REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

# Narcolepsy

Thomas E. Scammell, M.D.

From the Department of Neurology, Beth Israel Deaconess Medical Center and Boston Children's Hospital, Boston. Address reprint requests to Dr. Scammell at Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215, or at tscammel@bidmc.harvard.edu.

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Narcolepsy, one of the most common causes of chronic sleepiness, affects about 1 in 2000 people. Despite the frequency of narcolepsy, the average time from the onset of symptoms to diagnosis is 5 to 15 years, and narcolepsy may remain undiagnosed in as many as half of all affected people with narcolepsy, since many clinicians are unfamiliar with this disorder.[1] Fortunately, awareness of narcolepsy and other sleep disorders is increasing, and over the past several years researchers have made great progress in understanding narcolepsy. Clinicians now recognize two types of narcolepsy. Type 1 is caused by extensive loss of hypothalamic neurons that produce the neuropeptides orexin-A and -B (also referred to as hypocretin-1 and -2); type 2 includes most of the same symptoms, but its cause is unknown. This review focuses on the symptoms and pathologic and neurobiologic features of narcolepsy and provides a framework for diagnosis and effective treatment.

## SYMPTOMS

Narcolepsy usually begins between the ages of 10 and 20 years with the sudden onset of persistent daytime sleepiness, although it can also develop gradually. In many persons with narcolepsy, the sleepiness is severe, resulting in difficulty focusing and staying awake at school, at work, and during periods of inactivity (e.g., when watching a movie). Quite often, the diagnosis is made only after serious problems have arisen, such as declining grades at school, poor performance at work, or a motor vehicle accident. Although it may appear to be challenging to distinguish daytime sleepiness due to narcolepsy from that caused by insufficient sleep, especially in teenagers, people with narcolepsy are sleepy every day, even with adequate nighttime sleep. In contrast to people with disorders such as obstructive sleep apnea who have poor-quality sleep, those with narcolepsy usually feel refreshed after a full night's sleep or a brief nap, but their sleepiness returns 1 to 2 hours later, especially when they are sedentary.

Narcolepsy is also characterized by disordered regulation of rapid-eye-movement (REM) sleep. REM sleep normally occurs only during the usual sleep period and includes vivid, storylike dreams, rapid (saccadic) eye movements, and paralysis of nearly all skeletal muscles, except the muscle of respiration. REM sleep can occur in persons with narcolepsy at any time of day, and the classic elements of REM sleep often intrude into wakefulness, creating peculiar intermediate states.

The most dramatic of these REM sleep–like states is cataplexy — sudden episodes of partial or complete paralysis of voluntary muscles. These episodes are triggered by strong emotions (Fig. 1), most often by positive emotions such as those associated with laughing at a joke or unexpectedly encountering a friend. In some people, however, cataplexy can be triggered by intense negative emotions, such as frustration or anger. The paralysis usually evolves over many seconds, first affecting the face and neck and then causing weakness in the trunk and limbs, although the muscles associated with breathing are spared. With partial cataplexy, slurred

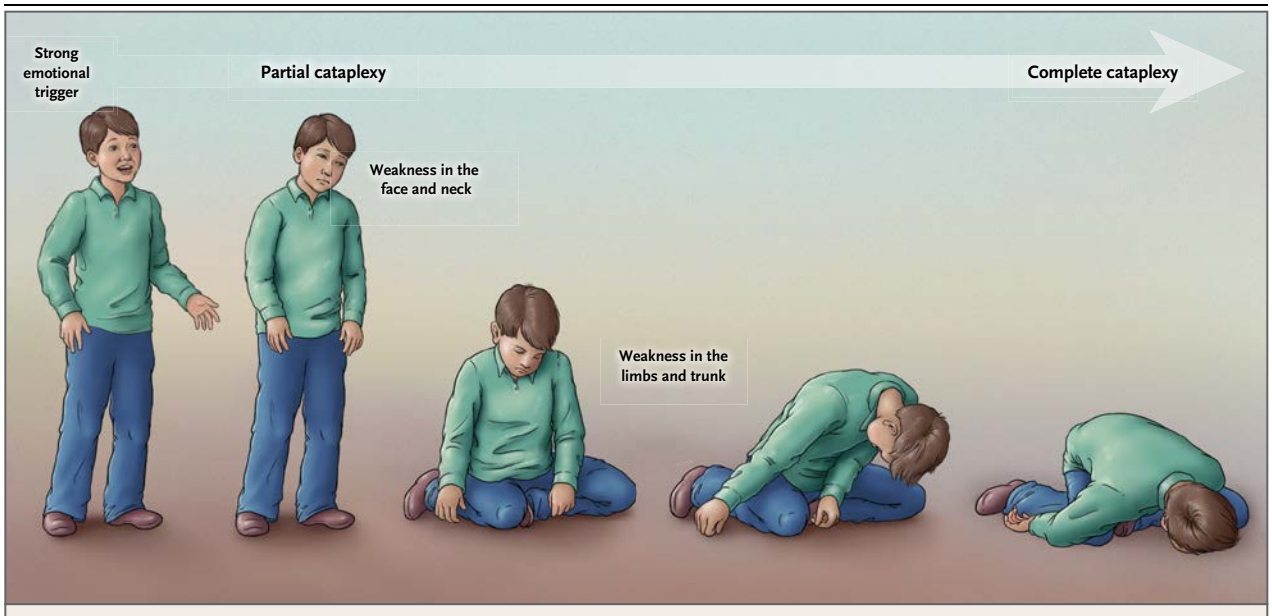


**Figure 1. Cataplexy.**

Cataplexy is characterized by sudden, emotionally triggered episodes of muscle weakness with preserved consciousness. These episodes typically begin with weakness of the muscles of the face and neck that then spreads to involve the muscles of the limbs and trunk.

speech and a sagging face are common; with complete episodes, the person may slump to the ground, fully conscious but immobile for as long as 1 or 2 minutes. Children with cataplexy can have long-lasting periods of low muscle tone, with a wobbly gait and perioral movements such as grimacing and tongue protrusion.[2] A patient's report of a history of cataplexy is diagnostically very helpful to the physician, since cataplexy occurs almost exclusively in type 1 narcolepsy.

The paralysis and dreams typical of REM sleep can also occur at the borders of sleep. Sleep paralysis is much like cataplexy, but it can occur spontaneously on awakening from sleep and occasionally as the person is falling asleep. Dreamlike and often disturbing hallucinations are common in narcolepsy. Those that occur at the onset of sleep are referred to as hypnagogic hallucinations, and those that occur on awakening as hypnopompic hallucinations. Typical hallucinations might include the sense that a threatening stranger is in the bedroom or that one is being attacked by animals. In contrast to people with psychotic disorders, those with narcolepsy rarely have complex auditory hallucinations or fixed delusions, although hypnopompic hallucinations can occasionally be so vivid that the person acts on them (e.g., calling the police to report that there is a burglar in the house).[3] Like cataplexy, sleep paralysis and hypnagogic hallucinations rarely last more than 1 or 2 minutes. Because hypnagogic hallucinations and sleep paralysis occur occasionally in about 20% of the general population, they are less informative diagnostically than a history of cataplexy.

Narcolepsy often includes additional problems that may require independent treatment. Although people with narcolepsy are sleepy much the day, they often have fragmented sleep at night[4] and sometimes require treatment with a sleep-promoting medication. They also have a tendency to gain excess weight; at the onset of narcolepsy, children can gain 20 to 40 lb (9 to 18 kg), and the body-mass index in adults is approximately 15% above average, possibly because of a low metabolic rate. Other sleep disorders that are more prevalent among persons with narcolepsy than in the general population include obstructive sleep apnea, periodic limb movement disorder (nocturnal myoclonus), sleepwalking, and REM sleep behavior disorder.[5] In addition, depression is common in persons with narcolepsy,[6] although it remains unclear whether this is due to the effect of narcolepsy on the person's life or the underlying neuropathologic state.

**Table 1. Differential Diagnosis of Chronic Daytime Sleepiness.***

| Diagnosis | Distinguishing Characteristics |
|---|---|
| Insufficient sleep | Sleepiness decreases with more sleep on weekends and holidays |
| Obstructive sleep apnea | Snoring, witnessed episodes of apnea, large tonsils, large tongue, long uvula, obesity |
| Narcolepsy | Cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, fragmented sleep |
| Delayed sleep phase disorder | Sleepiness in the morning, alertness at night |
| Periodic limb movement disorder | Sleep disrupted by kicking movements; often occurs with the restless legs syndrome, iron deficiency, uremia, and neuropathy |
| Shift-work sleep disorder | Sleepiness when working at night, insufficient sleep during the day |
| Use of sedating medications | Insomnia medications, opiates, anxiolytics, anticonvulsants, antipsychotics, antidepressants, antihistamines, among others |
| Idiopathic hypersomnia | Lengthy nighttime sleep and long naps, difficulty waking from sleep |
| Depression | Increased time in bed but little functional sleepiness on the multiple sleep latency test |
| Other medical disorders | Symptoms of hypothyroidism, Parkinson's disease, the Prader–Willi syndrome, myotonic dystrophy, among others |

* With most of these disorders, people do not feel rested when arising in the morning; however, most people with narcolepsy feel alert on awakening.

## DIAGNOSIS

The diagnosis of narcolepsy is often apparent from the clinical history, but it is essential to confirm the diagnosis with overnight polysomnography followed by a multiple sleep latency test the next day. The overnight sleep study helps rule out other potential causes of daytime sleepiness; in people with narcolepsy, it may show fragmented, light sleep and an early transition into REM sleep (<15 minutes after the onset of sleep).[7,8] During the multiple sleep latency test, the patient is encouraged every 2 hours to fall asleep for 20 minutes; the test usually begins at 8 a.m. and ends at approximately 5 to 6 p.m. Given the opportunity to nap, people with narcolepsy usually fall asleep in less than 8 minutes, whereas healthy people generally fall asleep in 15 minutes or more. In addition, people with narcolepsy usually have REM sleep during at least two of these daytime naps (known as sleep-onset REM sleep periods), whereas people without narcolepsy rarely have any daytime REM sleep. A positive multiple sleep latency test (defined as a short time to fall asleep plus REM sleep in at least two of the naps) provides strong, objective evidence of excessive sleepiness and poorly regulated REM sleep.

Because the diagnosis of narcolepsy relies heavily on the multiple sleep latency test, it is essential that the test be performed under the correct conditions.[9] Medications that suppress REM sleep should be discontinued well in advance of the test (e.g., 3 weeks for antidepressants with a long half-life), and any other psychoactive medications, especially stimulants, should be discontinued 1 week in advance. The patient should obtain and document with a sleep log an adequate amount of sleep each night in the week before the multiple sleep latency test, since inadequate nighttime sleep may result in short daytime sleep latencies. During the overnight sleep study preceding the test, adults should get at least 6 hours of sleep, and children should get more. Adherence to these conditions is important, because people with sleep deprivation or shift-work schedules and those who receive psychoactive medications can have test results that are similar to those seen in people with narcolepsy.[10,11]

Because persistent sleepiness can occur with many conditions, it is important in considering a diagnosis of narcolepsy to rule out other sleep disorders[12] (Table 1). Insufficient sleep is very common in teenagers and adults, and extending the sleep period to 8 or 9 hours each night for a week can be diagnostically helpful. The clinical history and results of the overnight sleep study can usually rule out sleep apnea, delayed sleep phase disorder, and periodic limb movement disorder. The effects of shift work or sedating medications should also be considered. Idio-

pathic hypersomnia is an uncommon cause of chronic sleepiness; in people with this condition, as in those with narcolepsy, the mean sleep latency on the multiple sleep latency test is short, but there is only one or no sleep-onset REM sleep periods. Some people with idiopathic hypersomnia can sleep for long periods (>10 hours) every day and have long, unrefreshing naps, but people with narcolepsy typically sleep for normal amounts of time over a 24-hour period and feel refreshed after a 15-to-20-minute nap.

## PATHOLOGIC AND GENETIC FEATURES

Clinicians now recognize two types of narcolepsy.[13] In both disorders, people have chronic daytime sleepiness and positive results on the multiple sleep latency test. Type 1 narcolepsy is characterized by cataplexy and very low levels of orexin-A in cerebrospinal fluid. In contrast, people with type 2 narcolepsy do not have cataplexy and have normal orexin-A levels. The difference in orexin levels suggests that type 1 and type 2 narcolepsy may be phenotypically similar disorders with different underlying causes. Sleepiness and other symptoms are generally more severe in type 1 narcolepsy, and the diagnosis is usually straightforward. In contrast, the diagnosis of type 2 narcolepsy can be a challenge, since other potential causes of sleepiness must be ruled out and the multiple sleep latency test can be falsely positive or falsely negative.[10-12]

Type 1 narcolepsy is caused by a severe loss of neurons that produce the orexin neuropeptides. Orexin-A and orexin-B are small peptide neurotransmitters made only by a cluster of neurons in the lateral hypothalamus.[14,15] In 1999, researchers discovered that mice and dogs with disrupted orexin signaling have symptoms similar to those of narcolepsy in humans,[16,17] and shortly thereafter, two groups of investigators found that type 1 narcolepsy is caused by a severe but highly selective loss of the orexin-producing neurons.[18-20] Type 2 narcolepsy may be caused by less extensive injury to these neurons,[21] but data on the disease process in type 2 are quite limited.

The process that destroys the orexin-producing neurons remains a mystery, but genetic factors are clearly important. More than 98% of people with type 1 narcolepsy carry HLA-DQB1*06:02, a finding that makes this the strongest association between HLA and disease known.[22,23] DQB1*06:02 is also detected in roughly 50% of people with type 2 narcolepsy, but only in 12 to 30% of the general population in the United States, Europe, and Japan. Overall, this gene is predicted to increase the risk of narcolepsy by a factor of about 200.[23] In persons who are positive for DQB1*06:02 and in whom it is difficult to make a diagnosis, measurement of orexin-A levels in cerebrospinal fluid can be very helpful, although the test is not yet commercially available.[24]

Type 1 narcolepsy has also been linked to polymorphisms in other genes. DQB1*06:02 is almost always accompanied by the linked DQA1*01:02 gene, and their gene products form a heterodimer that presents antigens to T-cell receptors on CD4 T cells.[25] Variations in other HLA-DQ alleles, HLA-DP, and HLA class I also contribute to genetic susceptibility, as do polymorphisms in other genes that affect immune function, such as *TCRA*, *TCRB*, *P2RY11*, *EIF3G*, *ZNF365*, *IL10RB-IFNAR1*, *CTSH*, and *TNFSF4*.[25-27] These genetic factors are clearly important, but they are not the whole story. Narcolepsy is usually sporadic, and the risk that an affected parent will have an affected child is only 1%. Even if one monozygotic twin has narcolepsy, there is only about a 30% chance that narcolepsy will develop in the other twin.

The onset of symptoms of narcolepsy most commonly occurs in the late spring; this suggests that the disease may be triggered by winter infections.[28] For example, high titers of antibodies against antistreptolysin O are common soon after the onset of narcolepsy, which suggests that streptococcal infections may trigger the disease.[29] In the winter of 2009–2010, a dramatic spike in new cases of narcolepsy provided the clearest evidence so far that the disease can be caused by an autoimmune process. During the H1N1 influenza pandemic that winter, a specific brand of vaccine against H1N1 (Pandemrix) that contained a potent adjuvant was used widely in Scandinavia and some other parts of Europe. In these regions, the number of new cases of narcolepsy increased by as much as a factor of 12, with onset of symptoms 1 to 2 months after vaccination, but only in children and teenagers carrying the DQB1*06:02 gene.[30,31] In China, H1N1 influenza infection was common in the winter of 2009–2010, and new cases of narcolepsy tripled in the subsequent year.[28] This surge in new cases suggests that the combination of DQB1*06:02, young age, and particular immune stimuli strongly increases the risk of narcolepsy.

These findings have spurred many researchers to hypothesize that narcolepsy is caused by an autoimmune process. It is probable that an immune stimulus such as influenza or streptococcus infection triggers a T-cell response and that, in genetically susceptible persons, this inflammatory reaction damages the orexin-producing neurons, perhaps through a process of molecular mimicry.[32] Countering this idea, however, are the facts that no signs of inflammation are detected in cerebrospinal fluid or seen on magnetic resonance imaging in people with narcolepsy and that there is no strong evidence of an increased prevalence of other autoimmune diseases among such persons. Furthermore, small trials of immunomodulating agents have produced little reduction in symptoms.

On rare occasions, narcolepsy occurs as part of a broader injury to the hypothalamus or to the projections of the orexin-producing neurons as a consequence of sarcoidosis, demyelination, or a stroke, tumor, or paraneoplastic disorder.[33] People with narcolepsy caused by a structural lesion are easily distinguished from those with typical narcolepsy, since they have increases in total amounts of sleep and additional signs of hypothalamic or brain-stem injury, such as pituitary dysfunction, abnormal eye movements, or upper-motor-neuron weakness.

## NEUROBIOLOGIC FEATURES

The discovery that type 1 narcolepsy is caused by the loss of orexin-producing neurons has greatly advanced understanding of the underlying neurobiologic features of this disorder. The orexin neurons are active during wakefulness,[34-36] and the orexin neuropeptides stimulate target neurons that promote wakefulness, including those in the cortex and basal forebrain and those in the brain stem and hypothalamus that produce norepinephrine, serotonin, dopamine, and histamine (Fig. 2). Orexins have long-lasting effects on target neurons, and this sustained activity may help maintain wakefulness throughout the day. Conversely, loss of orexin signaling in narcolepsy may result in inconsistent activity in these wakefulness-promoting brain regions, resulting in frequent lapses into sleep.[37]

Orexins increase activity in brain regions that suppress REM sleep, and reduced orexin signaling in narcolepsy may therefore enable elements of REM sleep — such as paralysis or dreamlike hallucinations — to occur during wakefulness.[38] Cataplexy is triggered by signals related to strong, positive emotions that may be relayed through the medial prefrontal cortex and amygdala to activate circuits in the pons that cause muscle paralysis.[39-41] Orexin signaling also increases metabolism, sympathetic tone, and rewarding behaviors such as drug seeking. It is possible that dysfunction in these pathways contributes to the obesity and depression that occur in many people with narcolepsy.[6,42]

## TREATMENT

Narcolepsy is treated with a combination of behavioral and pharmacologic approaches.[43,44] Daytime sleepiness often partially decreases with sufficient good-quality sleep at night and a 15-to-20-minute nap in the afternoon. Any additional sleep disorders in the patient, such as sleep apnea, should also be addressed.

Most people with narcolepsy also require treatment with wakefulness-promoting medications (Table 2).[45] For mild-to-moderate daytime sleepiness, modafinil is often a good choice, since it has an acceptable side-effect profile and has a low potential for abuse.[46] It is probable that modafinil improves wakefulness by reducing the reuptake of dopamine. Methylphenidate, as well as dextroamphetamine and similar amphetamines, can be more potent than modafinil, but side effects are more common with these drugs. Diversion and abuse of these medications can also be a source of concern, but the risk may be lower with slow-release formulations. These drugs probably promote wakefulness by blocking the reuptake and increasing the release of dopamine; they have similar effects on serotonin and norepinephrine signaling, though to a lesser extent.[47]

The Epworth Sleepiness Scale is a helpful tool for assessing subjective sleepiness and the response to medications.[48] The multiple sleep latency test and the maintenance of wakefulness test, which measures alertness during the day, can provide complementary, objective measures of the degree of sleepiness.[9]

Cataplexy often is reduced with a low dose of an antidepressant. Extended-release venlafaxine generally has an acceptable side-effect profile, and it is effective for most of the day. The anticholinergic effects of clomipramine (e.g., seda-

tion and dry mouth) can be bothersome, but it potently suppresses cataplexy and can be quite helpful when taken before an event that is likely to trigger cataplexy, such as a party or wedding. Norepinephrine and serotonin suppress REM sleep, and by blocking reuptake of these neurotransmitters, antidepressants reduce REM sleep and substantially reduce cataplexy. If withdrawal is necessary, they should be discontinued gradually, since sudden withdrawal can produce severe rebound cataplexy. Hypnagogic hallucinations and sleep paralysis are usually managed by patient education; when these symptoms are severe, however, the same antidepressants may lead to a reduction in symptoms.

Unlike the medications discussed above, which are taken in the morning or several times during the day, sodium oxybate (the sodium salt of γ-hydroxybutyrate) is a highly sedating liquid given at bedtime and 2.5 to 4 hours later. It produces very deep non-REM sleep, probably by activating γ-aminobutyric acid type B receptors.[49] After several weeks of treatment, sodium oxybate usually reduces daytime sleepiness and cataplexy[50] through an unknown mechanism. Because sodium oxybate can produce nausea, dizziness, and other side effects at typical doses, and coma with overdose, it is generally used only in persons with moderate-to-severe sleepiness or cataplexy.

Even with good nighttime sleep, daytime naps, and appropriate medications, many people with narcolepsy still have some lingering daytime sleepiness and inattentiveness. Thus, it is important for people with narcolepsy to have honest discussions with their family members and medical providers about lifestyle choices. For example, the risk of motor vehicle accidents among people with narcolepsy is increased by a factor of three to five; some people may therefore choose to take a stimulant before driving, drive only for short periods, or not drive at all. With regard to work, persons with narcolepsy can thrive in stimulating environments such as teaching, but sedentary jobs that require sustained attention may be a poor fit.

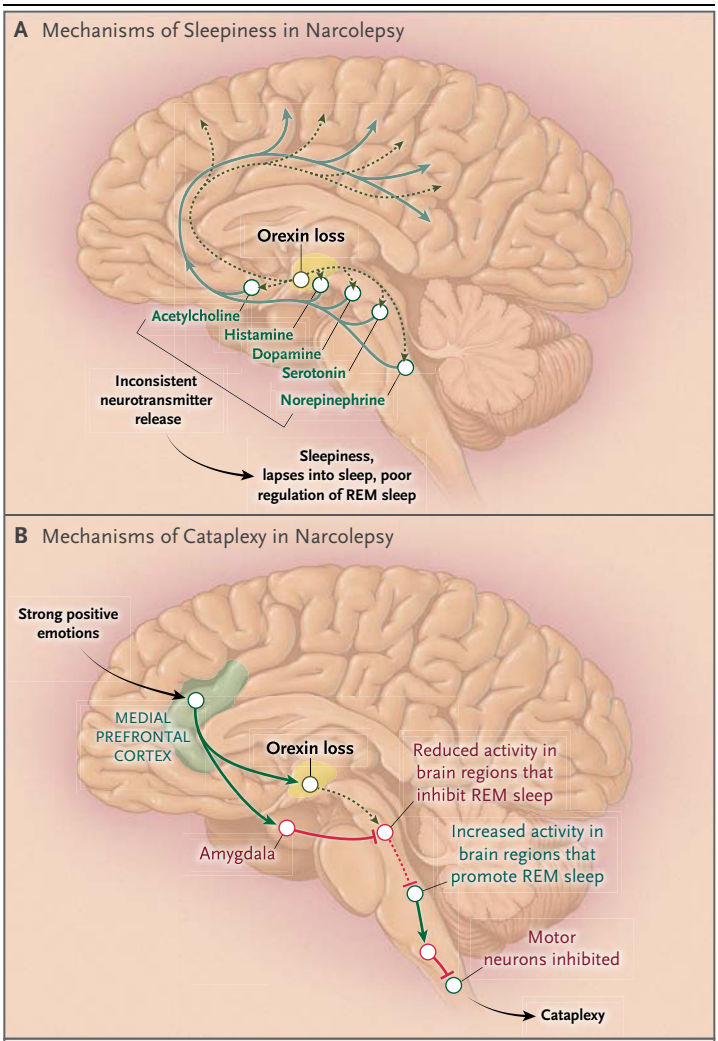


**Figure 2. Neurobiologic Mechanisms of Narcolepsy.**

The neurons that normally produce orexin help sustain wakefulness by stimulating a variety of wakefulness-promoting neurons in the cortex, brain stem, and basal forebrain (Panel A). With loss of the orexin-producing neurons in people with narcolepsy, neurons in these target regions may fire less consistently, leading to sleepiness and lapses into sleep. These neurons also excite brain-stem regions that suppress rapid-eye-movement (REM) sleep (Panel B). Strong positive emotions are thought to activate neurons in the medial prefrontal cortex that excite the orexin-producing neurons and the amygdala. With loss of the orexin neurons in narcolepsy, imbalance in this pathway inhibits brain regions that suppress REM sleep, thus permitting the activation of descending pathways that strongly inhibit motor neurons; the result is partial or complete cataplexy. Pathways shown in green are excitatory; those shown in red are inhibitory. Open circles indicate neuron-cell bodies, and dotted lines indicate reduced activity.

## FUTURE DIRECTIONS

Over the past several years, researchers and clinicians have made great advances in understanding narcolepsy and in developing effective therapies for this disorder, but many questions remain unanswered. Investigators are now working to clarify the pathologic process that destroys the orexin-producing neurons, because this information might provide an opportunity

**Table 2. Drugs Used in the Treatment of Narcolepsy.**

| Drug | Dose in Adults* | Common Side Effects | Serious Risks and Side Effects | Relative Cost† |
|---|---|---|---|---|
| **For excessive daytime sleepiness** | | | | |
| Modafinil | 100–400 mg every morning, or 200 mg twice daily | Headache, anxiety, nausea, insomnia | Severe rash | Moderate |
| Armodafinil | 150–250 mg every morning, or 125 mg (half of a 250-mg tablet) twice daily | Headache, anxiety, nausea, insomnia | Severe rash | Moderate |
| Methylphenidate | 10–30 mg twice daily, or 20 mg sustained-release formulation every morning with an additional 10–20 mg every afternoon | Reduced appetite, nausea, headache, insomnia | Potential for abuse; psychosis, mania, seizures, cardiovascular effects | Low |
| Dextroamphetamine | 5–30 mg twice daily, or 10 mg of a sustained-release formulation every morning with an additional 10–20 mg every afternoon | Reduced appetite, nausea, headache, insomnia | High potential for abuse; psychosis, mania, seizures, cardiovascular effects | Low |
| Amphetamine–dextroamphetamine | 10–30 mg twice daily, or 20 mg of a sustained-release formulation twice daily | Reduced appetite, nausea, headache, insomnia | High potential for abuse; psychosis, mania, seizures, cardiovascular effects | Low |
| Sodium oxybate (sodium salt of γ-hydroxybutyrate) | 2.25–4.5 g at bedtime and an additional 2.25–4.5 g given 2.5 to 4 hr later | Nausea, dizziness, urinary incontinence, sleepwalking, morning sedation, anxiety | Potential for abuse; confusion, psychosis, severe sedation or coma with overdose | High |
| **For cataplexy** | | | | |
| Venlafaxine | 37.5–75 mg twice daily, or 37.5–150 mg of an extended-release formulation every morning | Transient nausea, headache, insomnia; increase in blood pressure when administered in higher doses | None | Low |
| Fluoxetine | 20–80 mg every morning | Nausea, dry mouth, insomnia | None | Low |
| Clomipramine | 10–150 mg at bedtime or each morning | Dry mouth, constipation, sweating, dizziness, somnolence, weight gain, orthostatic hypotension | Cardiotoxicity, hypotension, seizures | Low |
| Sodium oxybate (sodium salt of γ-hydroxybutyrate) | 2.25–4.5 g at bedtime and an additional 2.25–4.5 g given 2.5–4 hr later | Nausea, dizziness, urinary incontinence, sleepwalking, morning sedation, anxiety | Potential for abuse; confusion, psychosis, severe sedation or coma with overdose | High |

* Wakefulness-promoting medications are usually taken in the morning; if necessary, additional doses can be taken at midday or in the early afternoon, 30 to 60 minutes before the morning dose wears off. The second dose should not be given late in the afternoon, because such late doses can cause insomnia. Sodium oxybate should not be combined with alcohol or sedatives. Adapted from Scammell.[45]

† Relative costs range from low to high.

to prevent or cure narcolepsy. Others are studying how the loss of these neurons results in sleepiness, cataplexy, and obesity; understanding the neurobiologic process involved may lead to new therapeutic opportunities. The restoration of orexin signaling in the brain may be an ideal therapy, akin to administering insulin to persons with type 1 diabetes. Currently, such treatment would be difficult, since the orexin neuropeptides cannot easily cross the blood–brain barrier; however, researchers have made some early progress in developing small-molecule orexin agonists. Although narcolepsy affects many facets of patients' daily lives, current treatments can be quite effective, and even better treatments may soon be available.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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