The Neurobiology, Diagnosis, and Treatment of Narcolepsy

Thomas E. Scammell, MD

Narcolepsy is a common cause of chronic sleepiness distinguished by intrusions into wakefulness of physiological aspects of rapid eye movement sleep such as cataplexy and hallucinations. Recent advances provide compelling evidence that narcolepsy may be a neurodegenerative or autoimmune disorder resulting in a loss of hypothalamic neurons containing the neuropeptide orexin (also known as hypocretin). Because orexin promotes wakefulness and inhibits rapid eye movement sleep, its absence may permit inappropriate transitions between wakefulness and sleep. These discoveries have considerably improved our understanding of the neurobiology of sleep and should foster the development of rational treatments for a variety of sleep disorders.

Narcolepsy was first described more than 100 years ago, but until recently, the cause of this common sleep disorder was largely unknown. Rare lesions of the posterior hypothalamus provided some hints, spurring von Economo to predict that, “It is very probable though not yet proved, that the narcolepsy of Gelineau, Westphal, and Redlich has its primary cause in a yet unknown disease of that region.”1 This review touches on the compelling, recent evidence that narcolepsy is a disorder of neurons in the posterior hypothalamus that produce the neuropeptide orexin.

Clinical Manifestations of Narcolepsy

Narcolepsy is characterized by chronic sleepiness and a marked disorganization of sleep/wake behavior. It usually begins with excessive daytime sleepiness and unintentional naps in the teens and early twenties, although symptoms can begin in young childhood or after the age of 40 years.2,3 All narcoleptic subjects have chronic sleepiness, but the intensity varies across the day and between individuals. This sleepiness is most troublesome during periods of inactivity and is often improved temporarily by a brief nap. As a consequence of sleepiness, patients may report inattention, poor memory, blurry vision, diplopia, and automatic behaviors such as driving without awareness.

Researchers have debated whether this sleepiness is caused by increased sleep drive or an impaired arousal system. The latter appears more likely because narcoleptic subjects have normal amounts of sleep over 24 hours,4,5 but disrupted nighttime sleep is common in narcolepsy and may partially contribute to this chronic sleepiness. Narcoleptic patients with the greatest sleep disturbance have more severe daytime sleepiness,6 but even those with good nighttime sleep still have substantial daytime sleepiness. Thus, the quality of nighttime sleep is probably just a minor contributor to the chronic sleepiness of most patients.6,7

Narcoleptic subjects often have abnormal manifestations of rapid eye movement (REM) sleep that intrude into wakefulness, including cataplexy, hypnagogic hallucinations, and sleep paralysis. Hypnagogic hallucinations are dream-like, often frightening hallucinations that typically occur with drowsiness or the onset of sleep. These hallucinations are usually visual, with reports of seeing people or animals, but tactile, auditory, or even vestibular hallucinations such as a sense of sudden falling are not uncommon. Sleep paralysis is profound weakness that occurs at the onset of sleep or on awakening. This is probably an intrusion of REM sleep paralysis into wakefulness, and can be associated with a sensation of fear or suffocation. Hypnagogic hallucinations and sleep paralysis are not specific to narcolepsy and can be seen with other conditions of increased sleep pressure such as chronic sleep deprivation or ob-

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Cataplexy is sudden muscle weakness brought on by strong emotions, particularly joking, laughter, or anger.\textsuperscript{2,0,11} Most likely, this also is an intrusion of REM sleep atonia into wakefulness, but in contrast with sleep paralysis, cataplexy occurs almost exclusively in narcolepsy (see below). Sixty percent of narcoleptic subjects develop cataplexy, usually around the onset of sleepiness or within 3 to 5 years.\textsuperscript{2,3} Severe episodes produce bilateral, generalized weakness sufficient to cause a fall, although usually without injury. Other episodes may be partial, affecting only the face, voice, or a limb. Consciousness is never impaired unless the patient subsequently falls asleep or begins having hypnagogic hallucinations. Episodes of cataplexy may begin with clonic inhibitory movements leading to a fall, followed by a period of atonia and areflexia usually lasting less than 2 minutes\textsuperscript{12} (a video of cataplexy is available at http://www-med.stanford.edu/school/Psychiatry/narcolepsy/). Many normal individuals report slight muscle weakness with intense emotion, and during laughter the H-reflex is markedly reduced in controls and in narcoleptic subjects.\textsuperscript{13,14} Cataplexy may result from excessive activation of these same descending motor inhibitory pathways that are active during strong emotions or REM sleep.\textsuperscript{15}

**Laboratory Findings**

The history alone is often very suggestive of narcolepsy, but a complete evaluation includes an overnight polysomnogram followed by a Multiple Sleep Latency Test (MSLT).\textsuperscript{16} The polysomnogram helps evaluate sleep quality and excludes other causes of sleepiness such as obstructive sleep apnea, periodic limb movements of sleep, or REM behavior disorder that are common in narcolepsy and may warrant specific treatment.\textsuperscript{6,17,18}

This overnight study is followed the next day by a MSLT in which a patient is given four or five opportunities to nap every 2 hours.\textsuperscript{19} Normal subjects fall asleep in approximately 10 to 15 minutes, but narcoleptic subjects often fall asleep in less than 5 minutes, providing objective evidence of their sleep propensity.\textsuperscript{20,21} The naps of narcoleptic subjects often include REM sleep,\textsuperscript{22} and the occurrence of these sleep-onset REM periods (SOREMs) in two or more naps is highly suggestive of narcolepsy. However, SOREMs can be seen with other disorders that increase REM sleep pressure such as sleep deprivation, sleep apnea, or withdrawal from REM sleep–suppressing medications.\textsuperscript{23}

**Differential Diagnosis**

In the absence of other neurological deficits, the combination of chronic sleepiness with cataplexy or more than two SOREMs is almost always caused by narcolepsy. Sleepiness, cataplexy, and SOREMs can occur in uncommon diseases such as Prader–Willi syndrome, Niemann–Pick disease type C, and Norrie disease,\textsuperscript{24–26} but all these individuals have mental retardation and other obvious neurological deficits. In patients without cataplexy, diagnosing narcolepsy can be difficult, and one should consider other causes of sleepiness such as narcolepsy, periodic limb movements of sleep, insufficient sleep, or the effects of sedating medications.\textsuperscript{21} Narcolepsy without cataplexy may overlap with idiopathic hypersomnia, a heterogeneous disorder of chronic sleepiness.\textsuperscript{27} By definition, patients with idiopathic hypersomnia lack cataplexy and have less than two SOREMs on the MSLT. Some of these individuals have deep, excessively long periods of sleep, difficulty waking from sleep, and long unrefreshing naps, but many have symptoms similar to narcolepsy.\textsuperscript{8,27}

**Secondary Narcolepsy**

On infrequent occasions, narcolepsy occurs as a consequence of a focal central nervous system lesion. These lesions almost always involve the posterior hypothalamus, and tumors are the most common cause.\textsuperscript{28–31} Strokes or arteriovenous malformations of the hypothalamus are rare but can cause narcolepsy.\textsuperscript{30,32,33} Hypothalamic sarcoidosis has caused narcolepsy in at least two cases, although neither had cataplexy.\textsuperscript{25,30} Postencephalitic sleepiness resembling narcolepsy was common in the 1920s,\textsuperscript{34–37} but we know of no similar epidemic since then. A recent report described patients with paraneoplastic anti–Ma antibodies who have hypothalamic inflammation, sleepiness, and cataplexy, but polysomnograms were not reported.\textsuperscript{38} Melberg and colleagues have described a Swedish family with autosomal dominant cerebellar ataxia, deafness, and narcolepsy.\textsuperscript{39} Affected members gradually develop chronic sleepiness and cataplexy in young adulthood along with enlargement of the third ventricle suggestive of hypothalamic atrophy.

Strokes or tumors of the brainstem can produce isolated cataplexy but rarely produce the full narcolepsy syndrome.\textsuperscript{29,40–42} Most likely, these lesions affect descending pathways from the hypothalamus that regulate motor tone but not arousal.

The association of narcolepsy with head injury and multiple sclerosis is more controversial. Most people with hypersomnia after closed head injury do not have narcolepsy,\textsuperscript{43} but some patients with narcolepsy report that their symptoms began after a head injury. On several occasions, narcolepsy has occurred with multiple sclerosis,\textsuperscript{30,44–47} but it is usually unclear whether the narcolepsy was caused by a focal plaque. Although these associations are rare, it remains possible...
that central nervous system inflammation or injury could increase the risk of developing narcolepsy.

**Epidemiology and Genetics of Idiopathic Narcolepsy**

Narcolepsy occurs in approximately 1 in 2,000 individuals, and most cases are sporadic.\(^3\,^4^8\) Genetic factors play an important role because first-degree relatives have a 40-fold increased risk of developing narcolepsy.\(^4^9\,^5^0\) Nevertheless, genetics are only a partial influence because even among monozygotic twins in which one has narcolepsy, the second twin is affected only approximately 25% of the time.\(^5^0\)

The most robust of these genetic factors are specific human leukocyte antigens (HLAs). Early studies using low-resolution serological techniques found that narcolepsy is associated with two HLA class II antigens, DR2 and DQ1. This association varies with ethnicity; DR2 is found in 100% of Japanese, 90 to 95% of whites, and 60% of African American narcoleptic subjects with cataplexy.\(^4^9\,^5^1\,^5^2\) High-resolution mapping of these regions demonstrated the existence of numerous alleles, and DQB1*0602, a DQ1 subtype allele, is strongly linked with narcolepsy. DQB1*0602 is found in 88 to 98% of narcoleptic subjects with unambiguous cataplexy, whereas it is found in only 12% of white American and 38% of African American controls.\(^5^3\,^5^4\)

Testing for DQB1*0602 can be helpful, especially in patients with questionable cataplexy, but this allele is hardly predictive of narcolepsy because greater than 99% of DQB1*0602-positive individuals do not have narcolepsy.

DQB1*0602 may influence the severity of narcolepsy. In part, this may be a direct effect on the expression of REM sleep because, even among normal adults, DQB1*0602-positive subjects enter REM sleep more quickly.\(^5^5\) DQB1*0602 also may affect the severity of narcolepsy because DQB1*0602-positive narcoleptic subjects have longer episodes of cataplexy, more nocturnal sleep disruption, and more daytime sleepiness.\(^5^6\) Whether this more severe phenotype is caused by more extensive neuropathology or altered regulation of REM sleep remains unknown.

As in some other HLA-linked diseases, tumor necrosis factor-α (TNF-α) has been implicated in narcolepsy. Polymorphisms in the TNF-α and TNF receptor 2 genes are associated with narcolepsy in Japan,\(^5^6\,^5^7\,^5^8\) with especially high susceptibility when these alleles are present in both genes.\(^5^8\) Plasma TNF-α levels are normal in narcolepsy,\(^5^9\) but these polymorphisms may still affect TNF-α signaling, thus contributing to an inflammatory or degenerative process. Because TNF-α promotes sleep in laboratory animals,\(^5^0\) altered TNF signaling also might directly influence the activity of sleep/wake regulatory pathways in the brain.
the flow of information to and from the cortex. During deep non-REM sleep, these cholinergic neurons are much less active, thus decreasing thalamic and cortical activity. Attention and full cortical activation depend on a separate population of cholinergic neurons in the basal forebrain, but it is unclear whether these cells are required for the production of wakefulness itself.

Wake-promoting aminergic neurons in the rostral brainstem also project through the pontine and midbrain tegmentum. These include noradrenergic neurons of the locus coeruleus (LC) and serotonergic neurons of the dorsal raphe (DR) nuclei. Histaminergic neurons of the tuberomamillary nucleus (TMN) in the ventral posterior hypothalamus also contribute to this pathway. All three of these aminergic nuclei diffuse innervate and activate much of the forebrain, firing most rapidly during wakefulness, slower in non-REM sleep, and then becoming silent in REM sleep.

Dopaminergic signaling also may promote wakefulness because dopamine antagonists can produce sleep, and amphetamines primarily increase wakefulness by increasing the extracellular concentrations of dopamine. The source of this dopaminergic signaling is unclear because the mean firing rates of neurons in the substantia nigra and ventral tegmental area do not vary with behavioral state. However, lesions of dopaminergic cells in the ventral midbrain can reduce wakefulness, and one population of dopaminergic neurons in the ventral periaqueductal gray is active during wakefulness, perhaps serving as a critical site for dopaminergic effects on wakefulness.

These cholinergic and aminergic regions interact to produce REM sleep. A distinct population of cholinergic neurons in the LDT/PPT activates the thalamus during REM sleep, producing cortical desynchrony. These REM-active cells also generate profound atonia through a polysynaptic, descending pathway that uses glycine to hyperpolarize α motor neurons. Noradrenergic and serotonergic afferents from the LC and DR inhibit the REM sleep–producing neurons during wakefulness and non-REM sleep, but during REM sleep, the LC and DR become inactive, thus disinhibiting the REM-generating neurons. This aminergic inhibition of REM sleep is commonly encountered in the sleep laboratory; patients taking selective serotonin reuptake inhibitors usually have a marked decrease in REM sleep.

Non-REM sleep is produced by neurons in the preoptic area and brainstem. The dorsal vagal complex, raphe nuclei, and ventral midbrain contain some non-REM–generating cells, but the ventrolateral preoptic area (VLPO) is the best characterized sleep-producing region. VLPO neurons are active during non-REM sleep and are necessary for sleep because lesions of the VLPO produce marked insomnia. These GABA-containing neurons innervate and probably inhibit neurons in the TMN, LC, and DR. In turn, VLPO neurons are inhibited by amines, thus creating a reciprocally inhibitory circuit in which wake- and sleep-promoting regions inhibit one another.

This type of mutually inhibitory circuit should demonstrate bistability, being most stable during full wakefulness or sleep. However, these elements alone could produce a system with low thresholds to transition between behavioral states. This may be the fundamental problem in narcolepsy in which irresistible sleep, intrusions of REM-like phenomena, and nocturnal awakenings result from abnormally low thresholds to transition between wakefulness, REM, and non-REM sleep. The importance of these thresholds is evident during periods of prolonged wakefulness when an individual must remain awake despite a gradually increasing sleep drive. An additional stabilizing influence is needed to help maintain wakefulness and other states.

**Neurobiology of Orexin/Hypocretin**

Just a few years ago, two research groups simultaneously discovered a new neuropeptide that may provide this stabilizing influence (for review, see Willie and colleagues). One group named this peptide orexin for its presumed role in appetite whereas another group named it hypocretin for its possible resemblance to secretin. This peptide exists in two forms, orexin-A and orexin-B, which are derived from the same precursor by proteolytic processing and are colocalized in the same neurons. Orexin-containing neurons are found only in the posterior and lateral hypothalamus, but they project widely throughout the central nervous system, innervating the aminergic and cholinergic regions that promote wakefulness (Fig. 2). These targets contain high levels of the two orexin receptors, ox1 and ox2 (also known as hypocretin-1 and -2 receptors). The ox1 and ox2 receptors are coupled to G proteins, and ligand binding generally has excitatory effects.

Recent animal studies provide considerable evidence that orexin promotes wakefulness and inhibits REM sleep. The orexin neurons are active during wakefulness as indicated by the expression of Foxp3 and extracellular concentrations of orexin are higher during periods of wakefulness. Electrophysiological recordings from the orexin neuron region identified many wake-active neurons, with particularly high firing rates when an animal is physically active. In vitro, orexin excites LC and other aminergic neurons. In vivo, injections of orexin into the lateral ventricles or near specific arousal regions such as the LC increase wakefulness and markedly suppress REM sleep. Currently, it is only partially known which regions are necessary for the wake-promoting effects of orexin, but the histaminergic neurons of the TMN may play an essential role.
In normal mice, infusion of orexin near the TMN increases wakefulness, but orexin does not increase wakefulness in mice lacking the histamine H1 receptor.\textsuperscript{104} In addition, narcoleptic dogs have low cortical concentrations of histamine,\textsuperscript{105} and a histamine antagonist partially blocks the wake-promoting effects of orexin.\textsuperscript{100} Suppression of REM sleep by orexin also may occur through activation of these aminergic areas that then inhibit the REM-producing neurons of the LDT/PPT.

**Impaired Orexin Signaling Causes Narcolepsy**

Four years ago, two laboratories simultaneously discovered that the orexin system plays a critical role in narcolepsy. After an extensive linkage analysis of dogs with autosomal recessive narcolepsy, Lin and colleagues found exon-skipping mutations in the ox2 receptor gene that probably result in a nonfunctional receptor.\textsuperscript{106} Meanwhile, Yanagisawa’s group found that orexin knockout mice or mice lacking the orexin receptors have a phenotype strongly resembling human narcolepsy, with brief periods of wakefulness, frequent transitions into REM sleep, and behavior resembling cataplexy.\textsuperscript{93,107,108} Mice lacking the ox2 receptor have a more severe phenotype than those lacking the ox1 receptor, providing additional evidence that the ox2 receptor may play a more prominent role in the control of sleep/wake behavior.

These studies demonstrated that congenitally impaired orexin signaling can produce symptoms of narcolepsy, but human narcolepsy is usually an acquired disease. To create a mouse model similar to human narcolepsy, Hara and colleagues produced mice in which the orexin promoter drives the expression of ataxin-3, a truncated Machado–Joseph disease gene product that induces apoptosis in neurons.\textsuperscript{109} These orexin/ataxin-3 mice have a normal number of orexin neurons at birth, but as they approach adulthood, the orexin neurons degenerate. This acquired loss of orexin neurons roughly parallels the typical timing of human narcolepsy, and, just as in humans, these mice cannot remain awake for long periods, rapidly enter REM sleep, and have behavioral arrest resembling cataplexy.

Mignot, Nishino, and colleagues rapidly confirmed that most narcoleptic subjects with cataplexy have impaired orexin signaling.\textsuperscript{110} Approximately 90% of narcoleptic subjects with cataplexy have no detectable orexin-A in their cerebrospinal fluid (CSF) even within a few months of symptom onset.\textsuperscript{110–115} In contrast, nearly all narcoleptic subjects without cataplexy have normal CSF concentrations of orexin.\textsuperscript{113,115} Undetectably low levels of orexin are not seen in other neurological diseases, except for some uncommon cases of severe Guillain–Barré syndrome or myxedema coma.\textsuperscript{111,115} Orexin levels may be low though not absent in some cases of secondary narcolepsy probably because of partial lesions of the orexin neurons and their projections to arousal regions.\textsuperscript{31,32,115,116} In some cases of familial narcolepsy, orexin levels are normal in younger patients but low in older patients, suggesting a gradual failure to produce orexin.\textsuperscript{115}

**Neuropathology of Narcolepsy**

Two landmark studies have shown that this marked decrease in CSF orexin most likely results from a loss of the orexin-producing neurons. Using in situ hybridization, Peyron and colleagues found no detectable

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**Fig 2.** (A) Orexin-containing neurons of the posterior and lateral hypothalamus heavily innervate and excite aminergic regions that promote wakefulness such as the tuberomammillary nucleus (TMN), raphe, and locus coeruleus (LC). These aminergic regions also inhibit rapid eye movement (REM)–producing neurons of the LDT/PPT. Decreases in orexin and amine signaling allow the occurrence of REM sleep, with thalamic activation and dreaming, and paralysis through intense inhibition of α motor neurons. (B) Innervation of the human locus coeruleus by orexin-containing fibers. Numerous black, orexin-immunoreactive boutons innervate a proximal dendrite of a brown, tyrosine hydroxylase–immunoreactive locus coeruleus neuron. Scale bar = 50 μm.
prepro-orexin mRNA in the hypothalamus of narcoleptic subjects with cataplexy. Thannickal and colleagues found a 90% reduction in the number of orexin immunoreactive neurons. This elimination of orexin-producing neurons is highly selective because both studies showed no reduction in the number of adjacent neurons containing melanin-concentrating hormone. These two studies included a total of five brains from narcoleptic subjects with cataplexy and one without, and the case without cataplexy had the greatest number of remaining orexin neurons. Further studies may determine whether narcoleptic subjects with cataplexy simply have a greater loss of orexin neurons than those without cataplexy.

The process that causes this loss of orexin is unknown. In general, narcoleptic subjects lack mutations in the genes coding for orexin or its receptors, although one individual with severe symptoms in infancy was found to have a mutation in the prepro-orexin gene that probably produces inappropriate trafficking of the peptide and possible degeneration of the orexin neurons. Alternatively, impaired transcription of the prepro-orexin gene or anti-orexin antibodies could produce a loss of orexin without a loss of the orexin neurons.

Many researchers have proposed that a selective loss of the orexin neurons could be caused by an autoimmune or neurodegenerative process, but, thus far, there is little evidence to support these ideas. Despite the association of narcolepsy with specific HLA and TNF alleles, no changes in immune function have been identified. Neuroimaging studies of idiopathic narcolepsy generally have found no abnormalities. The CSF of narcoleptic subjects lacks increased protein, although one individual with severe symptoms in infancy was found to have a mutation in the prepro-orexin gene that probably produces inappropriate trafficking of the peptide and possible degeneration of the orexin neurons. Alternatively, impaired transcription of the prepro-orexin gene or anti-orexin antibodies could produce a loss of orexin without a loss of the orexin neurons.

The orexin neurons may have a central role in this timing of sleep and wakefulness. The suprachiasmatic nucleus is the main generator of circadian rhythms. This nucleus sends timing information to many areas, but lesions dorsal and posterior to the suprachiasmatic nucleus can disrupt the timing of sleep/wake behavior without affecting other rhythms. This timing information then may be relayed to the orexin neuron region. Lesions of this area also upset the timing of sleep, and orexin knockout mice show a similar lack of rhythmicity, especially in the timing of REM sleep. By promoting wakefulness and inhibiting REM sleep during the day, orexin may fundamentally influence the circadian timing of sleep/wake behavior.

The orexin neurons may do more than just regulate sleep and wakefulness. Orexin also increases feeding, sympathetic tone, and motor activity. The importance of these effects becomes apparent in narcoleptic humans and mice. Around the time that their orexin neurons are lost, orexin/ataxin-3 mice become obese despite eating less than normal mice. The orexin neurons with cataplexy are approximately 10 to 15% overweight, even though they may eat less than average. Thus, this mild obesity may be caused by a decrease in metabolic rate. Considered together, these findings suggest that the orexin neurons may help ensure that one is alert, hungry, and metabolically active at the correct time of day.

**Timing and Coordination of Sleep/Wake Behavior with Other Hypothalamic Functions**

Unstable sleep/wake behavior is the hallmark of narcolepsy, but narcoleptic subjects also have poor circadian timing of sleep and wakefulness. In normal individuals, wakefulness is strongly promoted through much of the day, and REM sleep occurs mainly between 2 and 8 AM. Narcoleptic subjects have difficulty maintaining wakefulness, and their naps often include bouts of REM sleep, regardless of the time of day. Most likely, this is not caused by a simple disinhibition of sleep because narcoleptic subjects have normal amounts of sleep over 24 hours. In addition, this marked attenuation of the normal sleep/wake rhythm is not caused by an underlying defect in the generation of circadian rhythms because the rhythms of body temperature, cortisol, and melatonin are essentially normal.

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**Current Approaches to Treating Narcolepsy**

Narcolepsy is a chronic disorder, requiring long-term treatment. Symptoms sometimes worsen during the first few years, but then generally remain stable, although cataplexy may partially improve with age. For most patients with narcolepsy, chronic sleepiness is the most disabling symptom. Two 15-minute daytime naps can temporarily reduce sleepiness, especially in patients with more severe sleepiness. However, naps are rarely adequate as the sole therapy, and most patients require treatment with a wake-promoting drug. None of these drugs completely eliminates sleepiness, but these medications usually reduce sleepiness enough for substantial improvements in performance and quality of life.
Pharmacological Treatment of Chronic Sleepiness

Traditionally, daytime sleepiness has been treated with amphetamine-like drugs including methylphenidate, dextroamphetamine, or methamphetamine, with the latter two possibly being the most potent\textsuperscript{150} (Table 1). Although it is moderately effective, pemoline produces hepatic failure on rare occasions and should be used only when other drugs have failed. The wake-promoting activity of these drugs is proportionate to their ability to inhibit the reuptake of amines by the dopamine transporter.\textsuperscript{71,72,151} By blocking this transporter, these drugs increase the release and inhibit the reuptake of dopamine, norepinephrine, and serotonin, resulting in higher synaptic concentrations. This increased aminergic signaling may promote wakefulness through direct effects on the cortex or via activation of subcortical pathways. Side effects include nervousness, headaches, insomnia, loss of appetite, and palpitations, and all have potential for abuse.\textsuperscript{150} After a morning dose, many patients may experience some sleepiness in the afternoon or evening, and a combination of sustained-release methylphenidate or dextroamphetamine in the morning with additional short acting drugs in the afternoon is often effective.

Modafinil is a new, wake-promoting drug that effectively treats sleepiness with a minimum of side effects. Modafinil reduces subjective sleepiness and clearly improves the ability of narcoleptic subjects to stay awake, although their latency to sleep is still shorter than normal.\textsuperscript{152,153} Unlike high doses of amphetamines, modafinil does not reduce cataplexy, and an additional anticitapalexyp\textsuperscript{a} medication may be needed. Modafinil has a remarkably low incidence of side effects. Headache can occur in 13%, and nervousness, nausea, or dry mouth occurs in less than 10%,\textsuperscript{154,155} with fewer side effects if treatment is begun with a low dose.\textsuperscript{153} In contrast with amphetamines, typical doses of modafinil do not produce hypertension, arrhythmias, restlessness, anorexia, or disruption of nighttime sleep.\textsuperscript{153} Tolerance or difficulties during withdrawal are very rare,\textsuperscript{153} and modafinil appears to have little potential for addiction.\textsuperscript{156,157} Some patients find that modafinil is not as effective as amphetamines, but the low incidence of side effects and low potential for abuse have made it a very popular treatment.

The mechanism through which modafinil promotes wakefulness is only partially understood. Early work suggested that modafinil might act through α-adrenergic receptors, but modafinil does not bind to α receptors, or other receptors or reuptake site for noradrenaline, GABA, benzodiazepines, or adenosine.\textsuperscript{158} Modafinil can reduce the extracellular concentrations of GABA,\textsuperscript{159,160} and this decrease in GABA may disinhibit specific wake-promoting systems such as the tuberomamillary neurons. Compelling, recent evidence suggests that modafinil may increase dopaminergic signaling. All brain regions activated by modafinil receive dopaminergic innervation,\textsuperscript{161} and modafinil binds weakly to the dopamine reuptake transporter.\textsuperscript{158} In mice lacking the dopamine transporter, modafinil fails to increase wakefulness.\textsuperscript{72} Whether this dopaminergic mechanism is the entire explanation awaits further characterization of new derivatives of modafinil that do not bind to the dopamine transporter.\textsuperscript{162}

### Table 1. Drugs Commonly Used in the Treatment of Narcolepsy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects and Comments</th>
</tr>
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<tbody>
<tr>
<td>Excessive daytime sleepiness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>10–30mg bid, or 20mg SR qam with 10–20mg qpm</td>
<td>Irritability, headaches, insomnia</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>5–30mg bid, or 10mg SR qam with 10–20mg qpm</td>
<td>Same, reduced appetite</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>5–20mg bid</td>
<td>Same</td>
</tr>
<tr>
<td>Modafinil</td>
<td>100–400mg qam, or 200mg bid</td>
<td>Few side effects, headache, nervousness</td>
</tr>
<tr>
<td>Cataplexya\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75–150mg bid, or 75–150 mg XR qam</td>
<td>Few side effects, nausea</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20–80mg qam</td>
<td>Same, dry mouth</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>10–150mg qam or qhs</td>
<td>Dry mouth, sweating</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>5–60mg qam or qhs</td>
<td>Same, anxiety, disturbed nighttime sleep</td>
</tr>
<tr>
<td>γ-Hydroxybutyrate</td>
<td>1.5–4.5gm qhs and 2–3 hours later</td>
<td>Morning sedation, nausea, dizziness, urinary incontinence</td>
</tr>
<tr>
<td>Disrupted nighttime sleep\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5–10mg qhs</td>
<td>Few side effects, daytime sleepiness, dizziness</td>
</tr>
<tr>
<td>γ-Hydroxybutyrate</td>
<td>1.5–4.5gm qhs and 2–4 hours later</td>
<td>Sedation, nausea, dizziness, urinary incontinence</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Anti-cataplexy medications are also useful for problematic sleep paralysis or hypnagogic hallucinations.

\textsuperscript{b}Some sleep disruption in narcolepsy may be caused by additional sleep disorders that require specific treatment (for example, obstructive sleep apnea or periodic limb movements of sleep). 
bid = twice a day; qam = every morning; qpm = every evening; qhs = every bedtime.
**Pharmacological Treatment of Cataplexy**

Most patients with narcolepsy do not require treatment of their cataplexy because it is mild or infrequent, but in some patients, cataplexy occurs several times each day, producing embarrassment or even injury. Nearly all anticataplexy medications are potent inhibitors of REM sleep, a phenomenon consistent with the hypothesis that cataplexy is the inappropriate occurrence of REM sleep paralysis. Noradrenaline and serotonin inhibit REM-producing neurons in the dorsal pons, and cataplexy is substantially reduced by drugs that increase aminergic transmission, especially those that increase noradrenergic signaling by blocking the norepinephrine transporter. The norepinephrine-serotonin reuptake inhibitor venlafaxine has become the first choice of many clinicians because it is very effective and well tolerated. By blocking the reuptake of amines, tricyclics are highly effective, but their use often is limited by their anticholinergic side effects. Abrupt withdrawal from these drugs can markedly worsen cataplexy, producing status cataplecticus. 

\( \gamma \)-Hydroxybutyrate (GHB, sodium oxybate) can improve cataplexy and daytime sleepiness. GHB is a recently approved, sedating drug with a short half-life that is given at bedtime with another dose part way through the night. GHB occurs naturally in the brain as a metabolite of GABA and binds strongly to GHB-specific receptors with weak binding to GABA-B receptors, although how it influences sleep and the symptoms of narcolepsy is unknown. In uncontrolled studies, patients report clear reductions in the frequency and severity of cataplexy, and many feel more alert during the day. Some hypothesize that these improvements may be because of better nighttime sleep because GHB increases sleep continuity, non-REM sleep, and possibly REM sleep. In a small, early study, GHB at bedtime reduced subjective daytime sleepiness and the number of hypnagogic hallucinations and daytime naps. In a recent, larger study, 136 patients took 3 to 9gms GHB, with half of the dose at bedtime and the remainder 2.5 to 4 hours later. After 1 month of treatment the highest dose substantially reduced the frequency of cataplexy attacks and produced a moderate reduction in subjective sleepiness but lower doses were less effective. This high dose also produced nausea and dizziness in one third of the subjects, and 14% had urinary incontinence. Food and Drug Administration approval of GHB was difficult because of concerns about its safety and potential for abuse. GHB and related drugs can produce vomiting, incontinence, coma, respiratory depression, and death, and withdrawal can cause anxiety, insomnia, and delirium. GHB has achieved notoriety as a date-rape drug that is water soluble and tasteless, producing sedation, disinhibition, and amnesia. Although the clinical trials suggest clear benefits of GHB, the potential for harmful side effects and abuse warrants cautious use.

**Future Directions**

These recent advances in narcolepsy research have spurred a new look at the nosology of narcolepsy. As emphasized by Matsuki, Honda, and others, narcolepsy with cataplexy may be a somewhat different disease from narcolepsy without cataplexy or the related syndrome of idiopathic hypersomnia (Table 2).

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**Table 2. Features of Narcolepsy Syndromes**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Narcolepsy with Cataplexy</th>
<th>Narcolepsy without Cataplexy</th>
<th>Idiopathic Hypersomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nighttime sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>24</td>
<td>16</td>
<td>ND</td>
</tr>
<tr>
<td>Awakenings (n)</td>
<td>13.5</td>
<td>8.5</td>
<td>20</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>81</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily nap (%)</td>
<td>85</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Accidents due to sleepiness (%)</td>
<td>48</td>
<td>20</td>
<td>ND</td>
</tr>
<tr>
<td>Hypnagogic hallucinations (%)</td>
<td>70–86</td>
<td>15–60</td>
<td>40</td>
</tr>
<tr>
<td>Sleep paralysis (%)</td>
<td>50–70</td>
<td>25–60</td>
<td>40–50</td>
</tr>
<tr>
<td>MSLT Average sleep latency (min)</td>
<td>2.7</td>
<td>3–5</td>
<td>4.3</td>
</tr>
<tr>
<td>Sleep-onset REM periods (n)</td>
<td>3–3.7</td>
<td>2–3.3</td>
<td>0.2</td>
</tr>
<tr>
<td>DQB1*0602 (%)</td>
<td>90–100</td>
<td>40–60</td>
<td>52</td>
</tr>
<tr>
<td>CSF orexin</td>
<td>Undetectable in 90%</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Neuropathology</td>
<td>Markedly reduced number of orexin neurons</td>
<td>Possibly a partial loss of orexin neurons or injury to critical orexin pathways</td>
<td>Unknown</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Increased 5–15%</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Data are from articles cited in the text. ND = not determined; MSLT = Multiple Sleep Latency Test; REM = rapid eye movement; CSF = cerebrospinal fluid.
In contrast with these latter groups, nearly all narcoleptic subjects with cataplexy have very low CSF orexin concentrations and HLA DQB1*0602.\textsuperscript{112,113,115,176} Narcoleptic subjects with cataplexy also are sleepier, have more SOREMs on the MSLT, and generally have worse nighttime sleep.\textsuperscript{6,177}

Do narcoleptic subjects without cataplexy simply have milder or more focal neuropathology? Narcoleptic subjects without cataplexy may have sufficient orexin production to maintain normal CSF levels and stave off cataplexy, but the loss may still be great enough to produce sleepiness. Alternatively, patients with narcolepsy and normal CSF orexin concentrations may have sleepiness from a loss of orexin projections to essential wake-promoting regions, but other projections could be intact, resulting in normal CSF levels.\textsuperscript{178}

Perhaps narcolepsy is a disease similar to diabetes, with a severe phenotype due to ligand deficiency and a less severe phenotype without cataplexy when the ligand is present but somehow less effective. When treated with orexin, narcoleptic subjects with cataplexy might have a complete improvement in symptoms, but narcoleptic subjects without cataplexy might have a blunted or absent response because of abnormalities in the orexin receptors or their signaling pathways.

With the discovery that orexin deficiency causes narcolepsy with cataplexy researchers are now seeking to identify the cause. Might the orexin neurons be present but failing to produce orexin? Is there a focal hypothalamic encephalitis at the onset of narcolepsy? Do orexin neurons express a particular antigen that makes them susceptible to an autoimmune attack? If narcoleptic subjects can be identified just as symptoms are developing, would immune suppression alter the course of disease? These and other questions will undoubtedly be the focus of research in the years to come.

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