

# Narcolepsy and Idiopathic Hypersomnia

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## Objectives:

- To become familiar with the definition of narcolepsy
- To become familiar with the International Classification of Sleep Disorders-2 classification for hypersomnias of CNS origin
- To become familiar with the epidemiology of narcolepsy
- To discuss the etiology and pathophysiology of narcolepsy
- To discuss the diagnostic workup for the diagnosis of narcolepsy and idiopathic hypersomnia
- To be able to list the diagnostic criteria for narcolepsy
- To understand the rationale of new and emerging therapies in the treatment of narcolepsy and its associated symptoms

**Key words:** automatic behaviors; cataplexy; human leukocyte antigen; hypnagogic hallucinations; hypocretin/orexin; idiopathic hypersomnia; multiple sleep latency test; multiple sleep wakefulness test; narcolepsy; rapid eye movement sleep; sleep attacks; sleep paralysis

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## Epidemiology of Narcolepsy

The prevalence rate of narcolepsy is approximately 1 in 4,000 in North America and Europe. Male to female prevalence is equal. The prevalence is much higher in countries such as Japan (1/600) and much lower in countries such as Israel (1/500,000). The US prevalence is estimated from 0.03 to 0.07%. Of the 125,000 Americans who have narcolepsy, only 35% (43,000) have had the disease diagnosed and are receiving medical treatment.

## Sleepiness vs Fatigue

Unlike tiredness, fatigue, and weakness, sleepiness is associated with falling asleep or fighting sleep at inappropriate times. Fatigue is usually associated with other comorbid conditions such as cardiopulmonary disease, endocrine disorders, viral illness, neuromuscular disease, and chronic fatigue syndrome, and is usually not accompanied by episodes of inappropriate sleep unless disrupted sleep is part of the clinical picture.<sup>1</sup>

## Definitions of Narcolepsy

Narcolepsy is defined as a pentad of symptoms that include excessive daytime sleepiness (EDS), disturbed nocturnal sleep, cataplexy, hypnagogic hallucinations, and sleep paralysis; the latter three are abnormal manifestations of rapid eye movement (REM) sleep intrusion into wakefulness.<sup>1-3</sup>

## Historical Perspective

The first descriptions of narcolepsy and cataplexy and postencephalitic narcolepsy were made in the 1870s. In the 1950s came treatment with methylphenidate, and descriptions of the “narcolepsy tetrad” and idiopathic hypersomnia. In the 1960s came the first use of tricyclic antidepressants (TCAs) for cataplexy, discovery of sleep-onset REM periods, and the first reports of obstructive sleep apnea. In the 1970s came a consensus definition of narcolepsy, first sleep nosology, and the International Classification of Sleep Disorders (ICSD). In the 1980s, Honda et al<sup>3a</sup> first documented the association of human leukocyte antigen (HLA)-DR2 and narcolepsy. In the 1990s to 2000, Mignot et al<sup>3b-3f</sup> discovered that the canine narcolepsy was due to a mutation of the hypocretin receptor 2 gene, and hypocretin 1 was found to be reduced or absent in the cerebrospinal fluid (CSF) of patients with narcolepsy.

Narcolepsy was the first primary sleep disorder to be identified and characterized, with reports dating from > 100 years ago. The delineation of a tetrad of symptoms consisting of EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis provided a succinct focus for the clinical aspect of the disorders and the discovery that narcolepsy is associated with frequent occurrences of REM at the onset of sleep, which helped to identify narcolepsy as a specific disorder associated with REM sleep regulation disorder.<sup>2,3</sup> REM sleep behavior disorder is a condition seen with increased frequency in adults with narcolepsy. The condition is defined by the abnormal augmentation of limb or chin

electromyogram tone during REM sleep associated with dream enactment.

The onset of narcolepsy with cataplexy is most common during adolescence or young adulthood but can be encountered in early childhood. The onset of cataplexy is usually during the first few years after the onset of cataplexy, but may occasionally develop before or long after the onset of hypersomnolence.<sup>1</sup> The discovery of sleep apnea, the improved characterization of other syndromes of EDS, the use of the multiple sleep latency test (MSLT), and the discovery of association of narcolepsy with specific HLA markers have helped to clarify the clinical feature of narcolepsy.<sup>2</sup>

As the clinical variability of patients with excessive sleepiness was recognized in the early 20th century, terms such as *monosymptomatic narcolepsy* came into use, referring to patients with sleepiness but no cataplexy.<sup>2-8</sup> Initially, diagnosis was based solely on the clinical features, and it is clear now that many cases of sleep apnea were misdiagnosed as narcolepsy.<sup>2</sup>

## Narcolepsy Symptoms

EDS is the most common and initial symptom of narcolepsy. EDS is usually the first symptom to appear and often the most disabling. Many physicians erroneously think that sleep attacks are unique to narcolepsy or that excessive daytime drowsiness without sleep attacks cannot be due to narcolepsy. Sudden sleep episodes or sleep attacks can occur with any cause of sleepiness, including sleep deprivation sleep apnea, idiopathic hypersomnia, and medication-related drowsiness.<sup>2</sup> When present, this is an indication of the severity of sleepiness rather than a marker of qualitative different processes. Other symptoms are believed to be manifestations of REM sleep intrusion. These

include cataplexy, hypnagogic hallucinations, and sleep paralysis.<sup>1</sup> The propensity for early onset REM sleep probably accounts for hypnagogic hallucinations and sleep paralysis, which probably reflects intrusion of dream imagery and REM sleep atonia into the waking state.

The term *cataplexy* (Greek) means “to strike down.” It is characterized by sudden episodes of bilateral skeletal muscle weakness or paralysis triggered by intense emotions such as laughter (most common trigger), anger, grief, fear, embarrassment, excitement, and sexual arousal. Cataplexy occurs in the majority of narcolepsy patients (approximately 70%). Cataplexy is a unique feature of narcolepsy.<sup>1</sup> When present, it is virtually diagnostic of narcolepsy.<sup>2,4-8</sup> Attacks may be localized to specific body areas (eg, face) or involve all skeletal muscle groups in a generalized fashion. Respiration is never compromised, but subjective sensations of choking or dyspnea are sometimes reported by affected patients. The cataplexy spell is episodic, without altered consciousness, lasting seconds to minutes. Cataplexy may occur several times daily or less than once per month. Patients may stagger and fall or slump into a chair. Twitching around the face or eyelids may accompany the weakness. Minor episodes, which are much more common, may lead to sagging of the face, eyelids, or jaw; dysarthria; momentary head drop; blurred vision; knee buckling; or even just a sensation of weakness. Consciousness is uniformly preserved at the onset but prolonged periods may be associated with auditory, visual, or tactile hallucinations and may lead directly into REM sleep. Although cataplexy usually develops within a few months or years of the onset of the sleepiness, approximately 10 to 15% of patients do not have cataplexy until 10 to 40 years after the onset of sleepiness. Table 1 lists the differential diagnosis of cataplexy.

**Table 1.** *Differential Diagnosis of Cataplexy*

Variables	Vasovagal Attack	Arrhythmias	Epilepsy (Atonic Seizures)	Transient Ischemic Attack, Vertebrobasilar Insufficiency	Cataplexy
Prodrome	Yes	No	Possible	No	Humor, surprise, excitement
Trigger	Yes	No	Possible	No	
Recovery	Rapid	Rapid	Slow	Possible	Rapid
Focal deficits	No	Possible	Possible	Yes	No

The term *sleep paralysis* refers to an episode that lasts a few seconds or minutes of inability to move during the sleep onset or on awakening.<sup>1</sup> It occurs in 25 to 50% of patients with narcolepsy. Patients describe the sensation of struggling to move, and the paralysis usually ends spontaneously or after mild sensory stimulation but sometimes continues even after vigorous attempts at arousal. The inability to move lasts for a few seconds or minutes during sleep onset or offset.

*Hypnagogic* (drowsiness preceding sleep) and *hypnopompic* (drowsiness preceding wakefulness) hallucinations occur in approximately 20 to 40% of patients with narcolepsy. Hypnagogic hallucinations occur during the transition between sleep onset and wakefulness and may accompany sleep paralysis or occur independently. Visual dream-like hallucinations are the rule, although there may be auditory or tactile hallucinations. Some awareness of surroundings is preserved during these spells.

Disrupted nocturnal sleep occurs in approximately 70 to 80% of patients with narcolepsy. In some, it may be the prominent complaint, but it is not the major cause of daytime sleepiness. In addition to cataplexy, hypnagogic hallucinations, and sleep paralysis, which make up the narcolepsy tetrad, disrupted nocturnal sleep makes the narcolepsy pentad.

Automatic behaviors may be due to chronic sleepiness. These are amnesic episodes associated with semipurposeful activity that may occur in up to 8% of narcoleptics as well as patients with other sleep disorders. These episodes usually happen during monotonous or repetitive activities and last for seconds to  $\geq 30$  min, and may be associated with brief lapses of speech, or irrelevant words or remarks.

The ICSD-2 classifies conditions characterized by primary hypersomnolence into a single category, entitled "hypersomnias of central origin not due to a circadian rhythm disorder, sleep related breathing disorder, or other case of disturbed nocturnal sleep,"<sup>9</sup> as summarized in Table 2.

### I. Narcolepsy With Cataplexy

Narcolepsy with cataplexy is characterized by EDS and cataplexy. Sleepiness here is maximal during monotonous activities and may appear as

irresistible sleep attacks. Patients presenting with narcolepsy with cataplexy are often noted to have nocturnal sleep disruption. At times, sleep disruption can be severe enough to impose further exacerbation of daytime sleepiness.

### II. Narcolepsy Without Cataplexy

Narcolepsy without cataplexy is similar to narcolepsy with cataplexy in most clinical respects, except for the lack of definite cataplexy. Since cataplexy develops later in the course of their disease in some patients in this category, it is recognized that the diagnostic classification may change for some patients if new symptoms become apparent.<sup>9</sup>

### III. Narcolepsy Due to Medical Condition

Narcolepsy with and without cataplexy is found in a number of medical and neurologic conditions. Genetic disorders associated with narcolepsy include type C Niemann-Pick disease<sup>10</sup> and Prader-Willi syndrome.<sup>11</sup> Structural lesions in the hypothalamic region, including tumors, sarcoidosis, and multiple sclerosis, may also cause secondary narcolepsy.<sup>12,13</sup> Symptomatic narcolepsy may also be seen in several neurologic disorders not having demonstrable hypothalamic involvement,

**Table 2.** *The ICSD-2 Classification for Hypersomnias of CNS Origin\**

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1. Narcolepsy with cataplexy
  2. Narcolepsy without cataplexy
  3. Narcolepsy due to medical condition
  4. Narcolepsy, unspecified
  5. Recurrent hypersomnia
    - a. KLS
    - b. Menstrual-related hypersomnia
  6. Idiopathic hypersomnia with long sleep time
  7. Idiopathic hypersomnia without long sleep time
  8. Behaviorally induced insufficient sleep syndrome
  9. Hypersomnia due to medical condition
  10. Hypersomnia due to drug or substance
  11. Hypersomnia not due to substance or known physiologic condition (nonorganic hypersomnia, not otherwise specified)
  12. Physiological (organic) hypersomnia, unspecified (Organic hypersomnia, not otherwise specified)
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\*Adapted from American Academy of Sleep Medicine.<sup>9</sup>

including acute disseminated encephalomyelitis, multiple system atrophy, and head injury.<sup>14–16</sup>

#### **IV. Narcolepsy, Unspecified**

*Narcolepsy, unspecified* is defined by the ICSD-2 as a temporary classification for patients who meet clinical and laboratory criteria for narcolepsy but require additional evaluation for more precise classification.

#### **V. Recurrent Hypersomnia**

Recurrent hypersomnias are rare conditions in which prolonged episodes of excessive sleepiness are separated by periods of normal alertness and function.

**A:** In Kleine-Levin syndrome (KLS), which typically affects adolescent boys, patients may sleep for all but a few hours daily for periods lasting days to weeks.<sup>17</sup> The hypersomnia in KLS is often accompanied by variable disturbances of mood, cognition, and temperament, often including increased appetite and significantly aggressive or hypersexual behavior. Episodes may occur up to 10 times yearly, often with gradual improvement over time.<sup>9</sup> No specific etiology for KLS has been established, but intermittent hypothalamic dysfunction or autoimmune etiologies have been proposed.<sup>18</sup>

**B:** Menstrual-associated hypersomnia is a poorly characterized condition in which episodic sleepiness coincides with the menstrual cycle, and is postulated to be secondary to hormonal influences.

#### **VI. Idiopathic Hypersomnia With Long Sleep Time**

Idiopathic hypersomnia with long sleep time is characterized by pervasive daytime sleepiness despite longer-than-average nighttime sleep.<sup>19,20</sup> Prolonged nighttime sleep of  $\geq 10$  h with few or no awakenings still leave affected patients unrefreshed or confused (*sleep drunkenness*) on morning waking. Daytime naps tend to be longer and less refreshing than those of narcoleptic patients. The condition most often develops during the early adulthood with a chronic but stable course.

#### **VII. Idiopathic Hypersomnia Without Long Sleep Time**

Although earlier classifications allowed diagnosis of idiopathic hypersomnia only in the context of a prolonged nighttime sleep period, patients with comparable daytime sleepiness but normal to only slightly prolonged nighttime sleep have been reported.<sup>19,21</sup> As a result, idiopathic hypersomnia without long sleep time has been established as a separate diagnostic entity in ICSD-2. Although the severe, pervasive daytime somnolence and unrefreshing naps seen in this condition are identical to those seen in idiopathic hypersomnia with long sleep time, the nighttime sleep period is  $< 10$  h.

#### **VIII. Behaviorally Induced Insufficient Sleep Syndrome**

Habitually insufficient total nighttime sleep results in EDS. Review of a sleep diary or sleep history of affected patients usually reveals a chronically shortened nighttime sleep period that is either less than the patient's premorbid baseline. For children and adolescents, the sleep period is substantially reduced than normal for age. Daytime symptoms are those found in sleep deprivation, and include sleepiness, irritability, disturbed mood, and impaired school or work performance. Symptoms remit with lengthening of the nighttime sleep period, but transiently longer sleep periods (for example, on weekends, holidays, or vacations) often do not provide complete relief.

#### **IX. Hypersomnia Due to Medical Condition**

Hypersomnia due to medical condition may be diagnosed when sleepiness is thought to be the direct result of a medical or neurologic condition but the patient does not meet clinical or laboratory criteria for a diagnosis of narcolepsy. The severity of daytime somnolence and length of nighttime sleep vary considerably among patients.

A variety of conditions may underlie this disorder. Associated neurologic disorders may include encephalitis, cerebrovascular accidents, brain tumor, head trauma, and Parkinson disease.<sup>22–24</sup> Common genetic conditions associated with

sleepiness include Prader-Willi syndrome and myotonic dystrophy.<sup>25,26</sup> Associated endocrinopathies such as hypothyroidism and hypoadrenalism and toxic-metabolic disorders such as hepatic encephalopathy and renal failure have been implicated. Drug-induced and psychiatric causes are classified elsewhere.

### **X. Hypersomnia Due to Drug or Substance**

Hypersomnia due to drug or substance is characterized by excessive nighttime sleep, daytime somnolence, or excessive napping related either to use of drugs or alcohol, or related to their discontinuation.<sup>27</sup> Sleepiness is often seen in patients who abuse sedative-hypnotic compounds such as alcohol, benzodiazepines, barbiturates,  $\gamma$ -hydroxybutyric acid, or nonbenzodiazepine sedatives. Somnolence may also complicate the use of medically indicated prescription medications, including antihistamines, antiepileptic drugs, and analgesics. Hypersomnia may also occur following abrupt withdrawal of stimulant use, or occasionally following nonabrupt cessation after prolonged prior use.

### **XI. Hypersomnia Not Due to Substance or Known Physiologic Condition (Nonorganic Hypersomnia, Not Otherwise Specified)**

In hypersomnia not due to substance or known physiologic condition, excessive nighttime sleep, daytime somnolence, or excessive and nonrefreshing napping are associated with an identifiable psychiatric diagnosis, which sometimes becomes apparent only with time and detailed evaluation. Associated psychiatric conditions may include mood disorders, somatoform disorders, conversion disorders, and other psychiatric disturbances.<sup>28,29</sup> Affected individuals often demonstrate intense preoccupation with their symptoms and may miss substantial amounts of school or work. Sleep diaries often reveal prolonged bed time in conjunction with delayed sleep latency and fragmented nighttime sleep with variable daytime napping. The condition most commonly presents during early adulthood. Despite subjective complaints, objective sleepiness may be difficult to document on MSLTs.

### **XII. Physiologic (Organic) Hypersomnia, Unspecified (Organic Hypersomnia, Not Otherwise Specified)**

Chronic sleepiness for at least 3 months time with MSLT evidence of excessive of excessive sleepiness may be classified as *physiologic (organic) hypersomnia, unspecified*, provided that the symptoms are believed to be physiologic and do not meet criteria for other disorders of excessive somnolence.

### **Clinical Course**

Narcolepsy syndrome usually begins in the second or third decade of life, rarely before the age of 5 years or after the age of 60 years. With some patients, the onset is insidious; a decline in school performance from 1 year to the next may be the first indication of the disorder. In other patients, an apparent abrupt onset may be attributed to psychological stress, head trauma, minor infection, fever, drug abuse, or pregnancy.

### **Pathophysiology of Narcolepsy**

Evidence suggests that loss of hypocretin-1-secreting cells in the hypothalamus, possibly on an autoimmune basis, plays a pathogenetic role in the majority of cases.<sup>30,31</sup> Despite the substantial clinical similarities between narcolepsy without cataplexy and narcolepsy with cataplexy, some evidence suggests that the underlying pathophysiology of the two conditions is not identical.

CSF hypocretin-1 levels are most often normal in narcolepsy without cataplexy, whereas they are substantially decreased or undetectable when cataplexy is present.<sup>31</sup> This suggests that the underlying cause or causes for narcolepsy without cataplexy may not involve loss of hypocretin-1-secreting hypothalamic neurons.

The pathophysiology and pathogenesis of narcolepsy are remarkable for the tendency of REM sleep to occur within minutes of falling asleep. This is the “electrophysiologic signature” of narcolepsy. Narcolepsy is believed to represent a possible aberrant monoaminergic regulation of cholinergic REM sleeps mechanisms.

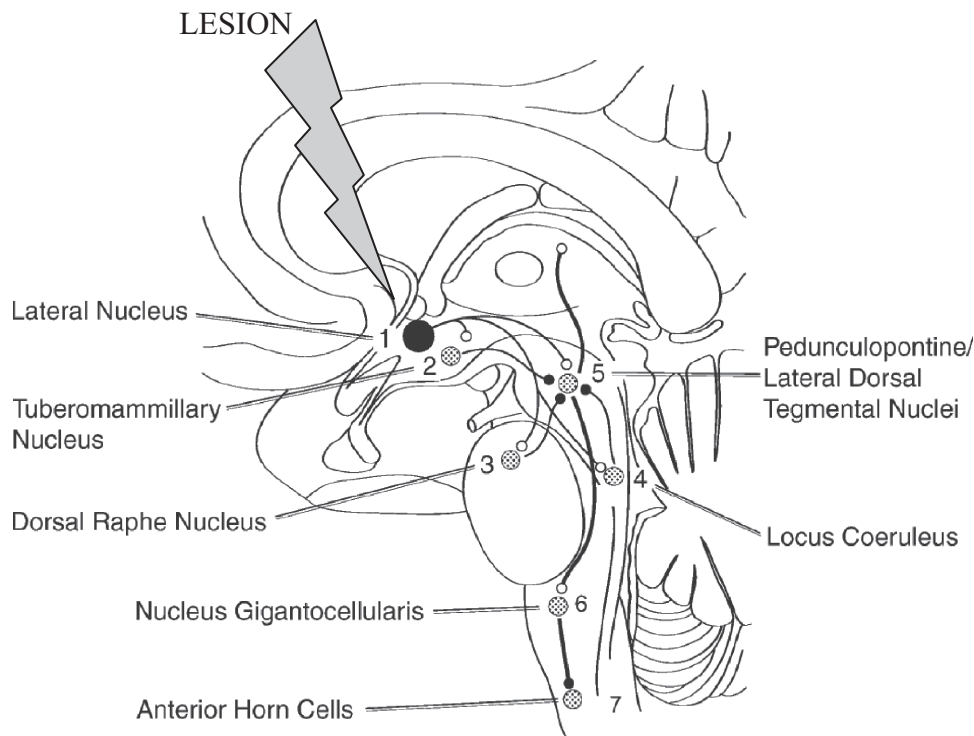
## Animal Studies

Animal models of narcolepsy have contributed considerably to a better understanding of the disease, its etiology, and its pathophysiology. In Doberman pinschers and Labrador retrievers, narcolepsy is transmitted as a single autosomal recessive gene (*carncarc1*) through mutations on the hypocretin-2 receptor. The model implicates hypocretins and the hypocretin-2 receptor in the pathophysiology of narcolepsy and regulation of REM sleep.<sup>30,32–34</sup>

The hypocretins (also called orexins) neuropeptides (hypocretin-1 and -2) are located in a subregion of the dorsolateral hypothalamus. Hypocretin neurons project widely throughout the brain, most notably onto monoaminergic and cholinergic neurons that are also involved in the regulation of sleep<sup>35,36</sup> (Fig 1). These peptides are excitatory in almost all cases. In human narcolepsy brains, most

cells producing hypocretin have been destroyed or cannot be detected (see damage to the lateral nucleus in Fig 1).<sup>37,38</sup>

The role of hypocretin in narcolepsy is supported by the finding that hypocretin levels are abnormally low or undetectable in the CSF of most narcoleptic patients.<sup>24,37,39–43</sup> Values < 110 pg/mL or one third of mean normal control values are highly diagnostic for narcolepsy in the absence of a severe brain pathology.<sup>24,44</sup> Neurochemical abnormalities have been observed in the brains of both animals and humans with narcolepsy. The most consistent abnormalities were observed in the amygdala, where increased dopamine and metabolite levels were found. An increase in M2 receptors in the pontine reticular formation, a region associated with REM sleep was also found. Serotonergic transmission does not seem to be affected by narcolepsy. The pathophysiology of cataplexy includes inappropriate REM sleep motor atonia during periods



**Figure 1.** Pathophysiological representation of the brainstem in the proposed mechanism and structures involved in the generation of REM-related muscle atonia in narcolepsy. The paucity of hypocretin (orexin) cells in the lesioned lateral nucleus of the hypothalamus (1), results in a loss of what otherwise would have been wake-promoting effects on the tuberosomammillary nucleus (2), the dorsal pontine raphe nucleus (3), the locus coeruleus (4), and the pedunclopontine (PPN)/lateral dorsal tegmental nucleus (LDTN). This leaves cholinergic “REM sleep-on” cells in the PPN/LDTN (5) uninhibited, allowing some of them to polysynaptically stimulate the nucleus gigantocellularis (6) [one of the medial groups of reticular nuclei in the medulla oblongata], which then causes a glycinemediated hyperpolarization of anterior horn cells (7) in the spinal cord, resulting in atonia. ○ = facilitatory; ● = inhibitory. Modified from Dyken ME, Yamada T. Narcolepsy and disorders of excessive somnolence. *Prim Care* 2005; 32:389–413.

of wakefulness and probably reflects an underlying deficit of hypocretin and an imbalance between excitatory and inhibitory motor systems.

## Genetics of Narcolepsy

Although up to one half of all narcoleptics have one or more first-degree relatives with narcoleptic symptoms, early description must be viewed with caution because diagnosis was often based solely on symptoms, and other causes of EDS were not well understood. Over the last 2 decades, class two HLAs governed by the major histocompatibility complex have classified the genetic basis of the disease. Narcolepsy is associated with both HLA-DR2 and HLA-DQ1.<sup>45-47</sup> DQB1\*0602 is a more sensitive marker for narcolepsy and appears to be correlated to both the frequency and severity of cataplexy.<sup>40,47</sup> Although a few patients with narcolepsy/cataplexy do not carry the HLA-DR2 or HLA-DQ1 antigens, the incidence of DR2 and DQ1 are > 90% in Japanese and white patients with narcolepsy and cataplexy. This suggests that narcolepsy may result from an autoimmune insult within the CNS.<sup>46</sup> However, attempts thus far to confirm this hypothesis have been disappointing. Although the HLA antigen may be important in the pathogenesis of narcolepsy, it is neither sufficient nor necessary for disease expression. The DR2 appears to occur almost as frequently in narcolepsy without cataplexy as it does in the narcolepsy-cataplexy syndrome.<sup>46</sup>

Narcolepsy is rarely transmitted from generation to generation; most cases occur sporadically. First-degree relatives of individuals with narcolepsy are usually unaffected but do have an increased rate of EDS. Discordance for narcolepsy has been reported in monozygotic twins, suggesting that, in addition to genetic factors, environmental triggers such as head trauma and infection may play a role in the development of the disease.<sup>46</sup>

## Diagnosis

### Subjective Assessment

*Epworth Sleepiness Scale:* The Epworth sleepiness scale (ESS) is an important instrument for

assessing the degree of daytime sleepiness among patients with sleep complaints (Table 3). This eight-item questionnaire asks patients to rate their propensity to fall asleep during different activities and situations (such as while watching television or sitting and reading) on a scale from 0 (no chance of dozing) to 3 (high chance of dozing). The maximum score on this scale is 24; however, scores > 10 are often considered to be consistent with some degree of daytime sleepiness, while scores > 15 are considered to be consistent with severe daytime sleepiness.<sup>48,49</sup>

*Stanford Sleepiness Scale:* The Stanford sleepiness scale is a 7-point Likert-type scale with descriptors ranging from “very alert” to “very sleepy” (Table 4). The subject is instructed to choose the set of descriptors that best describe his feeling of sleepiness at the given moment.<sup>50</sup>

*Clinical Global Impression of Change:* The clinical global impression of change is designed to assess global severity of illness and change in the clinical condition over time. This can usefully assess change from a specified baseline.

*Sleep Diary:* During the clinical evaluation of narcolepsy (Fig 2), a sleep log of several weeks’ duration may provide important information about the patient’s sleep habits.

**Table 3.** *The ESS\**

Chance of Dozing Situation	Score
Sitting and reading	0 1 2 3
Watching television	0 1 2 3
Sitting inactive in a public place (eg, in a theater or a meeting)	0 1 2 3
As a passenger in a car for an hour without a break	0 1 2 3
Sitting and talking to someone	0 1 2 3
Sitting quietly after a lunch without alcohol	0 1 2 3
In a car, while stopped for a few minutes in traffic	0 1 2 3

\*The ESS is widely used by sleep professionals to measure sleepiness. The questionnaire asks patients about how likely they are to doze off or fall asleep in several situations, in contrast to feeling just tired. The patient is instructed to use the scale to choose the most appropriate number for each situation: 0 = no chance of dozing, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing. Modified from Johns.<sup>48-49</sup>

**Table 4.** *An Introspective Measure of Sleepiness, the Stanford Sleepiness Scale\**

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

\*Patients are asked to rate their alertness taking into account the presence of two daily peak times of alertness (at approximately 9:00 AM and 9:00 PM). A scale rating < 3 indicates the presence of a potentially serious sleep debt and sleep deprivation.

*The Stanford Center for Narcolepsy Sleep Inventory:* The Stanford Center for Narcolepsy sleep inventory (SSI) is a 146-item questionnaire divided into nine sections. Sections I and II report demographic information. Section III includes the ESS. Section IV inquires about sleep habits, insomnia, sleep-related breathing disorders, abnormal motor activity during the night, and napping behavior. Section V consists of 51 items on cataplexy. Finally, Sections VI–VIII consist of questions regarding other REM intrusion phenomenon such as sleep paralysis, hypnagogic hallucinations, and automatic behavior. The SSI has been validated in patients with narcolepsy.<sup>51</sup> The SSI is most helpful in detecting definite cataplexy.<sup>51,52</sup>

*The Fatigue Severity Scale:* The fatigue severity scale (FSS) is a self-rated test that assesses the degree of fatigue intensity on various functional and behavioral aspects of life (Table 5). The FSS provides a subjective measurement of daytime fatigue that is largely independent of daytime sleepiness and depression.<sup>53</sup> Each item is rated from 1 (strongly disagree) to 7 (strongly agree). Scoring involves calculating the mean score for all statements, with the range of possible scores being from 1 to 7, with higher scores reflecting greater

fatigue. The FSS provides an adequate means of assessing fatigue intensity within a general population, has high internal consistency, strong validation data, and clearly distinguishes between patients and control subjects. A score of 3 has been used as the cut-off point for normal, above which implied pathologic fatigue should be suspected.<sup>53</sup> The FSS can be used to differentiate fatigue from clinical depression because both share some of the same symptoms. While there is not always a correlation between subjective and objective measures of sleepiness, gross disparities should compel the physician to consider hypersomnia associated with a psychiatric disorder.

### **Sleep Studies**

*Nocturnal Polysomnography:* Sleep studies are generally required for an accurate diagnosis of narcolepsy because of a variety of conditions that can cause excessive sleepiness. A complaint of sleepiness not explained by another medical condition is a clear indication for polysomnography.<sup>54</sup> Most typically, the nocturnal polysomnogram followed by the MSLT are required.<sup>55</sup> Polysomnography is performed with the patient medication free and on a regular schedule and after obtaining sufficient sleep for 10 to 21 days prior. It can determine the presence and severity of sleep apnea, periodic limb movements of sleep, and nocturnal sleep disturbances. Polysomnographic features of narcolepsy include sleep disruption, repetitive awakenings, and decreased REM sleep latency. The occurrence of a REM sleep onset (typically within < 20 min of sleep onset) during the polysomnography occurs in approximately 50% of patients with narcolepsy and cataplexy, and is very rare in control subjects.<sup>56</sup> A sleep-onset REM period (SOREMP) at night is highly predictive of narcolepsy.

*The MSLT:* The MSLT is performed during the main period of wakefulness and is designed to determine a patient's propensity to fall asleep.<sup>55,57,58</sup> To be a valid test, the MSLT is usually performed the day following nocturnal polysomnography.<sup>9</sup> Current criteria for narcolepsy include a mean sleep latency (MSL)  $\leq 8$  min and  $\geq 2$  SOREMPs.<sup>9</sup> Large studies<sup>59–61</sup> have shown, however, that from 4 to 9% of the general population may have multiple SOREMPs on routine clinical MSLTs, and 2 to 4% of these patients report daytime sleepiness

**SLEEP LOG**

NAME: \_\_\_\_\_

DATE LOG STARTED: \_\_\_\_\_

**INSTRUCTIONS:**

1. Leave the times you are awake **BLANK**
2. **SHADE** the times when you sleep
3. **ARROW UPWARD** when you awaken (include naps)
4. **ARROW DOWN** anytime you lay down to sleep
5. Enter "M" for meals, "S" for snacks, "D" for alcoholic drinks

EXAMPLE	A.M.						P.M.						A.M.										
DATE	6	7	8	9	10	11	1	2	3	4	5	6	7	8	9	10	11	1	2	3	4	5	6
		M				M			S			M				↓							↑

**WEEK ONE**

DATE	A.M.						P.M.						A.M.										
	6	7	8	9	10	11	1	2	3	4	5	6	7	8	9	10	11	1	2	3	4	5	6

**WEEK TWO**

DATE	A.M.						P.M.						A.M.										
	6	7	8	9	10	11	1	2	3	4	5	6	7	8	9	10	11	1	2	3	4	5	6

COMMENTS: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Figure 2.** The sleep log.

**Table 5.** *The FSS Questionnaire*

FSS Questionnaire	Disagree→ Agree						
During the past week, I have found that:	Score						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

that meets MSLT criteria for narcolepsy. SOREMPs can also occur with depression, sleep/wake schedule disorders, drug and alcohol withdrawal, and REM sleep deprivation from sleep apnea.<sup>62,63</sup> However, the absence of sleep-onset REM periods on an MSLT does not exclude narcolepsy, and their presence does not by itself confirm the diagnosis. SOREMPs must be interpreted cautiously particularly when sleep apnea is present.

Up to a third of the general population may have an MSL  $\leq$  8 min.<sup>55</sup> The finding of a short MSL alone, without any SOREMP, should be interpreted cautiously together with the clinical picture.<sup>61</sup> A very short MSL is likely to reflect a real CNS pathology. The MSL is highly sensitive to sleep deprivation.<sup>61,64</sup> The 2-week sleep log prior to testing is therefore very helpful, and information about sleep quantity from the previous night's polysomnography is critical in the eventual interpretation of the study. The MSLT can also be of some value in detecting sleepiness in patients who might otherwise deny sleepiness.<sup>65</sup>

### **Protocol for MSLT for Narcolepsy**

**I.** The MSLT consists of five nap opportunities performed at 2-h intervals. The initial nap

should begin about 1.5 to 3 h after termination of the nocturnal polysomnogram. The conventional MSLT recording montage includes central EEG and occipital derivations, left and right eye electrooculograms, mental or submental electromyograms, and ECG.

**II.** The MSLT should be performed following polysomnography recorded during the patient's major sleep period. The test should not be performed after a split-night sleep.

**III.** The patient should maintain a sleep diary for 2 weeks prior to sleep testing, which consists of the following questions:

- What time did you go to bed last night?
- What time did you turn off the light intending to sleep last night?
- How long did it take you to fall asleep?
- What time did you plan to wake up?
- What time did you actually wake up?
- Rate how rested/refreshed you feel now? 1 = very rested, to 10 = not at all
- Rate the quality of your sleep last night: 1 = excellent, to 10 = very poor
- How many times did you wake up during the night?
- Estimate the amount of time you spent awake after you fell asleep (in minutes)
- How long did you nap yesterday (in minutes)?

**IV.** Current medication list should be obtained, including over-the-counter and illicit drugs, stimulants, stimulant-like substances, and REM-suppressing medications. Medications that may suppress REM include antiepileptic drugs such as phenytoin; carbamazepine; fluoxetine; antidepressants; lithium; venlafaxine; chlorpromazine; haloperidol; progesterone;  $\beta$ -blockers; clonidine; diphenhydramine; lorazepam; promethazine; barbiturates; and benzodiazepines.

**V.** Patients should not be on any CNS-acting agents for at least 15 days prior to polysomnography and the MSLT. Urine toxicology screening may be needed to verify the absence of medications and illicit drugs on the night of the sleep study or the morning before the MSLT.

**VI.** The use of usual medications, such as antihypertensives, is generally planned by the

physician prior to the MSLT so that the undesired properties of the stimulating or sedating medications are minimized.

- VII.** The patient should be asked if they need to use the bathroom or need other adjustments for comfort prior to each nap opportunity on the MSLT.

*Maintenance of Wakefulness Test:* As opposed to the MSLT, which measures propensity for sleepiness, the Maintenance of Wakefulness Test (MWT) measures the ability of patients to stay awake. The MWT is a 40-min protocol consisting of four trials separated by 2-h intervals, and is performed in much the same way as the MSLT. Most normal persons without excessive sleepiness remain awake during these naps. The latency to onset of sleep is recorded. Healthy alert patients will not fall asleep within a mean of 15 min on the four or five nap opportunities.<sup>66,67</sup>

The major advantage of the MWT over the MSLT is its ability to measure sleepiness at higher levels of somnolence. It is usually performed to assess efficacy of pharmacotherapy for hypersomnia.<sup>67-69</sup> Unlike the MSLT, the performance of nocturnal polysomnography prior to the MWT is optional and is usually determined on a case-by-case basis.<sup>55,65,70</sup>

*Performance Vigilance Testing:* Hypersomnia can be assessed using tests that involve repetitive tasks. One example is a driving simulator, which evaluates performance, vigilance, attention, and alertness. The driving simulator is often applied in research protocols.

*Pupillometry:* This research measurement relies on the phenomenon that the level of arousal can affect the diameter of the pupil. This objective measurement is termed *pupillometry*. Pupillary instability and constriction is associated with sleepiness, as opposed to pupillary dilatation, which is seen with wakefulness.

*Actigraphy:* The wrist actigraph is an ambulatory activity-monitoring device produced by measure a person's movement that correlates with wakefulness. The actigraphy is worn on the wrist like a watch and is thus portable, permitting extended evaluation generally over several days to weeks. Clinically, actigraphy is utilized in assessing patterns of sleep and wakefulness and can validate the sleep diary. Actigraphy can

be used in the evaluation of hypersomnia and insomnia.

*Screening Blood Tests:* Drug screening for stimulants, opiates, and benzodiazepines may be considered, especially if the clinician suspects a history of substance abuse.<sup>67</sup>

*Psychiatric Evaluation and Psychological Testing:* Psychiatric evaluation and psychological testing are helpful when mood disorders, psychosis, malingering, or conversion disorder are suspected.

## Management

### Behavioral Therapy

The management of patients with narcolepsy is very rewarding. The first step should be a patient and family education and counseling about the syndrome, the importance of good sleep hygiene, the risks associated with sleepiness while driving and in the work place, and the role of medications. Adequate sleep at night is important because sleep deprivation or insufficient sleep will aggravate symptoms. It is customary to recommend that patients take power naps. One to three 20-min naps daily can lead to improvement in alertness and psychomotor performance without exacerbating nocturnal sleep disruption. Although few studies have been conducted regarding the effects of naps in narcolepsy, many clinicians and patients believe that naps are helpful.

### Pharmacotherapy for EDS

Pharmacotherapy for EDS is summarized in Table 6.

*CNS Stimulants:* CNS stimulants increase wakefulness, vigilance, performance, and decrease the sense of fatigue. Prior to the introduction of modafinil, they were probably the mainstay pharmacologic for treatment of sleepiness. Those used most commonly in the United States include methylphenidate dextroamphetamine and pemoline.

*Methylphenidate:* Methylphenidate can help improve the mean sleep latency on MSLT and computerized driving test performance. Formulations include 5-, 10-, and 20-mg tabs and 20-mg sustained-release (SR) tablets. Methylphenidate may be administered at up to 60 mg/d divided to

**Table 6.** *Pharmacotherapy for Sleepiness and Cataplexy*

Medications	Available Dosage, mg*	Adult Starting Dose, mg	Regimen	Adult Maintenance Dose, mg/d*	Potential Side Effects
Modafinil	100, 200	100–200 qd	qd, bid	100–400	Headache, GI irritability, nausea
Methylphenidate	5, 10, 20	5–10 qd, bid	qd, tid	20–60	Headache, tachycardia, arrhythmia, anorexia, weight loss, dependence and abuse
Methylphenidate extended release	10, 20, 30; SR 10, 20; SR 20, 30, 40; SR 20	10–20 qd	qd, bid	20–60	Headache, tachycardia, arrhythmia, anorexia, weight loss, dependence and abuse
Methylphenidate	18, 27, 36, 54 mg SR	18 qd	qd	18–54	Headache, tachycardia, arrhythmia, anorexia, weight loss, dependence and abuse
Amphetamine/dextroamphetamine	5, 7.5, 10, 12.5, 15, 20, 30	10 qd	qd, bid	10–60	Headache, tachycardia, arrhythmia, anorexia, weight loss, dependence and abuse, hypertension
Amphetamine/dextroamphetamine extended	5, 10, 15, 20, 30 SR	10–20 qd	qd	10–60	Headache, tachycardia, arrhythmia, anorexia, weight loss, dependence and abuse, hypertension
Dextroamphetamine	5, 10, 15 SR	10 qd	qd, bid	10–60	Anorexia, weight loss, headache, tachycardia, arrhythmia, behavioral change; hypertension, seizures
Sodium oxybate	2.25–4.5 g in 4.5–9.0 mL of fluid	2.25 g	Taken at bedtime and again 2- to 3-h later	2.25–4.5 g	Confusion, impaired waking, exacerbation of sleepwalking, hallucinations, psychosis, respiratory depression, abuse

\*Unless otherwise indicated.

bid or tid dosing. Side effects include nervousness, insomnia, akathisia, and headaches. Stimulants are schedule II medications

*Dextroamphetamine:* Formulations include 5-mg tablets, and 5-, 10-, and 15-mg capsules, administered up to 60 mg/d with bid or tid dosing. Side effects include cardiovascular effects, insomnia, and psychosis.

*Pemoline:* Pemoline is an oxazolidine derivative. Over the last few years, pemoline has fallen out of favor due to potential hepatotoxicity and need to follow-up liver function tests periodically. It is a schedule IV drug.

*Methylphenidate:* Methylphenidate is a commonly prescribed antinarcotic drug (schedule II) with a faster mode of action. It may be administered at a dose of 30 to 60 mg/d and has lower

incidence of side effects. Ninety-two percent of patients had a marked moderate improvement in sleep tendency, 91% of patients had decreased psychic tension, and 83% of patients had improvement in cataplexy. Adverse side effects include headaches, dry mouth, stomach discomfort, and sweating.

*Modafinil:* Modafinil was introduced in 1999 as a memory-enhancing psychostimulant. It acts at the level of the anterior hypothalamus, probably through its central  $\alpha_1$ -adrenergic agonistic effect. It was found to reduce daytime somnolence and promote daytime wakefulness with no effect on nighttime sleep. It is generally well-tolerated, but potential side effects are mild to moderate and include headaches and GI irritation. Modafinil is a schedule IV with lower abuse potential relative

to Schedule III or II drugs. For most patients with relatively mild sleepiness, we usually begin with a low dose of modafinil (100 mg and even 50 mg) and slowly titrate up over several weeks. The maintenance dose is usually 200 mg qd in the morning. Doses of 400 mg have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of 200 mg/d. Lower doses may be utilized in the elderly and hepatically impaired patients. Evaluation for individual response may take place as early as 1 week after therapy because steady state is reached in 4 days.

If patients fail to have an adequate control on modafinil, a stronger agent such as methylphenidate may be introduced. Some sleep physicians tend to avoid using pemoline because it is often associated with liver toxicity and elevated liver function test results.

If methylphenidate is insufficient in controlling symptoms, we usually switch to dextroamphetamine and again increase the dose on a titration schedule. Some experts prescribe methylphenamine, which has better CNS penetration than dextroamphetamine but it is generally more expensive. Long-term use of stimulants can lead to irritability, insomnia, habituation, addiction, psychosis, and other drug-related psychiatric and psychological conditions. Most of these side effects are dose related.

### **Pharmacotherapy for Treatment of Abnormal REM Sleep Intrusions**

Treatment for cataplexy and sleep paralysis is in the form of TCAs. Current therapy focuses on symptom management through a variety of REM sleep-suppressing medications that are used off-label. These include TCAs and serotonin-selective reuptake inhibitors. Once these medications are abruptly discontinued, one may precipitate a marked increase in number and severity of attacks, the so-called *rebound cataplexy*.

Anticataplectic agents probably inhibit cataplexy through blockade of serotonin and norepinephrine re-uptake. Proposed treatment of cataplexy include: protriptyline, 5 to 30 mg/d; imipramine, 50 to 250 mg/d; clomipramine, 20 to 200 mg/d; and nortriptyline, 50 to 200 mg/d.

TCAs are effective in approximately 80% of patients. At times, fluoxetine is useful in patients who cannot tolerate the anticholinergic side effects of the tricyclics. In patients with severe cataplexy, tolerance to the effects of tricyclics may develop, requiring gradual withdrawal followed by a 2-week drug holiday to restore efficacy.

Sodium oxybate, an endogenous metabolite of  $\gamma$ -aminobutyric acid, received Food and Drug Administration approval for the treatment of cataplexy in 2002. Reduction in cataplexy was seen within 2 weeks. Significant reduction in cataplexy was achieved within 4 weeks, and long-term effectiveness was maintained. This drug has abuse potential with some important CNS adverse events (including death). Even at recommended doses, its use has been associated with confusion, depression, neuropsychiatric events, and respiratory depression. Physicians who elect to prescribe dosage higher than those approved by the Food and Drug Administration have the responsibility to periodically assess whether or not presumed added benefit of higher doses outweigh potential or actual side effects.

### **Clinical Follow-up**

Scheduled long-term follow-up for all patients with hypersomnia is advised to monitor for symptom exacerbation, interval development of comorbid medical, and psychiatric and sleep disorders. The follow-up appointment will also ensure that any new symptoms, such as cataplexy and other REM-intrusion phenomenon in a patient who previously only exhibited sleepiness, are identified and treated. Continuous regular clinical monitoring will also help assess for medication compliance, monitoring for treatment-specific adverse events, and ensure optimal titration of treatment modalities based on the patient's current clinical status.

### **Complications and Consequences of Narcolepsy**

Approximately two thirds of narcoleptics report having fallen asleep while driving and eighty percent have fallen asleep at work. Motor vehicle accidents are common, and narcoleptics have greater work impairment and poorer driving record than epileptics. Many have a high prevalence of depression, which probably reflects a psychosocial problem and the effects of a chronic

illness, but there is little to suggest that narcolepsy is associated with specific psychopathology. Narcolepsy impacts a person's psychological and social functioning, especially since disease onset occurs at a time of increasing responsibility at school or work. Patients often experience social isolation to avoid potentially embarrassing situations

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