

Narcolepsy and Excessive Daytime Sleepiness: Diagnostic Considerations, Epidemiology, and Comorbidities

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Narcolepsy is a chronic, neurologic disorder that has severe disabling effects on affected patients. It usually becomes manifest between the ages of 10 and 25 years and is recognized by a tetrad of symptoms that includes excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. Excessive daytime sleepiness is common and associated with a broad range of medical, sleep, and psychiatric disorders; therefore, accurate diagnosis of narcolepsy and comorbid disorders is important for optimal treatment response. *(J Clin Psychiatry 2007;68[suppl 13]:5-8)*

DESCRIPTION AND EPIDEMIOLOGY

Narcolepsy is a chronic disorder affecting the regulation of the sleep-wake cycle that results in excessive daytime sleepiness (EDS) and several unique associated symptoms.^{1,2} EDS includes both a background feeling of sleepiness that is present much of the time and a strong, sometimes irresistible urge to sleep that recurs throughout the day.¹ Sudden episodes of sleep may occur several times a day, characteristically at inappropriate times such as during a meal, and the urge to sleep is heightened by monotonous circumstances. These sleep attacks usually last from a few seconds to several minutes, but can last an hour or more in rare cases.² Despite having these sleep episodes during the day, narcoleptic patients do not generally spend a greater amount of time asleep than people without narcolepsy.^{2,3}

In addition to EDS, narcolepsy is often accompanied by several other symptoms, together referred to as the narcolepsy tetrad; these additional symptoms include cataplexy, hypnagogic hallucinations, and sleep paralysis (Table 1).^{2,4,5} Cataplexy refers to a partial or generalized, mostly bilateral, loss of skeletal muscle tone and strength that occurs in response to emotion, especially amusement, anger, and elation. Generalized attacks can lead the sufferer to suddenly collapse.^{1,2,6} Awareness is usually pre-

served throughout the attacks, which typically last for less than a minute, but can occur several times a day. Irregular twitching of the limbs or face during attacks of cataplexy can easily be mistaken for epilepsy.¹

Although they do not tend to sleep more than the general population, people with narcolepsy often have abnormal sleep patterns. As part of the sleep cycle dysregulation, narcolepsy patients typically enter rapid eye movement (REM) sleep right after falling asleep instead of later in the sleep-wake cycle, as normal sleepers do. Entering REM sleep earlier leads to the occurrence of REM sleep manifestations, such as hypnagogic hallucinations and sleep paralysis, at the beginning of sleep.⁶⁻⁸ Hypnagogic hallucinations are often frightening or menacing hallucinations; sleep paralysis is a generalized flaccid paralysis that happens slightly before or at the time of falling asleep, or upon awakening.⁴

Other associated symptoms that are common in narcolepsy include disturbed nocturnal sleep, which may even lead to complaints of insomnia at night; many narcoleptic patients experience frequent awakenings during nighttime sleep. Increased rates of other sleep disorders, including apnea, sleep-related movement disorders, and REM sleep behavior disorder, have also been reported in narcolepsy.⁶ Automatic behavior, which refers to inattentive and often error-prone performance of routine tasks at a time of mounting sleepiness, also occurs.^{1,2,6} Secondary symptoms related to sleepiness include visual blurring, diplopia, and difficulties with memory and concentration. Cognitive difficulties (attention/concentration, praxis, delayed recall, orientation, and prospective memory) are increased in narcoleptic patients compared with controls, unrelated to age.⁹ In combination, the symptoms of narcolepsy often have a major impact on relationships, education, employment, driving, mood, and general quality of life.¹

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Table 1. Prevalence of Symptoms in Narcolepsy Patients^a

Symptom	% of Patients With Symptom
Excessive daytime sleepiness	100
Cataplexy	70
Sleep paralysis	30–50
Sleep-related hallucinations	20–40
All 4 symptoms	11–14

^aReprinted with permission from Green and Stillman.⁵

In most cases, the symptoms of narcolepsy appear between the ages of 10 and 25 years, but narcolepsy can manifest at any age (Figure 1).^{2,9} In a survey of 157 narcoleptics, the majority had experienced symptoms of the disorder before 30 years of age; only 21.3% of the sample had the first symptom after 30 years of age.⁹ Daytime sleepiness was the first symptom to appear in 65.5% of the cases, with the percentage of patients experiencing daytime sleepiness as their first symptom higher in the younger population. In narcoleptics who developed the condition at 60 years or older, for example, cataplexy was the most common first symptom.⁹

The exact prevalence of narcolepsy is uncertain, and estimates have differed over the years depending on study design, disease definition, age groups, and geographic regions.^{2,10} In the high range, prevalence estimates have been reported to be between 168 and 799 per 100,000; at the lower end, they range from 25 to 50 per 100,000.¹⁰ Investigators at the Mayo Clinic (Rochester, Minn.) used the records-linkage system of the Rochester Epidemiology Project to estimate the incidence rates and prevalence of narcolepsy in Olmsted County, Minn. Between 1960 and 1989, the average incidence was 0.74 per 100,000 person-years for narcolepsy with cataplexy and 1.37 per 100,000 person-years for narcolepsy with or without cataplexy.¹¹ As in other studies, the most common decade for onset of the disorder was the second decade of life.

Risk factors that have been associated with narcolepsy include a genetic or familial risk and increased body mass index (overweight and obesity).¹⁰ However, the association between narcolepsy and obesity may reflect a consequence rather than a cause of the disease. Additionally, there appears to be a slightly higher risk of narcolepsy in men than in women (relative risk, 1.6:1); increased rates of narcolepsy have also been reported for those born in March.¹⁰ The presence of the HLA DQB1*0602 allele has been associated with narcolepsy, suggesting the possibility of an autoimmune process at work in the development of the disease.^{12,13}

DIFFERENTIAL DIAGNOSIS

Of the symptoms commonly associated with narcolepsy, EDS is most consistently experienced by almost all narcoleptic patients, and falling asleep at inappropriate times is the primary complaint.⁴ However, EDS is associ-

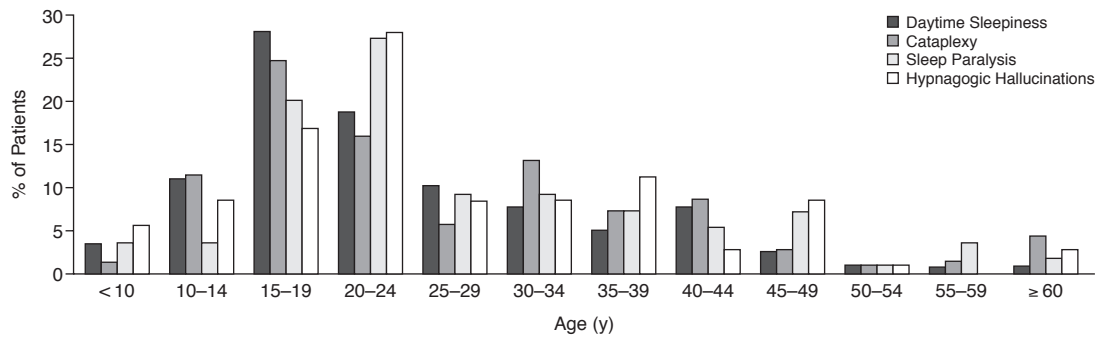
ated with a broad range of disorders (Table 2); it affects about 15% of the general adult population, whereas narcolepsy affects only about 1 in 2000 people.¹⁴ Other common primary sleep disorders include insufficient sleep or sleep deprivation, circadian rhythm disorders, sleep fragmentation caused by obstructive sleep apnea or periodic limb movements during sleep, idiopathic hypersomnia, and recurrent hypersomnias such as the Kleine-Levin syndrome and menstrual-related hypersomnia (Table 2).^{1,15}

EDS is also common in patients with neurologic illnesses, particularly parkinsonism, in which it affects 20% to 50% of patients.¹⁶ The etiology of EDS in Parkinson's patients is not fully understood, but appears to be related to fragmented nocturnal sleep or sleep-related movement disorders. In addition, dopaminergic agents can worsen EDS and have been associated with sleep attacks, although the mechanism by which this occurs is also unknown. Removal or replacement of dopamine agonists may offer some relief for EDS,¹⁶ but may lead to worsening of Parkinson's symptoms. A variety of other neurologic disorders also can present with EDS, including head trauma, encephalitis, and Alzheimer's disease. Medical disorders commonly associated with EDS include fibromyalgia, rheumatoid diseases, congestive heart failure, cancer, and hypothyroidism.¹⁵

EDS is also commonly associated with psychiatric disorders. In a population-based study,¹⁷ 46.5% of those with hypersomnia also met criteria for psychiatric disorders. Another epidemiologic study¹⁸ of young adults has demonstrated a strong association between EDS and the presence of psychiatric illnesses as well.

In addition to the various medical and psychiatric disorders associated with EDS, a number of prescription medications (e.g., sedatives, sedating antidepressants, anti-convulsants) may contribute to increased sleep tendency. Individuals complaining of EDS should also be screened for substance abuse, because a number of agents can cause EDS from either use or withdrawal.

Distinguishing narcolepsy from other conditions associated with EDS usually involves also identifying another symptom associated with narcolepsy that is less common to other diagnoses, such as cataplexy. Cataplexy may occur in up to 70% of all narcoleptic patients, but is less commonly associated with other conditions. Sleep paralysis and hallucinations are somewhat less common among narcoleptic patients (Table 1).^{2,5} Diagnostic criteria for narcolepsy have evolved around this clinical tetrad,¹⁰ although it has been estimated that only 10% to 25% of patients experience all major symptoms during the course of their illness.^{2,5} Formal sleep studies such as the Multiple Sleep Latency Test (MSLT) can be used to document sleepiness and sleep-onset REM periods. Diagnostic criteria have been published by the American Academy of Sleep Medicine to distinguish between narcolepsy with cataplexy, nar-

Figure 1. Age at Which the First Manifestations of Narcolepsy Symptoms Occur^a

^aReprinted with permission from Ohayon et al.⁹ A total of 321 participants were included in the study: 157 were patients with narcolepsy from 2 sleep disorders clinics and 164 were control participants. Narcoleptic patients were evaluated and diagnosed at the sleep disorders clinics. All participants were interviewed by telephone using the Sleep-EVAL system.

Table 2. Disorders Associated With Excessive Daytime Sleepiness

Sleep disorders	Medical disorders
Chronic insufficient sleep syndrome	Cancer and chemotherapy
Circadian rhythm disorders	Cerebrovascular disease
Idiopathic hypersomnia	Chronic fatigue syndrome
Kleine-Levin syndrome	Congestive heart failure
Narcolepsy	Endocrine disorders
Obstructive sleep apnea	Fibromyalgia
Periodic limb movements	Hypothyroidism
Restless legs syndrome	Infections
Shift-work sleep disorder	Pain
Neurologic/degenerative disorders	Rheumatoid diseases
Alzheimer's disease	Psychiatric disorders
Encephalitis	Anxiety disorders
Head trauma	Bipolar disorder
Parkinson's disease	Depression

colepsy without cataplexy, and narcolepsy due to another underlying condition.^{10,19} However, a diagnosis of narcolepsy in the absence of cataplexy should be cautiously evaluated, because formal sleep studies are not always sensitive or specific.¹⁰ For example, in a study²⁰ of a population-based sample of 333 subjects plus 206 individuals who were subjectively sleepy, 3.9% of the combined groups had 2 or more sleep-onset REM periods. These results suggest that individuals suffering with EDS from a variety of causes, such as apnea, shift work, or sleep deprivation, may also show objective abnormalities or sleep testing results that are suggestive of narcolepsy.

A distinction also should be made between EDS and fatigue. Both symptoms are highly prevalent, usually not distinguished from each other by patients or clinicians, and have overlapping presentations. However, fatigue more typically consists of "tiredness" and a "lack of energy"; it commonly occurs with insomnia and a broad range of medical and psychiatric disorders. A patient with fatigue may be experiencing listlessness or lethargy, rather than a tendency to fall asleep.¹⁵ Individuals with fatigue

often have relatively normal results on the MSLT. On the other hand, sleepiness includes reports of falling asleep in low-stimulus situations, and subjects with true EDS will show short sleep latencies on the MSLT.¹⁵ An important characteristic of EDS in narcolepsy is that a short nap (10–15 minutes) has only transitory effects. It often reduces sleepiness, and patients may report feel refreshed after napping⁶; however, patients become sleepy again in a short period of time.

PSYCHIATRIC AND NEUROLOGIC COMORBIDITIES

As stated earlier, narcolepsy is sometimes associated with psychiatric illness; however, the relationship is complicated because it is difficult to separate problems associated with narcolepsy itself from problems associated more generally with EDS.¹⁵ A study²¹ of adults with narcolepsy showed reduced quality of life in the areas of bodily pain, social functioning, and general health in both men and women. A recent study²² examined the psychosocial problems of children aged 5 to 18 years who were diagnosed with narcolepsy and compared this group with children who had EDS and normal controls. Children with narcolepsy and children with EDS were indistinguishable from each other, but both groups differed significantly from controls in having poorer peer relations, more conduct and emotional problems, and a greater number of total behavioral and educational problems. The authors concluded that whereas children with narcolepsy experienced a range of psychosocial problems, the similar profile of children with EDS suggested that sleepiness may have been the main cause of these problems.²²

Distinguishing narcolepsy from some psychiatric illnesses has remained problematic, and misdiagnoses may be more prevalent than commonly believed.²³ The diagnosis of narcolepsy may be confused with major depres-

sive disorder (MDD), schizophrenia, and bipolar disease, and sometimes narcolepsy may be comorbid with these disorders.²⁴ Between 10% and 20% of patients with MDD have EDS, and EDS has been reported in up to 36% of patients with atypical MDD.²⁴ Although there are fewer reports of misdiagnosis between narcolepsy and bipolar disorder, bipolar disorder may also present with psychotic symptoms and hypersomnia during the depressive stage.²³

Because of many overlapping symptoms and similarities between narcolepsy and schizophrenia, misdiagnosis and inappropriate treatment may be more common than with other disorders.²⁵ Schizophrenia and narcolepsy share a number of features, including onset in the teens and 20s and overlapping symptoms. Reports of treatment-nonresponsive schizophrenia have sometimes turned out to be stimulant-responsive narcolepsy, for example.²⁶ REM sleep disturbances that are common in narcolepsy, such as hypnagogic hallucinations, can be similar to the hallucinations associated with schizophrenia.²⁶ However, the patient's illness history, along with the clinical features and a careful psychopathologic assessment, can help to avoid misdiagnoses.²⁶ For instance, narcolepsy and schizophrenia often can be distinguished by the type of the reported hallucinations. In a comparison of narcoleptics, schizophrenics, and healthy subjects, auditory hallucinations were reported by 81% of schizophrenic patients but only 45% of narcoleptics and 9% of controls; visual hallucinations were reported by 83% of narcoleptic patients but only 29% of patients with schizophrenia and 19% of controls; and kinetic hallucinations were experienced by 71% of patients with narcolepsy in contrast to 53% of normal subjects and only 5% with schizophrenia.²⁶ Most of the hallucinations in narcoleptics were sleep related and dependent on body posture, whereas in patients with schizophrenia, they were not. Thus, careful assessment of symptoms may aid in distinguishing narcolepsy from psychotic disorders; these results also demonstrate that even unusual symptoms such as hallucinations may be reported by healthy individuals.

In summary, narcolepsy is recognized by a tetrad of symptoms that includes EDS, cataplexy, sleep paralysis, and hypnagogic hallucinations. The MSLT following all-night polysomnography is standard testing for patients suspected of having narcolepsy. Because EDS is common and associated with a broad range of medical, sleep, and psychiatric disorders, accurate diagnosis of narcolepsy and comorbid disorders is important for optimal treatment response. The next section of this supplement will discuss the pharmacology and underlying neuropathology of narcolepsy.

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