CME

Narcolepsy: A clinical review

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ABSTRACT

Narcolepsy continues to be a significantly underdiagnosed/misdiagnosed condition worldwide. According to the National Institutes of Health (NIH), an estimated 135,000 to 200,000 patients in the United States are living with narcolepsy. However, due to the number of patients who either do not seek medical advice for their symptoms or receive an incorrect initial diagnosis at onset, this number may be higher. This article reviews the different subtypes of narcolepsy along with the pathophysiology, screening guidelines, clinical features, diagnosis, and management of the disorder. Educational awareness from a healthcare and patient standpoint can enhance early detection and accurate diagnosis of narcolepsy and improve patient quality of life.

Keywords: narcolepsy, cataplexy, hypocretin, excessive daytime sleepiness, multiple sleep latency test, rapid-eye-movement sleep

Learning objectives

- Discuss the epidemiology and delay in diagnosis of patients living with narcolepsy.
- Differentiate the pathophysiology and clinical presentation of narcolepsy type 1 from narcolepsy type 2.
- Describe the treatment options available to manage patients with narcolepsy and improve their quality of life.

Narcolepsy is a chronic neurologic disorder affecting the sleep-wake cycle in the brain. It is divided into two subtypes based on clinical presentation and referred to as type 1 and type 2. Incidence for both types combined is about 1 in 2,000.[1,2] This number is considered by many to be underestimated due to multiple factors such as misdiagnosis or failure of symptom recognition by the patient and/or healthcare provider. Age at symptom onset ranges from early adolescence to early adulthood.[3] Current data demonstrate that narcolepsy has a significant effect on functioning, employment, productivity, and quality of life.[4] A recent study analyzing data collected from 2006 to 2010 found that patients with narcolepsy had nearly double the health-service use costs as patients without narcolepsy.[4]

NEUROBIOLOGY OF SLEEP

Human sleep-wake cycles are regulated by specific neuronal pathways in the brain, originating from the hypothalamus.[5] Hypocretin (also known as orexin) and histamine neurons are housed in the hypothalamus, and activate wake-promoting neurons throughout the brain.[6] Hypocretin neuropeptides increase activity in areas of the brain that suppress rapid eye movement (REM) sleep.[7] The normal human sleep cycle architecture is designed to alternate between REM and non-rapid eye movement (NREM) stages in such a way that hormone secretion

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Key points

- The delay in diagnosis for patients with narcolepsy averages 5 to 15 years, and the condition may remain undiagnosed in up to half of all patients.
- Narcolepsy has no cure. Treatment is aimed at symptom management to help improve quality of life.
- Although most patients with narcolepsy can fall asleep without much effort, their night-time sleep cycles are disrupted, causing alterations in hormone secretion patterns.
- Memory impairment, weight gain, depression/anxiety, and automatic behavior are recognized symptoms of narcolepsy.

occurs at intervals throughout the night, maintaining homeostasis.

Historical studies of sleep deprivation on animals and humans have identified numerous adverse reactions to sleep-wake cycle disruption. Chronic sleep deprivation is related to cognitive deficits, changes in mood (such as depression and irritability), decreased concentration, and diminished short- and long-term memory.[8] Immune system changes such as alterations in interleukin-6 levels and increases in C-reactive protein also occur during chronic sleep deprivation.[9] Epidemiologic studies have demonstrated an increase in cardiovascular events and cardiovascular morbidity associated with reduced sleep duration.[9]

PATHOPHYSIOLOGY

The two subtypes of narcolepsy are differentiated clinically by the presence or absence of cataplexy, which is the sudden loss of skeletal muscle tone in one or multiple areas of the body without loss of consciousness.[1] In type 1 narcolepsy, patients have a loss of about 90% of hypocretin neurons in the hypothalamus, causing inhibition of wakefulness-promoting hormones in addition to the loss of REM sleep regulation (Figure 1).[10] This results in disorganization of the normal sleep-wake cycle, leading to excessive daytime sleepiness, in which the patient is unable to maintain wakefulness/alertness during the day. Cataplexy also is a known result of hypocretin cell deficiency.[11]

In contrast, patients with narcolepsy type 2 have not been found to have significant loss of hypocretin in the brain, and do not experience cataplexy. The exact cause of hypocretin destruction leading to narcolepsy type 1 is unknown; however, recent studies have led researchers to hypothesize that it is a T-cell-mediated autoimmune disease targeting these hypocretin neurons.[12] Family history also is a contributing factor: up to 10% of patients with cataplexy report a positive family history of narcolepsy.[1] In addition, the HLA-DQB1*06:02 gene is present in more than 98% of patients with narcolepsy type 1, and detected in about 50% of those with narcolepsy type 2.[11] Head injury or brain tumors can result in damage to the region of the brain responsible for hypocretin production, leading to secondary narcolepsy.[13]

SYMPTOMS

The most prominent symptom associated with narcolepsy types 1 and 2 is excessive daytime sleepiness.[1] This may include *sleep attacks*, which are described as episodes of overwhelming sudden sleepiness that can occur at any time without warning.

Cataplexy, a unique symptom of narcolepsy type 1, usually is preceded by a strong emotional trigger such as laughter, crying, or stress. Cataplexy can be subtle, such as the patient slurring words, or extreme, such as the patient collapsing on the floor. The patient maintains consciousness throughout each episode, which can last anywhere from a few seconds to several minutes.[14]

Sleep paralysis and hypnagogic/hypnopompic hallucinations also are symptoms of narcolepsy.[15] Sleep paralysis is the temporary inability to physically move during the transition from or to the sleep state. The frequency of occurrence varies among patients with narcolepsy; these episodes can last anywhere from a few seconds to several minutes.[16] Patients may describe sleep paralysis as a frightening experience because it usually occurs with hallucinations.[16] Hallucinations that are hypnagogic occur while the patient is transitioning to sleep, and those that are hypnopompic occur upon the transition to wakefulness.[15] In either case, hallucinations can be visual, auditory, or tactile.

Memory impairment, vivid dreams, weight gain, fragmented sleep patterns, depression/anxiety, and automatic behavior also are recognized symptoms of narcolepsy, although not every patient with the disorder experiences all these symptoms. For instance, only about 50% of patients with narcolepsy exhibit automatic behavior--when the body continues to carry out familiar tasks during wakefulness while the brain is in the sleep state, resulting in complete retrograde amnesia.[16]

Symptoms of narcolepsy can wax and wane, and no discrete evidence exists to support that the condition worsens or improves with age. Age of symptom onset is most commonly between 10 and 25 years, although the time from initial display of symptoms to formal diagnosis often is delayed by several years. For example, cataplexy, if present before other symptoms of narcolepsy, may be misdiagnosed as a seizure disorder. Similarly, cataplexy can be mistaken for a transient ischemic attack if muscle tone in the face is involved. Excessive daytime sleepiness can be misdiagnosed initially as depression.[14] Patients with obesity may be labeled as having obstructive sleep apnea (OSA) episodes to account for their daytime sleepiness.

Psychiatric comorbidities pose a difficulty with the diagnosis of narcolepsy. Often, it is unclear whether symptoms such as depression and anxiety are a result of the disabling

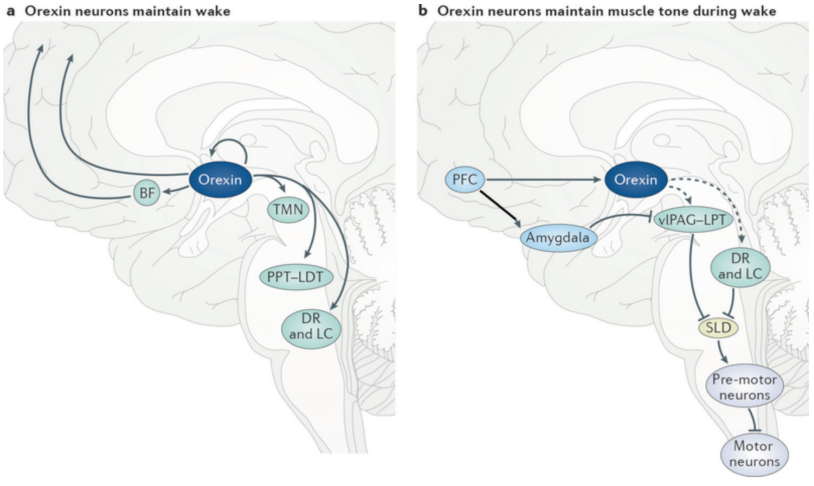

FIGURE 1. Wake-promoting and cataplexy-suppressing orexin pathways. Orexin neurons maintain patient wakefulness (image a) by exciting various wake-promoting neurons, including those in the cortex, basal forebrain (BF), tuberomammillary nucleus (TMN), pedunculopontine and laterodorsal tegmental nuclei (PPT–LDT), dorsal raphe (DR), and locus coeruleus (LC). Normally, orexin neurons block muscle paralysis during wakefulness by activating REM sleep-suppressing regions such as neurons in the ventral lateral periaqueductal gray and lateral pontine tegmentum (vlPAG–LPT), DR, and LC (image b). All these nuclei inhibit the sublaterodorsal nucleus (SLD), which drives muscle paralysis during REM sleep by activating premotor neurons that inhibit motor neurons. In patients with narcolepsy, the excitatory drive from the orexin neurons is absent, and signals from the amygdala can inhibit these REM sleep-suppressing regions, enabling activity in the SLD and resulting in cataplexy.

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nature of narcolepsy or if a shared pathophysiology exists.[15] Narcolepsy can interfere substantially with patient quality of life, ranging from impairing the ability to operate a motor vehicle or heavy machinery, to hindering patients' being able to remain awake and alert to care for children or other family members. Patients often feel as if they are "missing out" because of sleep attacks during the day, or trying to hide certain emotions such as laughter or anger in efforts to prevent a cataplexy episode.

DIAGNOSIS

The diagnosis of narcolepsy is based on the American Academy of Sleep Medicine clinical guidelines, and evaluation should include a thorough workup of other possible contributing factors of excessive daytime sleepiness. Genetic testing for HLA-DQB1*06:02 is not recommended, because up to 30% of the healthy general population possesses this gene.[11]

The Epworth Sleepiness Scale is a widely used subjective screening questionnaire that measures the level of daytime sleepiness in patients. A total score of 11 or greater warrants further evaluation for a potential sleep disorder (**Table 1**).[17] Another increasingly used screening tool is the Swiss Narcolepsy Scale.[18] This questionnaire consists of five questions relating to different aspects of sleep-wake habits and symptoms to provide a potentially more extensive clinical assessment.

The Multiple Sleep Latency Test (MSLT) is the standard diagnostic test of choice.[19] This is an objective measure of a patient's ability or tendency to fall asleep.[19] The patient is given five opportunities to nap during the day under standardized conditions (usually at a medical sleep facility).[19] Each scheduled nap is 20 minutes in length, with anywhere from 1.5 to 3 hours between naps.[20] A mean sleep-onset latency of 8 minutes or less, and two or more sleep-onset REM episodes (SOREMs) during the naps is consistent with narcolepsy.[20] The MSLT should be immediately preceded by a polysomnogram to rule out any underlying secondary causes of excessive daytime sleepiness, such as insomnia or OSA.[19] The polysomnogram is an overnight study, also typically performed at a facility where continuous monitoring can occur to ensure accurate data collection. At least 2 weeks before the test, patients must discontinue any medication that could potentially affect test results, such as serotonin, norepinephrine, and dopamine neurotransmitters. Drugs such as benzodiazepines or opioids that may cause sedation or drowsiness also should be discontinued. Beta-blockers, which can cause drowsiness and suppression of REM sleep, should be held for 2 weeks before the study if approved by the prescriber.[21] Patients also complete a sleep log for 1 week before testing, to assess their routine sleep/wake schedule.[19]

MANAGEMENT

Narcolepsy has no known cure; management is aimed at reducing symptoms to improve patient quality of life.[1] Treatment options vary greatly and depend on patient symptoms, lifestyle, comorbidities, and pharmacotherapeutic tolerance. Good sleep hygiene is critical for patients with narcolepsy, and often includes scheduled naps during the day. Naps can range anywhere from 20 minutes to 2 hours, and often can result in the person feeling somewhat refreshed for a short period of time. Having a consistent bedtime routine and avoiding screen time (such as television, computers/tablets, or cell phones) for at least 2 hours before bed has been proven beneficial for overall sleep quality.[22] Exercising for at least 20 minutes per day also improves sleep quality and may help prevent excess weight gain in patients with narcolepsy.[1] Diet modifications such as limiting consumption of caffeine, sugar, and carbohydrates can improve narcolepsy symptoms. Patients also should avoid eating a heavy meal right before bed.

Patients with narcolepsy should avoid medications that can potentially worsen excessive daytime sleepiness,

including cough remedies containing codeine, first-generation antihistamines, opioids, benzodiazepines, or other sedatives, and any prescribed or over-the-counter medications that list drowsiness as a potential adverse reaction.

Current pharmacotherapy for narcolepsy is geared toward reducing cataplexy and excessive daytime sleepiness in order to improve patient quality of life and minimize nighttime sleep disruption.[23] Because the pathophysiology of narcolepsy involves various pathways, pharmacologic interventions have multiple targets.[23] Combination therapy often is needed for patients with severe narcolepsy. Regular follow-ups are necessary to monitor treatment and patient adaptation to the disorder.[24]

TABLE 1. Epworth Sleepiness Scale

A score of 11 or greater warrants further evaluation for a potential sleep disorder.

Activity	Chance of dozing			
	0 (never)	1 (slight)	2 (moderate)	3 (high)
Sitting and reading				
Sitting inactive in a public place (such as a theater or meeting)				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting and talking to someone				
Sitting quietly after a lunch without alcohol				
In a car, while stopped for a few minutes in traffic				
Total score:				

Adapted with permission from Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14(6):540-545.

Wake-promoting agents (stimulants) such as modafinil and armodafinil have been shown to reduce excessive daytime sleepiness in patients with narcolepsy by inhibiting the reuptake of dopamine, and are considered to be the first-line treatment in pharmacologic therapy.[23,25] Modafinil and armodafinil are schedule IV controlled substances in the United States. Advise patients that these drugs reduce the effectiveness of oral or steroidal contraceptives taken concurrently.

Methylphenidate and amphetamine, stimulants available in immediate- and delayed-release formulations, also are used to treat narcolepsy. They work by limiting dopamine and norepinephrine uptake. Because of their potential for addiction and abuse, these drugs should be used cautiously. Start at the lowest possible dose and reevaluate the patient's symptoms every 3 to 4 weeks. Adverse reactions include tachycardia, hypertension, heart palpitations, anxiety, and weight loss.[26]

Sodium oxybate is the only FDA-approved medication available for treating cataplexy, and has been shown to improve excessive daytime sleepiness and nighttime sleep quality.[23] Due to this, sodium oxybate is considered a first-line treatment for excessive daytime sleepiness and cataplexy symptoms in patients who have these symptoms concomitantly.[27] Sodium oxybate is a GABA receptor beta-agonist thought to affect activity at noradrenergic, dopaminergic, and thalamocortical neuroreceptor sites.[23] Its mechanism of action on cataplexy is unclear. Sodium oxybate is a liquid central nervous system (CNS) depressant with abuse potential and is available only through a restricted distribution program in the United States. It is taken at night, and split into two doses 2.5 to 4 hours apart. Sodium oxybate typically is titrated to help reduce adverse reactions, and maximum efficacy is reached in 4 to 8 weeks from the start of treatment.[26] Because this drug contains sodium, patients with sensitivity to high sodium intake (such as those with concomitant heart failure, kidney disease, or hypertension) should be monitored closely for hypernatremia.[28] Contraindications include other CNS depressants and alcohol, which can markedly impair consciousness and induce respiratory depression. Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency.[29] Even at the recommended dosages, sodium oxybate can cause confusion, depression, and other neuropsychiatric events.[30] A single-dose formulation of sodium oxybate and a reduced-sodium formulation have both recently completed phase III clinical trials.[31,32] The reduced sodium-formulation of calcium, magnesium, potassium, and sodium oxybate was approved by the FDA in July 2020 for treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

Pitolisant was approved by the FDA in 2019 for treatment of excessive daytime sleepiness associated with narcolepsy. This selective histamine H3 agonist is taken orally once daily, and typically is titrated upon initiation. Because pitolisant reduces the effectiveness of oral contraceptives, patients taking both drugs should use alternative nonhormonal contraception for the duration of pitolisant treatment and for 21 days or more after discontinuing the drug.[33] Pitolisant is contraindicated in patients with severe hepatic impairment and is not recommended in those with end-stage renal disease (ESRD).[33] Pitolisant can prolong the QT interval and should be used with caution in patients with hepatic or renal impairment.[34]

Solriamfetol, a wake-promoting agent approved in 2019, is used to treat excessive daytime sleepiness symptoms in patients with narcolepsy or OSA; the once-daily oral drug inhibits dopamine and norepinephrine reuptake in the brain.[23] The most common adverse reactions are headaches, decreased appetite, problems sleeping, insomnia, and anxiety.[23] Solriamfetol should not be used concomitantly with or within 14 days after a patient discontinues monoamine oxidase inhibitors (MAOIs).

Per AASM guidelines, tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine, and reboxetine also may be effective off-label treatments for cataplexy.[24] Prescribers must be aware of the rebound cataplexy phenomenon that may occur for up to several weeks following discontinuation (particularly abrupt discontinuation) of these drugs.[23]

Several newer agents are under development for treatment of excessive daytime sleepiness and cataplexy symptoms associated with narcolepsy. Reboxetine, a selective norepinephrine reuptake inhibitor approved for treatment of depression in Europe, recently completed a CONCERT phase II trial evaluating efficacy of management of narcolepsy symptoms.[35] Another drug, THN 102, which combines flecainide and modafinil, completed phase II clinical trials for excessive daytime sleepiness symptoms in patients with narcolepsy.[36]

SUPPORT GROUPS

Narcolepsy can pose a significant burden on quality of life for patients and families. Many local and web-based support groups are available for patients with sleep disorders. Online support groups such as Project Sleep (www.project-sleep.com) and Wake Up Narcolepsy (www.wakeupnarcolepsy.org) are not-for-profit organizations dedicated to providing resources for individuals living with narcolepsy, in addition to their family and friends. Many of these groups also raise public awareness of the disorder and promote advocacy for advancing sleep research and developing effective treatment options for narcolepsy.

CONCLUSION

Narcolepsy, a chronic neurologic disorder affecting the sleep/wake cycle in the brain, affects about 1 in 2,000 patients. Symptoms of narcolepsy such as excessive daytime sleepiness and cataplexy can greatly impair a person's quality of life. Delay in diagnosis averages 5 to 15 years and up to half of all people with narcolepsy may remain undiagnosed.[2] Because no cure exists, treatment is aimed at symptom management to improve quality of life. Further research is needed to develop a better understanding of the cause of narcolepsy. Promoting awareness of the disorder to the public as well as to clinicians is crucial to help patients who may remain undiagnosed and/or symptomatic. **JAAPA**

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