

# Narcolepsy



U.S. DEPARTMENT OF HEALTH  
AND HUMAN SERVICES  
Public Health Service  
National Institutes of Health



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## What is narcolepsy?

**N**arcolepsy is a chronic brain disorder that involves poor control of sleep-wake cycles. People with narcolepsy experience periods of extreme daytime sleepiness and sudden, irresistible bouts of sleep that can strike at any time. These “sleep attacks” usually last a few seconds to several minutes.

Narcolepsy can greatly affect daily activities. People may unwillingly fall asleep while at work or at school, when having a conversation, playing a game, eating a meal, or, most dangerously, when driving or operating other types of machinery. In addition to daytime sleepiness, other major symptoms may include *cataplexy* (a sudden loss of voluntary muscle tone while awake that makes a person go limp or unable to move), vivid dream-like images or hallucinations, as well as total paralysis just before falling asleep or just after waking-up.

Contrary to common beliefs, people with narcolepsy do not spend a substantially greater proportion of their time asleep during a 24-hour period than do normal sleepers. In addition to daytime drowsiness and uncontrollable sleep episodes, most individuals also experience poor sleep quality that can involve frequent waking during nighttime sleep, and other sleep disorders.

For most adults, a normal night's sleep lasts about 8 hours and is composed of four to six separate sleep cycles. A sleep cycle is defined by a segment of non-rapid eye movement (NREM) sleep followed by a period of rapid eye movement (REM) sleep. The NREM segment can be further divided into increasingly deeper stages of sleep according to the size and frequency of brain waves. REM sleep is accompanied by bursts of rapid eye movement along with sharply heightened brain activity and temporary paralysis of the muscles that control posture and body movement. When subjects are awakened, they report that they were "having a dream" more often if they had been in REM sleep than if they had been in NREM sleep. Transitions from NREM to REM sleep are controlled by interactions among groups of neurons (nerve cells) located in different parts of the brain.

For normal sleepers a typical sleep cycle is about 100 to 110 minutes long, beginning with NREM sleep and transitioning to REM sleep after 80 to 100 minutes. People with narcolepsy frequently enter REM sleep within a few minutes of falling asleep.

### **Who gets narcolepsy?**

**N**arcolepsy affects both males and females equally and appears throughout the world. Symptoms often start in childhood or adolescence, but can occur later in life. The condition is life-long. Narcolepsy is not rare, but it is an underrecognized and underdiagnosed condition. Narcolepsy with

cataplexy is estimated to affect about one in every 3,000 Americans. More cases without cataplexy are also likely to exist.

### **What are the symptoms?**

**P**eople with narcolepsy experience various types of day- and nighttime sleep problems that are associated with REM sleep disturbances that tend to begin subtly and may change dramatically over time. The most common major symptom, other than excessive daytime sleepiness (EDS), is cataplexy, which occurs in about 70 percent of all people with narcolepsy. Sleep paralysis and hallucinations are somewhat less common. Only 10 to 25 percent of affected individuals, however, display all four of these major symptoms during the course of their illness.

### ***Excessive daytime sleepiness (EDS)***

EDS, the symptom most consistently experienced by almost all individuals with narcolepsy, is usually the first to become clinically apparent. Generally, EDS interferes with normal activities on a daily basis, whether or not individuals had sufficient sleep at night. People with EDS describe it as a persistent sense of mental cloudiness, a lack of energy, a depressed mood, or extreme exhaustion. Some people experience memory lapses, and many have great difficulty maintaining their concentration while at school, work, or home. People tend to awaken from such unavoidable sleeps feeling refreshed and finding that their drowsiness and fatigue subsides for an hour or two.

Involuntary sleep episodes are sometimes very brief, lasting no more than seconds at a time. As many as 40 percent of people with narcolepsy are prone to *automatic behavior* during such “microsleeps.” Automatic behavior involves performing a task during a short period of sleep but without any apparent interruption. During these episodes, people are usually engaged in habitual, essentially “second nature” activities such as taking notes in class, 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.

EDS, the most common of all narcoleptic symptoms, can be the result of a wide range of medical conditions, including other sleep disorders such as sleep apnea, various viral or bacterial infections, mood disorders such as depression, and chronic illnesses such as anemia, congestive heart failure, and rheumatoid arthritis that disrupt normal sleep patterns. Some medications can also lead to EDS, as can consumption of caffeine, alcohol, and nicotine. Finally, sleep deprivation has become one of the most common causes of EDS among Americans.

### **Cataplexy**

Cataplexy is a sudden loss of muscle tone while the person is awake that leads to feelings of weakness and a loss of voluntary

muscle control. Attacks can occur at any time during the waking period, with individuals usually experiencing their first episodes several weeks or months after the onset of EDS. But in about 10 percent of all cases, cataplexy is the first symptom to appear and can be misdiagnosed as a seizure disorder. Cataplectic attacks vary in duration and severity. The loss of muscle tone can be barely perceptible, involving no more than a momentary sense of slight weakness in a limited number of muscles, such as mild drooping of the eyelids. The most severe attacks result in a complete loss of tone in all voluntary muscles, leading to physical 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 seizure disorders. Although cataplexy can occur spontaneously, it is more often triggered by sudden, strong emotions such as fear, anger, stress, excitement, or humor. Laughter is reportedly the most common trigger.

The loss of muscle tone during a cataplectic episode resembles the interruption of muscle activity that naturally occurs during REM sleep. A group of neurons in the brain stem halts activity during REM sleep, inhibiting muscle movement. Using an animal model, scientists have learned that this same group of neurons becomes inactive during cataplectic attacks, a discovery that provides a clue to at least one of the neurological abnormalities contributing to human narcoleptic symptoms.

## ***Sleep paralysis***

The temporary inability to move or speak while falling asleep or waking is similar to REM-induced inhibitions of voluntary muscle activity. This natural inhibition usually goes unnoticed by people who experience normal sleep because it occurs only when they are fully asleep and entering the REM stage at the appropriate time in the sleep cycle. The attacks usually last a few seconds or minutes. Experiencing sleep paralysis resembles undergoing a cataplectic attack affecting the entire body. 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***

Hallucinations can accompany sleep paralysis and occur when people are falling asleep, waking, or during sleep. Referred to as *hypnagogic* hallucinations when occurring during sleep onset and as *hypnopompic* hallucinations when occurring during waking, these images are unusually vivid, seem real, and can be frightening. Most often, the content is primarily visual, but any of the other senses can be involved.

## ***Disrupted nocturnal sleep***

While individuals with narcolepsy have no difficulties falling asleep at night, most experience difficulties staying asleep. Sleep may be disrupted by insomnia, vivid dreaming, sleep talking, acting out while dreaming, and periodic leg movements.



## **Obesity**

After developing narcolepsy, many individuals suddenly gain weight, a side effect that can be prevented by active treatment.

## **When do symptoms appear?**

**I**n most cases, symptoms first appear when people are between the ages of 7 and 25. In rare cases, however, narcolepsy may appear at younger age or in older adults. If left undiagnosed and untreated, early onset narcolepsy can interfere with psychological, social, and cognitive function and development and can undermine academic and social activities.

## **What causes narcolepsy?**

**N**arcolepsy may have several causes. Most people with narcolepsy have low levels of the neurotransmitter *hypocretin*, which promotes wakefulness. Neurotransmitters are chemicals that neurons produce to communicate with each other and to regulate biological processes.

Most cases of narcolepsy are sporadic, meaning the disorder occurs in individuals with no known family history of the disorder. But clusters in families sometimes occur—up to 10 percent of individuals diagnosed with narcolepsy with cataplexy report having a close relative with the same symptoms. In extremely rare cases, narcolepsy is caused by a genetic defect that prevents normal production of hypocretin molecules. While close relatives of people with narcolepsy

have a statistically higher risk of developing the disorder than do members of the general population, that risk remains low when compared to diseases that are purely genetic in origin.

When cataplexy is present, the cause is most often the discrete loss of brain cells that produce hypocretin. Although the reason for such cell loss remains unknown, it appears to be autoimmune in nature (an autoimmune disorder is when the body's immune system mistakenly attacks healthy cells or tissue). That is, the body's immune system selectively attacks hypocretin-containing brain cells.

Other factors appear to play important roles in the development of narcolepsy. Some rare cases are known to result from traumatic injuries to parts of the brain involved in REM sleep or from tumor growth and other disease processes in the same regions. Infections, exposure to toxins, dietary factors, stress, hormonal changes such as those occurring during puberty or menopause, and alterations in a person's sleep schedule are just a few of the many factors that may exert direct or indirect effects on the brain, thereby possibly contributing to disease development.

### **How is narcolepsy diagnosed?**

**A** clinical examination and exhaustive medical history are essential for diagnosis and treatment. Your doctor may ask you 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 is exclusive to narcolepsy, cataplexy is the

most specific symptom and is rarely present outside of narcolepsy.

A physical exam can rule out or identify a condition that may be causing the symptoms. A battery of specialized tests, which can be performed in a sleep disorders clinic, is usually required before a diagnosis can be confirmed.

Two tests in particular are essential in confirming a diagnosis of narcolepsy: the polysomnogram (PSG) and the multiple sleep latency test (MSLT). The PSG is an overnight test that takes continuous multiple measurements while the individual is asleep to document abnormalities in the sleep cycle. It records heart and respiratory rates, electrical activity in the brain using electroencephalography, and nerve activity in muscles through electromyography. A PSG can help reveal whether REM sleep occurs at abnormal times in the sleep cycle and can rule out the possibility that an individual's symptoms result from another condition.

The MSLT is performed during the day to measure a person's tendency to fall asleep and to determine whether isolated elements of REM sleep intrude at inappropriate times during the waking hours. The sleep latency test measures the amount of time it takes for a person to fall asleep. As part of the test, an individual is asked to take four or five short naps usually scheduled 2 hours apart over the course of a day. Because sleep latency periods are normally 12 minutes or longer, a latency period of 8 minutes or less suggests a disorder of excessive daytime sleepiness. However, a

sleep latency of 8 minutes or less can be due to many conditions other than narcolepsy. The MSLT also measures heart and respiratory rates, records nerve activity in muscles, and pinpoints the occurrence of abnormally timed REM episodes through EEG recordings.

If a person enters REM sleep either at the beginning or within a few minutes of sleep onset during at least two of the scheduled naps, this is considered an indication of narcolepsy. Other reasons for REM sleep on the MSLT must be ruled out, such as the effects of medication and disrupted sleep from sleep apnea or an irregular work-rest schedule.

In some cases, human leukocyte antigen (HLA) typing (a marker of viral infection) may be helpful. Most HLA-associated disorders are autoimmune in nature. Certain alleles (genetic information found on a specific location on specific chromosomes) located on chromosome 6 are strongly associated with narcolepsy-cataplexy. To definitively identify a lack of hypocretin as the cause of narcolepsy, a sample of the cerebrospinal fluid (CSF) is removed by using a lumbar puncture and the level of hypocretin-1 is measured. When no other serious medical condition is present, low CSF hypocretin-1 can establish hypocretin deficiency as the cause of narcolepsy.

When cataplexy is not present, diagnosis must be made after excluding other possible causes of daytime sleepiness and fatigue, along with a positive MSLT.

## What treatments are available?

**N**arcolepsy cannot yet be cured, but 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 life-long. But EDS and cataplexy can be controlled in most individuals with drug treatment. Modafinil and sodium oxybate are two drugs that have been approved by the U.S. Food and Drug Administration for the treatment of narcolepsy.

Doctors prescribe central nervous system alerting agents such as modafinil and amphetamine-like stimulants such as methylphenidate to alleviate EDS and reduce the incidence of sleep attacks. For most people these medications are generally quite effective at reducing daytime drowsiness and improving levels of alertness. However, use of these medications may be associated with several undesirable side effects and must be carefully monitored. Common side effects include irritability and nervousness, shakiness, disturbances in heart rhythm, stomach upset, nighttime sleep disruption, and anorexia. Individuals may also develop tolerance with long-term use, leading to the need for increased dosages to maintain effectiveness. In addition, doctors should be careful when prescribing these drugs and people should be careful using them because the potential for abuse is high with any amphetamine.

Two classes of antidepressant drugs have proved 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 do amphetamines. But troublesome side effects still occur in some individuals, including impotence, high blood pressure, and heart rhythm irregularities.

In addition to central nervous system alerting agents and antidepressants, sodium oxybate or gamma hydroxybutyrate, also known as GHB or Xyrem<sup>®</sup>, can be used to treat narcolepsy. Sodium oxybate is a strong sedative that must be taken during the night. Sodium oxybate induces sleep and reduces the symptoms of daytime sleepiness and cataplexy. Due to safety concerns associated with the use of this drug, the distribution of sodium oxybate is tightly restricted.

### **What behavioral strategies help people cope with symptoms?**

**C**urrently available medications do not enable all people with narcolepsy to consistently maintain a fully normal state of alertness. Drug therapy should accompany various behavioral strategies according to the needs of the affected individual.

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

Improving the quality of nighttime sleep can combat EDS and help relieve persistent feelings of fatigue. Among the most important common-sense measures people can take to enhance sleep quality are:

- maintain a regular sleep schedule—go to bed and wake up at the same time every day
- avoid alcohol and caffeine-containing beverages for several hours before bedtime
- avoid large, heavy meals just before bedtime
- avoid smoking, especially at night
- maintain a comfortable, adequately warmed bedroom environment, and
- engage in relaxing activities such as a warm bath before bedtime.

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.

Safety precautions, particularly when driving, are particularly important for all persons with narcolepsy. 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. People with untreated narcoleptic symptoms are involved in automobile accidents roughly 10 times more frequently than the general population. However, accident rates are normal among individuals who have received appropriate medication.

Support groups frequently prove extremely beneficial because people with narcolepsy may become socially isolated due to embarrassment about or misunderstandings related to their symptoms. Many people also try to avoid strong emotions, since humor, excitement, and other intense feelings can trigger cataplectic attacks. Support groups also provide individuals with a network of social contacts who can offer practical help and emotional support.

The Americans with Disabilities Act requires employers to provide reasonable accommodations for all employees with disabilities. Adults 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 regarding special needs, including medication requirements during the school day, and to modify class schedules.

### **What is the state of the science involving narcolepsy?**

**D**uring the past decade, scientists have made considerable progress in understanding narcolepsy-cataplexy pathogenesis and in identifying genes strongly associated with the disorder. The majority of people diagnosed with narcolepsy and cataplexy are known to have a specific HLA gene variant called DQB1\*0602. They also frequently have specific alleles at a gene called the T-cell



receptor alpha (TCRA), a protein on T cells that recognize HLA proteins. However, some people with narcolepsy-cataplexy do not have the variant genes, while many people in the general population without narcolepsy do possess these variant genes. Specific variations in HLA and TCRA genes increase an individual's predisposition to develop the disorders—possibly through a yet-undiscovered route involving changes in immune-system function—when other causative factors are present.

Many other genes besides those making up the HLA complex and the T-cell receptor may contribute to the development of narcolepsy. Groups of neurons in several parts of the brain stem and the central brain, including the thalamus and hypothalamus, interact to control sleep. Large numbers of genes on different chromosomes control these neurons' activities, any of which could contribute to the development of the disease. Scientists studying narcolepsy in dogs have identified a mutation that appears to cause the disorder in Dobermans, Labradors, and Dachshunds. This mutated gene disrupts the ability to receive the signal from hypocretins (also known as orexins) that are produced by neurons located in the hypothalamus. The neurons that produce hypocretins are active during wakefulness, and research suggests that they keep the brain systems needed for wakefulness from shutting down unexpectedly. Mice born without functioning hypocretin genes develop symptoms of narcolepsy.

Except in rare cases, narcolepsy in humans is not associated with mutations of the hypocretin gene. However, scientists have found that brains from humans with narcolepsy often contain greatly reduced numbers of hypocretin-producing neurons. It is believed that certain HLA and TCRA subtypes increase susceptibility to an immune attack on hypocretin neurons in the hypothalamus, leading to degeneration of these important cells. Other factors also may interfere with proper functioning of this system. The hypocretins regulate appetite and feeding behavior in addition to controlling sleep. Therefore, the loss of hypocretin-producing neurons may explain not only how narcolepsy develops in some people, but also why people with narcolepsy have higher rates of obesity compared to the general population.

Narcolepsy onset follows a seasonal pattern of higher rates in spring and early summer, following winter upper airway infection season. When studied close to disease onset, individuals with narcolepsy have high levels of antibodies to a marker called ASO, indicating response to a recent bacterial infection such as strep throat. In addition, there is growing evidence that exposure to H1N1 virus (also called swine flu), or a special form of H1N1 vaccine (administered in Europe) can act as a rare trigger for the disease. It is not yet known if these infectious agents are direct triggers for the disease, or whether they increase likelihood of disease indirectly.

## What research is being done?

**W**ithin the Federal government, the National Institute of Neurological Disorders and Stroke (NINDS), a component of the National Institutes of Health (NIH), has primary responsibility for sponsoring research on neurological disorders. As part of its mission, the NINDS supports research on narcolepsy and other sleep disorders through grants to medical institutions across the country.

Within the National Heart, Lung, and Blood Institute, also a component of the NIH, the National Center on Sleep Disorders Research (NCSDR) 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/ncsdr/index.htm](http://www.nhlbi.nih.gov/about/ncsdr/index.htm).

NINDS-sponsored researchers are conducting studies devoted to further clarifying the wide range of genetic factors—both HLA genes and non-HLA genes—that may cause narcolepsy. Other scientists are conducting investigations using animal models to identify neurotransmitters other than the hypocretins that may contribute to disease development. A greater understanding of the complex genetic and biochemical bases of narcolepsy will eventually lead to the formulation of new therapies to control symptoms and may lead to a cure.

Researchers are also investigating the modes of action of wake-promoting compounds to widen the range of available therapeutic options.

Abnormal immunological processes may be an important element in the cause of narcolepsy. NINDS-sponsored scientists have demonstrated the presence of unusual, possibly pathological, forms of immunological activity in narcolepsy. Further, strep throat is now suggested to be involved as a trigger in some predisposed individuals. These researchers are now investigating whether drugs that suppress immunological processes may interrupt the development of narcolepsy.

Finally, the NINDS continues to support investigations into the basic biology of sleep, including the brain mechanisms involved in generating and regulating REM sleep. A more comprehensive understanding of the complex biology of sleep will undoubtedly further clarify the pathological processes that underlie narcolepsy and other sleep disorders.

### **How can I help research?**

**T**he NINDS contributes to the support of the Human Brain and Spinal Fluid Resource Center in Los Angeles. This bank supplies investigators around the world with tissue from individuals with neurological and other disorders. Tissue

from individuals with narcolepsy is needed to enable scientists to study this disorder more intensely. Prospective donors may contact:

**Human Brain and Spinal Fluid**

**Resource Center**

Building 212

West Los Angeles Healthcare Center

11301 Wilshire Blvd. (127A)

Los Angeles, CA 90073

310-268-3536

24-hour pager: 310-636-5199

*[www.loni.ucla.edu/uclabrainbank](http://www.loni.ucla.edu/uclabrainbank)*

The NINDS supports genetic and immunological research in narcolepsy at Stanford University. This research involves the study of blood samples. 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

650-721-7550

*[www.med.stanford.edu/school/psychiatry/narcolepsy](http://www.med.stanford.edu/school/psychiatry/narcolepsy)*

## Where can I get more information?

**F**or 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 also is available from the following organizations:

### **Narcolepsy Network, Inc.**

129 Waterwheel Lane  
North Kingstown, RI 02852  
401-667-2523  
888-292-6522  
*www.narcolepsynetwork.org*

### **National Sleep Foundation**

1010 N. Glebe Road, Suite 310  
Arlington, VA 22201  
703-243-1697  
*www.sleepfoundation.org*

### **National Heart, Lung, and Blood Institute (NHLBI)**

Health Information Center  
National Institutes of Health, DHHS  
P.O. Box 30105  
Bethesda, MD 20892-0105  
301-592-8573  
240-629-3255 (TTY)  
*www.nhlbi.nih.gov*





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