT1 patients, according to several studies[118]. As shown in multiple trials [148] including the longest follow-up research (18 months), this impact might be noticed after weeks to months of medication with a dose-dependent effect. Status cataplectic is not caused by abrupt sodium oxybate withdrawal.

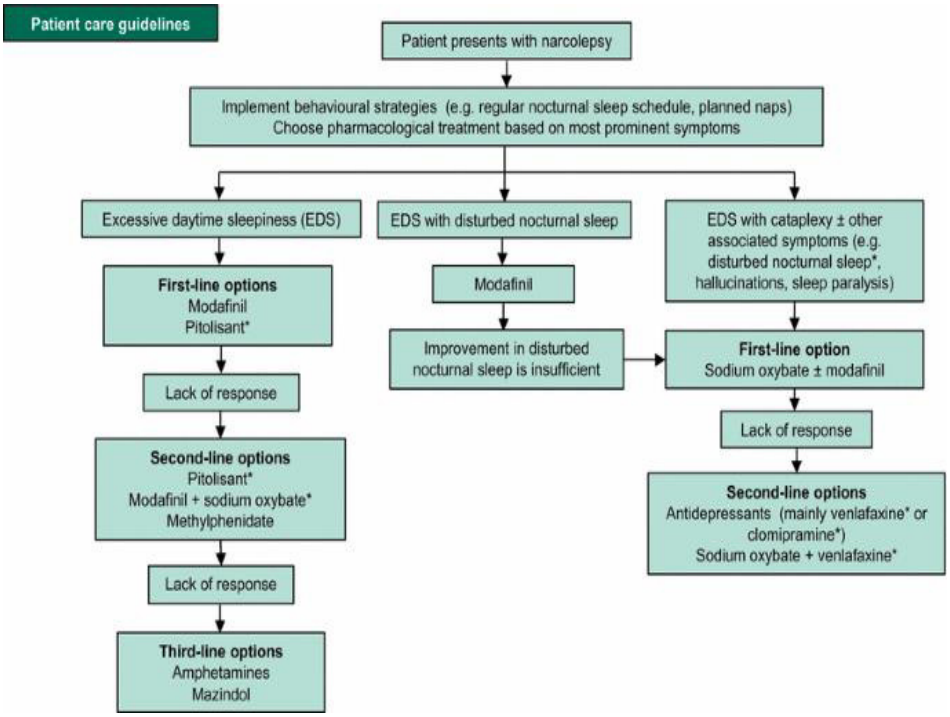

Fig 4: Flowchart of Narcolepsy Treatment[149]

10.10.1 Venlafaxine

Venlafaxine is a selective norepinephrine reuptake inhibitor that is exclusively given to NT1 patients based on professional advice [118]. The anticataleptic effect usually lasts a few days, is well-tolerated, and has a few common adverse effects, including elevated blood pressure, headache, dry mouth, nausea, and dizziness. The prescription suggests starting with 37.5 mg and gradually increasing to 225 mg in the morning [150]. Withdrawal can have a rebound effect up to "cataplectic status" [151], which is defined as sub continuous invalidating cataplexy bouts. Despite its widespread use, venlafaxine has not been approved for the treatment of narcolepsy.

10.10.2 Pitolisant

Pitolisant's efficacy in daily cataplexy attacks was documented and validated in a recent study by a reduction in attack frequency in NT1 patients when compared to placebo. Furthermore, the anticataleptic effects were recently verified in a well-designed randomized, double-blind, placebo-controlled trial involving 105 individuals with narcolepsy and cataplexy which showed a reduction in the average frequency of cataplexy. The European Medicines Agency (EMA) has approved pitolisant for the treatment of cataplexy in NT1 [152].

10.11 Second-Line Treatments

10.11.1 Other antidepressants: fluoxetine, citalopram, and clomipramine

Fluoxetine (10–20 up to 60 mg/day) and citalopram (10–20 up to 40 mg/day) are the most often used selective serotonin reuptake inhibitors (SSRIs) in NT1 [118]. Side effects and tolerance, on the other hand, should not be overlooked, since they may pose a problem in clinical practice [122]. Excitation, gastrointestinal issues, sleeplessness, and sexual difficulties are the most common side effects. Sudden withdrawal can cause status cataplectic, so patients should be treated with considerable caution, especially if they are elderly. Since 1960, clomipramine (10–25 up to 75 mg/day) has been the major tricyclic antidepressant used to treat cataplexy and it has been shown to reduce attacks significantly [118]. Dry mouth, sweating, constipation, diarrhea, tachycardia, weight gain, hypotension, difficulty peeing, and impotence have all been reported as side effects. Except clomipramine, fluoxetine, citalopram, and clomipramine are not approved as treatments for narcolepsy in Germany [122].

10.11.2 Immunotherapy

Several pieces of evidence point to autoimmune mechanisms as a cause of NT1, providing a basis for using immunomodulation therapy with intravenous immunoglobulins G (IVIG) early in the disease's course. Only a few researchers[153] have attempted IVIG in early-onset narcoleptic patients to see if it works, but the results are mixed due to the small sample size, open-label design, and self-report observations The findings point to a reduction in the incidence and severity of cataplexy, as well as lessened daytime sleepiness, which is supported by additional evidence. More controlled investigations are needed due to the likelihood of spontaneous improvement of cataplexy [153]. Other immunosuppressive treatments used in narcolepsy patients are unknown (i.e., T cell immunity).

Table 2: Drugs used in the treatment of narcolepsy

Drug	Mechanism of Action	Dose	Side Effects
First line agents			
Modafinil	Increases dopamine secretion	200-400mg/day	headache, nausea, Anxiety, insomnia
Armodinafil	D2 receptor partial agonist	100-250mg/day	-
Pitolisant	H3R antagonist	4.5mg-36mg	headache, nausea
Sodium oxybate	GABA B-subtype receptor agonist	-	-
Second line agents			
Methylphenidate	Increases dopamine and Norepinephrine transmission	10-20mg, 60mg/day	hypotension, anxiety

10.11.3. Xywav

In July 2020, the FDA approved Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solutions for the treatment of cataplexy or excessive daytime sleepiness in patients seven years of age and older with narcolepsy[154].

11. CONCLUSION

Researchers and physicians have made significant progress in understanding narcolepsy and creating effective treatments for the illness in recent years, but many concerns remain unresolved. From our study we conclude that have an almost gold standard diagnostic test, CSF hypocretin-1, at least for the subtype of narcolepsy that includes cataplexy. However, researchers are currently striving to understand the pathologic process that destroys orexin-producing neurons in the hopes of one day being able to prevent or cure narcolepsy. Others are looking into how the loss of these neurons causes sleepiness, cataplexy, and obesity; figuring out the neurobiological process could lead to new therapeutic options. Clinical symptoms that, when elicited correctly, are diagnostic in and of themselves. Narcolepsy is still a diagnosis of exclusion, so clinicians need to look into other possibilities. Although diagnostic tests can be helpful, doctors should be aware of their limitations. Despite the fact that narcolepsy impacts many aspects of a patient's life, current treatments can be quite effective, and even better treatments may be available in the future.

12. AUTHORS CONTRIBUTION STATEMENT

Dr. Naga Prashant Koppuravuri and Sangeetha N had developed the conceptual ideas and need for the review, Dr. Naga Prashant Koppuravuri and Sangeetha N performed literature search, Sangeetha N, Thasvin U R, and V Siva Ganesh collected data and prepared raw manuscript, Dr. Naga Prashant Koppuravuri, Dr. T Y Pasha, and Dr. Rajesh Venkataraman V finalized the manuscript. All authors read and approved final version of manuscript.

13. CONFLICT OF INTEREST

Conflict of interest declared none.

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