Narcolepsy

U.S. DEPARTMENT OF HEALTH
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What is narcolepsy?

Narcolepsy is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles. People with narcolepsy usually feel rested after waking, but then feel very sleepy throughout much of the day. Many individuals with narcolepsy also experience uneven and interrupted sleep that can involve waking up frequently during the night.

Narcolepsy can greatly affect daily activities. People may unwillingly fall asleep even if they are in the middle of an activity like driving, eating, or talking. Other symptoms may include sudden muscle weakness while awake that makes a person go limp or unable to move (cataplexy), vivid dream-like images or hallucinations, and total paralysis just before falling asleep or just after waking up (sleep paralysis).

In a normal sleep cycle, a person enters rapid eye movement (REM) sleep after about 60 to 90 minutes. Dreams occur during REM sleep, and the brain keeps muscles limp during this sleep stage, which prevents people from acting out their dreams. People with narcolepsy frequently enter REM sleep rapidly, within 15 minutes of falling asleep. Also, the muscle weakness or dream activity of REM

sleep can occur during wakefulness or be absent during sleep. This helps explain some symptoms of narcolepsy.

If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities.

Who is most at risk for narcolepsy?

Narcolepsy affects both males and females equally. Symptoms often start in childhood, adolescence, or young adulthood (ages 7 to 25), but can occur at any time in life. It is estimated that anywhere from 135,000 to 200,000 people in the United States have narcolepsy. However, since this condition often goes undiagnosed, the number may be higher. Since people with narcolepsy are often misdiagnosed with other conditions, such as psychiatric disorders or emotional problems, it can take years for someone to get the proper diagnosis.

What are the symptoms?

Narcolepsy is a lifelong problem, but it does not usually worsen as the person ages. Symptoms can partially improve over time, but they will never disappear completely. The most typical symptoms are excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. Though all have excessive daytime sleepiness, only 10 to 25 percent of affected individuals will experience all of the other symptoms during the course of their illness.

- **Excessive daytime sleepiness (EDS)**. All individuals with narcolepsy have EDS, and it is often the most obvious symptom. EDS is characterized by persistent sleepiness, regardless of how much sleep an individual gets at night. However, sleepiness in narcolepsy is more like a "sleep attack", where an overwhelming sense of sleepiness comes on quickly. In between sleep attacks, individuals have normal levels of alertness, particularly if doing activities that keep their attention.
- **Cataplexy.** This sudden loss of muscle tone while a person is awake leads to weakness and a loss of voluntary muscle control. It is often triggered by sudden, strong emotions such as laughter, fear, anger, stress, or excitement. The symptoms of cataplexy may appear weeks or even years after the onset of EDS. Some people may only have one or two attacks in a lifetime, while others may experience many attacks a day. In about 10 percent of cases of narcolepsy, cataplexy is the first symptom to appear and can be misdiagnosed as a seizure disorder. Attacks may be mild and involve only a momentary sense of minor weakness in a limited number of muscles, such as a slight drooping of the eyelids. The most severe attacks result in a total body collapse during which individuals are unable to move, speak, or keep their eyes open. But even during the most severe episodes, people remain fully conscious, a characteristic that distinguishes cataplexy from fainting or seizure disorders. The loss of muscle tone during cataplexy resembles

paralysis of muscle activity that naturally occurs during REM sleep. Episodes last a few minutes at most and resolve almost instantly on their own. While scary, the episodes are not dangerous as long as the individual finds a safe place in which to collapse.

- **Sleep paralysis.** The temporary inability to move or speak while falling asleep or waking up usually lasts only a few seconds or minutes and is similar to REM-induced inhibitions of voluntary muscle activity. Sleep paralysis resembles cataplexy except it occurs at the edges of sleep. As with cataplexy, people remain fully conscious. Even when severe, cataplexy and sleep paralysis do not result in permanent dysfunction —after episodes end, people rapidly recover their full capacity to move and speak.
- **Hallucinations.** Very vivid and sometimes frightening images can accompany sleep paralysis and usually occur when people are falling asleep or waking up. Most often the content is primarily visual, but any of the other senses can be involved.

Additional symptoms of narcolepsy include:

- **Fragmented sleep and insomnia.** While individuals with narcolepsy are very sleepy during the day, they usually also experience difficulties staying asleep at night. Sleep may be disrupted by insomnia, vivid dreaming, sleep apnea, acting out while dreaming, and periodic leg movements.
- **Automatic behaviors.** Individuals with narcolepsy may experience temporary sleep episodes that can be very brief, lasting no

more than seconds at a time. A person falls asleep during an activity (e.g., eating, talking) and automatically continues the activity for a few seconds or minutes without conscious awareness of what they are doing. This happens most often while people are engaged in habitual activities such as typing or driving. They cannot recall their actions, and their performance is almost always impaired. Their handwriting may, for example, degenerate into an illegible scrawl, or they may store items in bizarre locations and then forget where they placed them. If an episode occurs while driving, individuals may get lost or have an accident. People tend to awaken from these episodes feeling refreshed, finding that their drowsiness and fatigue has temporarily subsided.

What are the types of narcolepsy?

There are two major types of narcolepsy:

- **Type 1 narcolepsy** (previously termed narcolepsy with cataplexy). This diagnosis is based on the individual either having low levels of a brain hormone (hypocretin) or reporting cataplexy and having excessive daytime sleepiness on a special nap test.
- **Type 2 narcolepsy** (previously termed narcolepsy without cataplexy). People with this condition experience excessive daytime sleepiness but usually do not have muscle weakness triggered by emotions. They usually also have less severe symptoms and have normal levels of the brain hormone hypocretin.

A condition known as secondary narcolepsy can result from an injury to the hypothalamus, a region deep in the brain that helps regulate sleep. In addition to experiencing the typical symptoms of narcolepsy, individuals may also have severe neurological problems and sleep for long periods (more than 10 hours) each night.

What causes narcolepsy?

Narcolepsy may have several causes. Nearly all people with narcolepsy who have cataplexy have extremely low levels of the naturally occurring chemical hypocretin, which promotes wakefulness and regulates REM sleep. Hypocretin levels are usually normal in people who have narcolepsy without cataplexy.

Although the cause of narcolepsy is not completely understood, current research suggests that narcolepsy may be the result of a combination of factors working together to cause a lack of hypocretin. These factors include:

- **Autoimmune disorders.** When cataplexy is present, the cause is most often the loss of brain cells that produce hypocretin. Although the reason for this cell loss is unknown, it appears to be linked to abnormalities in the immune system. Autoimmune disorders occur when the body's immune system turns against itself and mistakenly attacks healthy cells or tissue. Researchers believe that

in individuals with narcolepsy, the body's immune system selectively attacks the hypocretin-containing brain cells because of a combination of genetic and environmental factors.

- **Family history.** Most cases of narcolepsy are sporadic, meaning the disorder occurs in individuals with no known family history. However, clusters in families sometimes occur—up to 10 percent of individuals diagnosed with narcolepsy with cataplexy report having a close relative with similar symptoms.
- **Brain injuries.** Rarely, narcolepsy results from traumatic injury to parts of the brain that regulate wakefulness and REM sleep or from tumors and other diseases in the same regions.

How is narcolepsy diagnosed?

A clinical examination and detailed medical history are essential for diagnosis and treatment of narcolepsy. Individuals may be asked by their doctor to keep a sleep journal noting the times of sleep and symptoms over a one- to two-week period. Although none of the major symptoms are exclusive to narcolepsy, cataplexy is the most specific symptom and occurs in almost no other diseases.

A physical exam can rule out or identify other neurological conditions that may be causing the symptoms. Two specialized tests, which can be performed in a sleep disorders

clinic, are required to establish a diagnosis of narcolepsy:

- **Polysomnogram (PSG or sleep study).** The PSG is an overnight recording of brain and muscle activity, breathing, and eye movements. A PSG can help reveal whether REM sleep occurs early in the sleep cycle and if an individual's symptoms result from another condition such as sleep apnea.
- **Multiple sleep latency test (MSLT).** The MSLT assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter REM sleep. On the day after the PSG, an individual is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in less than 8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, individuals with narcolepsy also have REM sleep start abnormally quickly. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy.

Occasionally, it may be helpful to measure the level of hypocretin in the fluid that surrounds the brain and spinal cord. To perform this test, a doctor will withdraw a sample of the cerebrospinal fluid using a lumbar puncture (also called a spinal tap) and measure the level of hypocretin-1. In the absence of other serious medical conditions, low hypocretin-1 levels almost certainly indicate type 1 narcolepsy.

What treatments are available?

Although there is no cure for narcolepsy, some of the symptoms can be treated with medicines and lifestyle changes. When cataplexy is present, the loss of hypocretin is believed to be irreversible and lifelong. Excessive daytime sleepiness and cataplexy can be controlled in most individuals with medications.

Medications

- **Modafinil.** The initial line of treatment is usually a central nervous system stimulant such as modafinil. Modafinil is usually prescribed first because it is less addictive and has fewer side effects than older stimulants. For most people these drugs are generally effective at reducing daytime drowsiness and improving alertness.
- **Amphetamine-like stimulants.** In cases where modafinil is not effective, doctors may prescribe amphetamine-like stimulants such as methylphenidate to alleviate EDS. However, these medications must be carefully monitored because they can have such side effects as irritability and nervousness, shakiness, disturbances in heart rhythm, and nighttime sleep disruption. In addition, health care professionals should be careful when prescribing these drugs and people should be careful using them because the potential for abuse is high with any amphetamine.

- **Antidepressants.** Two classes of antidepressant drugs have proven effective in controlling cataplexy in many individuals: tricyclics (including imipramine, desipramine, clomipramine, and protriptyline) and selective serotonin and noradrenergic reuptake inhibitors (including venlafaxine, fluoxetine, and atomoxetine). In general, antidepressants produce fewer adverse effects than amphetamines. However, troublesome side effects still occur in some individuals, including impotence, high blood pressure, and heart rhythm irregularities.
- **Sodium oxybate.** Sodium oxybate (also known as gamma hydroxybutyrate or GHB) has been approved by the U.S. Food and Drug Administration to treat cataplexy and excessive daytime sleepiness in individuals with narcolepsy. It is a strong sedative that must be taken twice a night. Due to safety concerns associated with the use of this drug, the distribution of sodium oxybate is tightly restricted.

Lifestyle changes

Not everyone with narcolepsy can consistently maintain a fully normal state of alertness using currently available medications. Drug therapy should accompany various lifestyle changes. The following strategies may be helpful:

- **Take short naps.** Many individuals take short, regularly scheduled naps at times when they tend to feel sleepiest.

- **Maintain a regular sleep schedule.** Going to bed and waking up at the same time every day, even on the weekends, can help people sleep better.
- **Avoid caffeine or alcohol before bed.** Individuals should avoid alcohol and caffeine for several hours before bedtime.
- **Avoid smoking**, especially at night.
- **Exercise daily.** Exercising for at least 20 minutes per day at least 4 or 5 hours before bedtime also improves sleep quality and can help people with narcolepsy avoid gaining excess weight.
- **Avoid large, heavy meals right before bedtime.** Eating very close to bedtime can make it harder to sleep.
- **Relax before bed.** Relaxing activities such as a warm bath before bedtime can help promote sleepiness. Also make sure the sleep space is cool and comfortable.

Safety precautions, particularly when driving, are important for everyone with narcolepsy. People with untreated symptoms are more likely to be involved in automobile accidents although the risk is lower among individuals who are taking appropriate medication. EDS and cataplexy can lead to serious injury or death if left uncontrolled. Suddenly falling asleep or losing muscle control can transform actions that are ordinarily safe, such as walking down a long flight of stairs, into hazards.

The Americans with Disabilities Act requires employers to provide reasonable accommodations for all employees with disabilities. Adults with narcolepsy can often negotiate with employers to modify their work schedules so they can take naps when necessary and perform their most demanding tasks when they are most alert. Similarly, children and adolescents with narcolepsy may be able to work with school administrators to accommodate special needs, like taking medications during the school day, modifying class schedules to fit in a nap, and other strategies.

Additionally, support groups can be extremely beneficial for people with narcolepsy who want to develop better coping strategies or feel socially isolated due to embarrassment about their symptoms. Support groups also provide individuals with a network of social contacts who can offer practical help and emotional support.

What is the state of the science involving narcolepsy?

In the past few decades, scientists have made considerable progress in understanding narcolepsy and identifying genes strongly associated with the disorder.

Groups of neurons in several parts of the brain interact to control sleep, and the activity of these neurons is controlled by a large number

of genes. The loss of hypocretin-producing neurons in the hypothalamus is the primary cause of type 1 narcolepsy. These neurons are important for stabilizing sleep and wake states. When these neurons are gone, changes between wake, REM sleep, and non-REM sleep can happen spontaneously. This results in the sleep fragmentation and daytime symptoms that people with narcolepsy experience.

It remains unclear exactly why hypocretin neurons die. However, research increasingly points to immune system abnormalities. HLA—human leukocyte antigen—genes play an important role in regulating the immune system. This gene family provides instructions for making a group of related proteins called the HLA complex, which helps the immune system distinguish between good proteins from an individual's own body and bad ones made by foreign invaders like viruses and bacteria. One of the genes in this family is *HLA-DQB1*. A variation in this gene, called *HLA-DQB1*06:02*, increases the chance of developing narcolepsy, particularly the type of narcolepsy with cataplexy and a loss of hypocretins (also known as orexins). *HLA-DQB1*06:02* and other HLA gene variations may increase susceptibility to an immune attack on hypocretin neurons, causing these cells to die. Most people with narcolepsy have this gene variation and may also have specific versions of closely related HLA genes.

However, it is important to note that these gene variations are common in the general population and only a small portion of the people with the *HLA-DQB1*06:02* variation will develop narcolepsy. This indicates that other genetic and environmental factors are important in determining if an individual will develop the disorder.

Narcolepsy follows a seasonal pattern and is more likely to develop in the spring and early summer after the winter season, a time when people are more likely to get sick. By studying people soon after they develop the disorder, scientists have discovered that individuals with narcolepsy have high levels of anti-streptolysin O antibodies, indicating an immune response to a recent bacterial infection such as strep throat. Also, the H1N1 influenza epidemic in 2009 resulted in a large increase in the number of new cases of narcolepsy. Together, this suggests that individuals with the *HLA-DQB1*06:02* variation are at risk for developing narcolepsy after they are exposed to a specific trigger, like certain infections that trick the immune system to attack the body.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a

component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

The NINDS, along with several other NIH Institutes and Centers, supports research on narcolepsy and other sleep disorders through grants to medical institutions across the country. Additionally, the NIH's National Heart, Lung, and Blood Institute manages the National Center on Sleep Disorders Research (NCSDR), which coordinates Federal government sleep research activities, promotes doctoral and postdoctoral training programs, and educates the public and health care professionals about sleep disorders. For more information, visit the NCSDR website at www.nhlbi.nih.gov/about/org/ncsdr/.

Genetics and biochemicals

NINDS-sponsored researchers are conducting studies devoted to further clarifying the wide range of genetic—both HLA genes and non-HLA genes—and environmental factors that may cause narcolepsy. Other investigators are using animal models to better understand hypocretin and other chemicals such as glutamate that may play a key role in regulating sleep and wakefulness. Researchers are also investigating wake-promoting compounds to widen the range of available therapeutic options and create treatment options that reduce undesired side effects and decrease the potential for abuse. A greater understanding of the

complex genetic and biochemical bases of narcolepsy will eventually lead to new therapies to control symptoms and may lead to a cure.

Immune system

Abnormalities in the immune system may play an important role in the development of narcolepsy. NINDS-sponsored scientists have demonstrated the presence of unusual immune system activity in people with narcolepsy. Further, strep throat and certain varieties of influenza are now thought to be triggers in some at-risk individuals. Other NINDS researchers are also working to understand why the immune system destroys hypocretin neurons in narcolepsy in the hopes of finding a way to prevent or cure the disorder.

Sleep biology

The NINDS continues to support investigations into the basic biology of sleep, such as examining the brain mechanisms involved in generating and regulating REM sleep and other sleep behaviors. Since sleep and circadian rhythms are controlled by networks of neurons in the brain, NINDS researchers are also examining how neuronal circuits function in the body and contribute to sleep disorders like narcolepsy. A more comprehensive understanding of the complex biology of sleep will give scientists a better understanding of the processes that underlie narcolepsy and other sleep disorders.

How can I help research?

The NINDS supports the **NIH NeuroBioBank**, a national resource for investigators using human post-mortem brain tissue and related biospecimens for their research to understand conditions of the nervous system. The NeuroBioBank serves as a central point of access to collections that span neurological, neuropsychiatric, and neurodevelopmental diseases and disorders. Tissue from individuals with narcolepsy is needed to enable scientists to study this disorder more intensely. Participating groups include brain and tissue repositories, researchers, NIH program staff, information technology experts, disease advocacy groups, and, most importantly, individuals seeking information about opportunities to donate. More information about NeuroBioBank and opportunities to donate tissue is available at https://neurobiobank.nih.gov/.

Additionally, the NINDS supports genetic and immunological research in narcolepsy at Stanford University. Blood samples from individuals with narcolepsy can be sent by mail and are needed to enable scientists to study this disorder more intensely. Prospective donors may contact:

Stanford University Center for Narcolepsy
450 Broadway Street
M/C 5704
Redwood City, CA 94063
650-721-7574
https://med.stanford.edu/narcolepsy.html

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information is also available from the following organizations:

Narcolepsy Network
46 Union Drive #A212
North Kingstown, RI 02852
401-667-2523
888-292-6522
www.narcolepsynetwork.org

National Sleep Foundation
1010 N. Glebe Road, Suite 420
Arlington, VA 22201
703-243-1697
www.sleepfoundation.org

Wake Up Narcolepsy
P.O. Box 60293
Worcester, MA 01606
978-751-3693
www.wakeupnarcolepsy.org

National Heart, Lung, and Blood Institute (NHLBI) Health Information Center
National Institutes of Health/DHHS
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Bethesda, MD 20824-0105
301-592-8573
800-575-9355
www.nhlbi.nih.gov

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