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NARCOLEPSY INFORMATION

What is Narcolepsy?

Narcolepsy is a chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally. At various times throughout the day, people with narcolepsy experience fleeting urges to sleep. If the urge becomes overwhelming, patients fall asleep for periods lasting from a few seconds to several minutes. In rare cases, some people may remain asleep for an hour or longer.

Narcoleptic sleep episodes can occur at any time, and thus frequently prove profoundly disabling. People may involuntarily fall asleep while at work or at school, when having a conversation, playing a game, eating a meal, or, most dangerously, when driving an automobile or operating other types of potentially hazardous machinery. In addition to daytime sleepiness, three other major symptoms frequently characterize narcolepsy: **cataplexy**, or the sudden loss of voluntary muscle tone; vivid **hallucinations** during sleep onset or upon awakening; and brief episodes of total **paralysis** at the beginning or end of sleep.

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 involuntary sleep episodes, most patients also experience frequent awakenings during nighttime sleep. For these reasons, narcolepsy is considered to be a disorder of the normal boundaries between the sleeping and waking states.

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 stages according to the size and frequency of brain waves. REM sleep, in contrast, is accompanied by bursts of **r**apid **e**ye **m**ovement (hence the acronym **REM** sleep) along with sharply heightened brain activity and temporary paralysis of the muscles that control posture and body movement. When subjects are awakened from sleep, 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 governed by interactions among groups of neurons (nerve cells) in certain parts of the brain.

Scientists now believe that narcolepsy results from disease processes affecting brain mechanisms that regulate REM sleep. For normal sleepers a typical sleep cycle is about 100 - 110 minutes long, beginning with NREM sleep and transitioning to REM sleep after 80 - 100 minutes. But, people with narcolepsy frequently enter REM sleep within a few minutes of falling asleep.

Who Gets Narcolepsy?

Narcolepsy is not rare, but it is an underrecognized and underdiagnosed condition. The disorder is estimated to affect about one in every 2,000 Americans. But the exact prevalence rate remains uncerntain, and the disorder may affect a larger segment of the population.

Narcolepsy appears throughout the world in every racial and ethnic group, affecting males and females equally. But prevalence rates vary among populations. Compared to the U.S. population, for example, the prevalence rate is substantially lower in Israel (about one per 500,000) and considerably higher in Japan (about one per 600).

Most cases of narcolepsy are sporadic-that is, the disorder occurs independently in individuals without strong evidence of being inherited. But familial clusters are known to occur. Up to 10 percent of patients diagnosed with narcolepsy with cataplexy report having a close relative with the same symptoms. Genetic

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factors alone are not sufficient to cause narcolepsy. Other factors-such as infection, immune-system dysfunction, trauma, hormonal changes, stress-may also be present before the disease develops. Thus, 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 in comparison to diseases that are purely genetic in origin.

* Obstructive sleep apnea is a temporary cessation of breathing that occurs repeatedly during sleep and is caused by a narrowing of the airway. Restless legs syndrome is a neurological disorder characterized by unpleasant sensations-burning, creeping, tugging-in the legs and an uncontrollable urge to move when at rest

What are the Symptoms?

People with narcolepsy experience highly individualized patterns of 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 patients. Sleep paralysis and hallucinations are somewhat less common. Only 10 to 25 percent of patients, however, display all four of these major symptoms during the course of their illness.

Excessive daytime sleepiness

EDS, the symptom most consistently experienced by almost all patients, is usually the first to become clinically apparent. Generally, EDS interferes with normal activities on a daily basis, whether or not patients have 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. Many find that they have great difficulty maintaining their concentration while at school or work. Some experience memory lapses. Many find it nearly impossible to stay alert in passive situations, as when listening to lectures or watching television. People tend to awaken from such unavoidable sleeps feeling refreshed and finding that their feelings of drowsiness and fatigue subside 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 all people with narcolepsy are prone to *automatic behavior* during such "microsleeps." They fall asleep for a few seconds while performing a task but continue carrying it through to completion 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 during a microsleep. 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, patients may get lost or have an accident.

Cataplexy

Cataplexy is a sudden loss of muscle tone that leads to feelings of weakness and a loss of voluntary muscle control. Attacks can occur at any time during the waking period, with patients 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 manifestation of 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 total physical collapse in which patients 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 frequent 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 brainstem ceases activity during REM sleep, inhibiting muscle movement. Using an animal model, scientists have recently 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 up also parallels 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. Experiencing sleep paralysis resembles undergoing a cataplectic attack affecting the entire body. As with cataplexy, people remain fully conscious. Cataplexy and sleep paralysis are frightening events, especially when first experienced. Shocked by suddenly being unable to move, many patients fear that they may be permanently paralyzed or even dying. However, 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 or can occur in isolation when people are falling asleep or waking up. Referred to as *hypnagogic* hallucinations when accompanying sleep onset and as *hypnopompic* hallucinations when occurring during awakening, these delusional experiences are unusually vivid and frequently frightening. Most often, the content is primarily visual, but any of the other senses can be involved. These hallucinations represent another intrusion of an element of REM sleep-dreaming-into the wakeful state.

When Do Symptoms Appear?

In most cases, symptoms first appear when people are between the ages of 10 and 25 but narcolepsy can become clinically apparent at virtually any age. Many patients first experience symptoms between the ages of 35 and 45. A smaller number initially manifest the disorder around the ages of 50 to 55. Narcolepsy can also develop early in life, probably more frequently than is generally recognized. For example, 3-year-old children have been diagnosed with the disorder. Whatever the age of onset, patients find that the symptoms tend to get worse over the two to three decades after the first symptoms appear. Many older patients find that some daytime symptoms decrease in severity after age 60.

Narcoleptic symptoms, especially EDS, often prove more severe when the disorder develops early in life rather than during the adult years. Experts have also begun to recognize that narcolepsy sometimes contributes to certain childhood behavioral problems, such as attention-deficit hyperactivity disorder, and must be addressed before the behavioral problem can be resolved. If left undiagnosed and untreated, narcolepsy can pose special problems for children and adolescents, interfering with their psychological, social, and cognitive development and undermining their ability to succeed at school. For some young people, feelings of low self-esteem due to poor academic performance may persist into adulthood.

What Causes Narcolepsy?

The cause of narcolepsy remains unknown but during the past decade, scientists have made considerable progress in understanding its pathogenesis and in identifying genes strongly associated with the disorder. Researchers have also discovered abnormalities in various parts of the brain involved in regulating REM sleep that appear to contribute to symptom development. Experts now believe it is likely that-similar to many other complex, chronic neurological diseases-narcolepsy involves multiple factors interacting to cause neurological dysfunction and REM sleep disturbances.

A number of variant forms (*alleles*) of genes located in a region of chromosome 6 known as the HLA complex have proved to be strongly, although not invariably, associated with narcolepsy. The HLA complex comprises a large number of interrelated genes that regulate key aspects of immune-system function. The majority of people diagnosed with narcolepsy are known to have specific variants in certain HLA genes. However, these variations are neither necessary nor sufficient to cause the disorder. Some people with narcolepsy do not have the variant genes, while many people in the general population without narcolepsy do possess these variant genes. Thus it appears that specific variations in HLA genes increase an individual's predisposition to develop the disorder-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 may contribute to the development of narcolepsy. Groups of neurons in several parts of the brainstem 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 development of the disease. Scientists studying narcolepsy in dogs have identified a mutation in a gene on chromosome 12 that appears to contribute to the disorder. This mutated gene disrupts the processing of a special class of neurotransmitters called hypocretins (also known as orexins) that are produced by neurons located in the hypothalamus. Neurotransmitters are special proteins that neurons produce to communicate with each other and to regulate biological processes. 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 many 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. Certain HLA subtypes may increase susceptibility to an immune attack on hypocretin neurons in the hypothalamus, leading to degeneration of neurons in the hypocretin system. 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.

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?

Narcolepsy is not definitively diagnosed in most patients until 10 to 15 years after the first symptoms appear. This unusually long lag-time is due to several factors, including the disorder's subtle onset and the variability of symptoms. As important, however, is the fact that the public is largely unfamiliar with the disorder, as are many health professionals. When symptoms initially develop, people often do not recognize

that they are experiencing the onset of a distinct neurological disorder and thus fail to seek medical treatment.

A clinical examination and exhaustive medical history are essential for diagnosis and treatment. However, none of the major symptoms is exclusive to narcolepsy. EDS-the most common of all narcoleptic symptoms-can result from 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 painful chronic illnesses such as congestive heart failure and rheumatoid arthritis that disrupt normal sleep patterns. Various 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.

This lack of specificity greatly increases the difficulty of arriving at an accurate diagnosis based on a consideration of symptoms alone. Thus, a battery of specialized tests, which can be performed in a sleep disorders clinic, is usually required before a diagnosis can be established.

Two tests in particular are considered 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 a patient is asleep to document abnormalities in the sleep cycle. It records heart and respiratory rates, electrical activity in the brain through electroencephalography (EEG), and nerve activity in muscles through electromyography (EMG). A PSG can help reveal whether REM sleep occurs at abnormal times in the sleep cycle and can eliminate 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. 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. As the name suggests, the sleep latency test measures the amount of time it takes for a person to fall asleep. Because sleep latency periods are normally 10 minutes or longer, a latency period of 5 minutes or less is considered suggestive of 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 also considered a positive indication of narcolepsy.

What Treatments are Available?

Narcolepsy cannot yet be cured. But EDS and cataplexy, the most disabling symptoms of the disorder, can be controlled in most patients with drug treatment. Often the treatment regimen is modified as symptoms change.

For decades, doctors have used central nervous system stimulants-amphetamines such as methylphenidate, dextroamphetamine, methamphetamine, and pemoline-to alleviate EDS and reduce the incidence of sleep attacks. For most patients these medications are generally quite effective at reducing daytime drowsiness and improving levels of alertness. However, they are associated with a wide array of undesirable side effects so their use must be carefully monitored. Common side effects include irritability and nervousness, shakiness, disturbances in heart rhythm, stomach upset, nighttime sleep disruption, and anorexia. Patients 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 patients should be careful using them because the potential for abuse is high with any amphetamine.

In 1999, the FDA approved a new non-amphetamine wake-promoting drug called modafinil for the treatment of EDS. In clinical trials, modafinil proved to be effective in alleviating EDS while producing fewer, less serious side effects that do amphetamines. Headache is the most commonly reported adverse effect. Long-term use of modafinil does not appear to lead to tolerance.

Two classes of antidepressant drugs have proved effective in controlling cataplexy in many patients: tricyclics (including imipramine, desipramine, clomipramine, and protriptyline) and selective serotonin reuptake inhibitors (including fluoxetine and sertraline). In general, antidepressants produce fewer adverse effects than do amphetamines. But troublesome side effects still occur in some patients, including impotence, high blood pressure, and heart rhythm irregularities.

On July 17, 2002, the FDA approved Xyrem (sodium oxybate or gamma hydroxybutyrate, also known as GHB) for treating people with narcolepsy who experience episodes of cataplexy. Due to safety concerns associated with the use of this drug, the distribution of Xyrem is tightly restricted.

What Behavioral Strategies Help People Cope With Symptoms?

None of the currently available medications enables people with narcolepsy to consistently maintain a fully normal state of alertness. Thus, drug therapy should be supplemented by various behavioral strategies according to the needs of the individual patient.

To gain greater control over their symptoms, many patients take short, regularly scheduled naps at times when they tend to feel sleepiest. 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. The Americans with Disabilities Act requires employers to provide reasonable accommodations for all employees with disabilities. Children and adolescents with narcolepsy can be similarly accommodated through modifying class schedules and informing school personnel of special needs, including medication requirements during the school day.

Improving the quality of nighttime sleep can combat EDS and help relieve persistent feelings of fatigue. Among the most important common-sense measures patients can take to enhance sleep quality are: (1) maintaining a regular sleep schedule; (2) avoiding alcohol and caffeine-containing beverages for several hours before bedtime; (3) avoiding smoking, especially at night; (4) maintaining a comfortable, adequately warmed bedroom environment; and (5) engaging 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 of paramount importance for all persons with narcolepsy. Although the disorder, in itself, is not fatal, 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 patients who have received appropriate medication.

Finally, patient support groups frequently prove extremely beneficial because people with narcolepsy may become socially isolated due to embarrassment about their symptoms. Many patients also attempt to avoid experiencing strong emotions, since humor, excitement, and other intense feelings can trigger cataplectic attacks. Moreover, because of the widespread lack of public knowledge about the disorder, people with narcolepsy are too often unfairly judged to be lazy, unintelligent, undisciplined, or unmotivated. Such stigmatization often increases the tendency toward self-imposed isolation. The empathy and understanding that support groups offer people can be crucial to their overall sense of well-being and provide them with a network of social contacts who can offer practical help and emotional support.

What Research is Being Done?

Within 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 with a neurological basis through grants to major 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 and shares information with private and nonprofit groups. NCSDR staff also promote doctoral and postdoctoral training programs, and educates the public and health care professional about sleep disorders. For more information, go to the NCSDR website at **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.

Scientists have long suspected that abnormal immunological processes may be an important element in the cause of narcolepsy, but until recently clear evidence supporting this suspicion has been lacking. NINDS-sponsored scientists have recently uncovered evidence demonstrating the presence of unusual, possibly pathological, forms of immunological activity in narcoleptic dogs. These researchers are now investigating whether drugs that suppress immunological processes may interrupt the development of narcolepsy in this animal model.

Recently there has been a growing awareness that narcolepsy can develop during childhood and may contribute to the development of behavior disorders. A group of NINDS-sponsored scientists is now conducting a large epidemiological study to determine the prevalence of narcolepsy in children aged 2 to 14 years who have been diagnosed with attention-deficit hyperactivity disorder.

Finally, the NINDS continues to support investigations into the basic biology of sleep, including the brain mechanisms involved in generating and regulating REM sleep. Scientists are now examining physiological processes occurring in a portion of the hindbrain called the amygdala in order to uncover novel biochemical processes underlying 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?

The 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 patients 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
Neurology Research (127A)
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310-268-3536
24-hour pager: 310-636-5199
Email: RMNbbank@ucla.edu
http://www.loni.ucla.edu/~nnrsb/NNRSB

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
http://www.ninds.nih.gov

Information also is available from the following organizations:

Narcolepsy Network, Inc.
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North Kingstown, RI 02852
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