

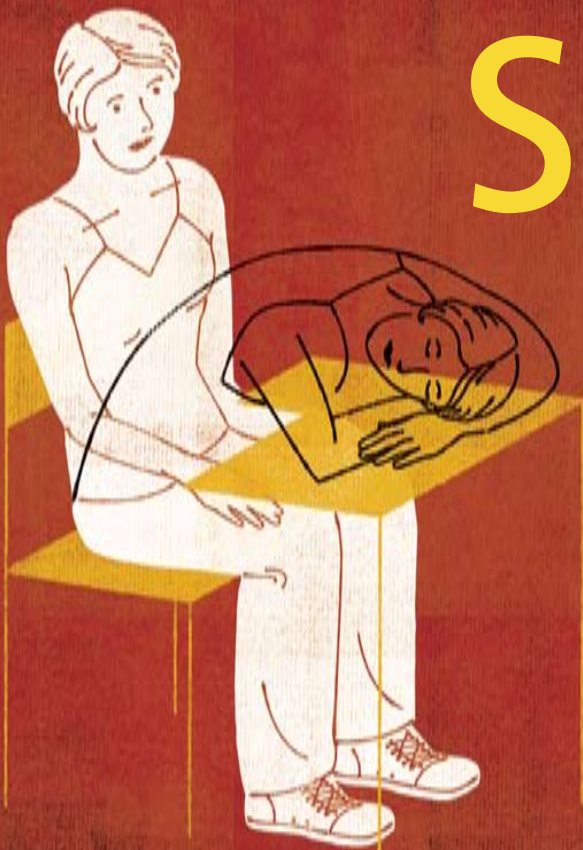
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December 2007



Stay awake!

Understanding,
diagnosing, and successfully
managing narcolepsy

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Understanding, diagnosing, and successfully managing narcolepsy



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Credit hours: 1.5

Certification: CME

Release date: December 2007

Expiration date: December 2008

Target audience: Psychiatrists and primary care clinicians

Overview: Narcolepsy is a chronic, neurologic sleep disorder resulting from the dysregulation of sleep-wake cycles. Although the exact etiology of narcolepsy is still unknown, clinical understanding of the underlying causes as well as the treatment options have increased in the last decade. This supplement will review the epidemiology, diagnosis, pathophysiology, pharmacology, and treatment strategies for narcolepsy, and is intended to provide a current, evidence-based examination of narcolepsy.

LEARNING OBJECTIVES:

After completing the CME activity, participants should:

- Describe the clinical and diagnostic features of narcolepsy
- Evaluate the similarities and differences between narcolepsy and other sleep disorders related to other psychiatric or medical diagnoses
- Explain the neurobiological mechanisms that currently are believed to bring about narcolepsy and cataplexy
- Differentiate the pharmacologic management of cataplexy and excessive daytime sleepiness and explain why narcolepsy is treated symptomatically

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SPONSORSHIP AND SUPPORT:

This activity is sponsored by

This activity is supported by an educational grant from



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Stay awake! Understanding, diagnosing, and successfully managing narcolepsy

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Sleep is a physiologic state that performs an essential restorative function and facilitates learning and memory consolidation.¹ When sleep is disrupted for more than a short time, normal daily functions decline. Mood, attention, and behavior deteriorate. Sleepiness and disrupted sleep can result from a large number of pathological disorders. Currently, 88 sleep disorders are listed in the International Classification of Sleep Disorders, as established by the American Academy of Sleep Medicine, and sleep disorders adversely affect more than an estimated 70 million Americans.² Most of these disorders can be classified as causing insomnia and/or hypersomnia. Insomnia results from disorders that cause difficulty with falling asleep and staying asleep; examples are hyperarousal, circadian dysrhythmia, and homeostatic dysregulation.^{3,4} In contrast, hypersomnia refers to difficulty in staying awake and is characterized by recurrent episodes of excessive daytime sleepiness (EDS) or prolonged nighttime sleep.

Hypersomnia can result from several primary sleep disorders, including narcolepsy, sleep apnea, restless legs syndrome, idiopathic hypersomnia, and periodic limb movement disorder.⁵ The effects of some of these sleep disorders and other chronic illnesses on daytime sleepiness are measured using the Epworth Sleepiness Scale (ESS; **TABLE 1**).^{6,7} Narcolepsy was found to cause some of the highest measures of excessive sleepiness (**FIGURE 1**).

This supplement uses a case-based approach to describe the underlying pathology and symptoms of narcolepsy. Differential diagnosis of narcolepsy and current treatment options will be discussed.

Overview of narcolepsy

Narcolepsy is a chronic, neurologic sleep disorder that results from the dysregulation of sleep-wake cycles.^{8,9} Its 4 classic symptoms are EDS, cataplexy (a sudden drop in muscle tone that is triggered by emotional factors), sleep paralysis (a generalized flaccid paralysis that happens slightly before

TABLE 1

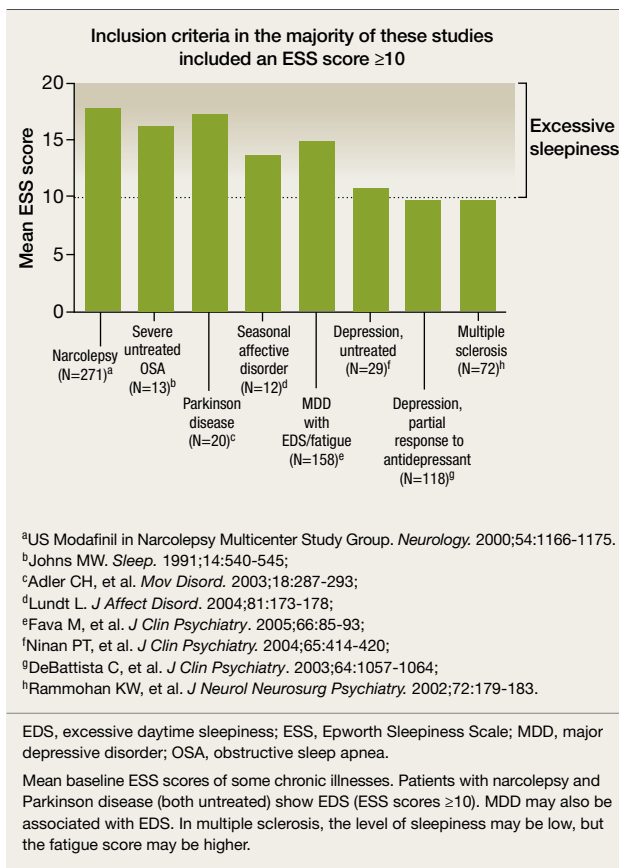
Epworth Sleepiness Scale

Situation	Chance of dozing (0-3)			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place — for example, a theater or meeting	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch (when you've had no alcohol)	0	1	2	3
In a car, while stopped in traffic	0	1	2	3
0 = Would never doze 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing		ESS total score ≥10 indicates excessive daytime sleepiness or sleep disorder		

ESS, Epworth Sleepiness Scale.
 The ESS is used to determine the level of daytime sleepiness.
 A score of 10 or more is considered sleepy; a score of 18 or more is very sleepy.
 With permission from Johns MW. *Sleep*. 1991;14:540-545.

FIGURE 1

Baseline ESS scores in clinical studies



or at the time of falling asleep or on awakening), and hypnagogic hallucinations (hallucinations that occur while falling asleep).^{8,10,11}

EDS is the symptom that is experienced by almost all patients with narcolepsy.¹⁰ Cataplexy is present in about 70% of patients with narcolepsy, whereas sleep paralysis (30% to 50%) and hypnagogic hallucinations (20% to 40%) are experienced less often; all 4 symptoms are present in an estimated 11% to 14% of patients with narcolepsy.¹¹

Although the origins of narcolepsy are still not well known, clinical understanding of the neurologic dysfunction that underlies narcolepsy as well as treatment options have increased markedly in the last decade.

Prevalence and risk factors

According to the National Institute of Neurological Disorders and Stroke, narcolepsy is the third most frequently diagnosed primary sleep disorder found in patients who seek treatment at sleep clinics, after obstructive sleep apnea and restless legs syndrome.⁸ Narcolepsy appears throughout the world in every racial and ethnic group, but prevalence rates vary.^{8,12} Reports in the United States estimate a prevalence of 1 per 2000 population, whereas the prevalence in Japan

is considerably higher (about 1 per 600 population) and in Israel it is much lower (about 1 per 500,000 population).^{8,9,11,12} Its incidence has been estimated to be about 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.¹³ Although narcolepsy is about as common as multiple sclerosis, it is underdiagnosed and undertreated^{8,12}; the delay between the emergence of the initial symptoms and diagnosis is usually more than 10 years.¹⁴

The initiating event for narcolepsy is not well understood, but infection, immune system dysfunction, trauma, hormonal changes, or stress may be present before narcoleptic symptoms become manifest.⁸ Some risk factors for narcolepsy include heredity, obesity, and gender. A genetic or familial risk has been associated with narcolepsy, and up to 10% of patients diagnosed with narcolepsy with cataplexy report a close relative with the same symptoms.¹² However, most

cases occur sporadically, without strong evidence of inheritance.⁸ Being overweight or obese has also been identified as a risk factor for narcolepsy, but this may be a consequence, rather than a cause, of the disease.¹² There appears to be a slightly higher risk of narcolepsy in men than in women.¹²

Quality of life

Patients with narcolepsy have much poorer health and quality of life than people without narcolepsy (FIGURE 2).^{10,15} Narcoleptic episodes can occur at any time, causing severe, detrimental effects on daily functioning and work. Patients may fall asleep involuntarily while at work or school, during social activities, or while driving or operating hazardous machinery. The naps typically last from a few seconds to several minutes but can continue for an hour or more.⁸ Although no cure is available, diagnosis and treatment of narcoleptic symptoms can minimize its deleterious effects.

CASE STUDY

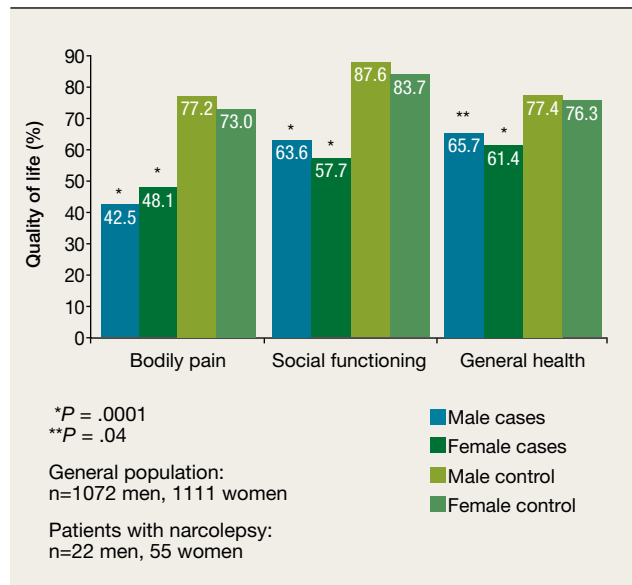
An 18-year-old woman, 5 feet 6 inches tall and weighing 105 pounds, presents with a chief complaint of headaches. She is a nonsmoker and does not drink alcohol. When she is asked about how the headaches affect her day, she says that she is tired all the time. This complaint is further delineated to be sleepiness (drowsiness, need to sleep) and not fatigue (lack of energy or stamina, desire to rest). She is asked about her sleep: she has no trouble falling asleep at bedtime—or anytime for that matter. In fact, she often falls asleep in class, especially when it is boring. The patient goes to bed regularly at 8 PM and always needs an alarm clock to wake her up at 6 AM. She often feels somewhat tired and unrefreshed upon awakening, and this worsens as the day goes on. She drinks caffeinated soft drinks to stay awake. She takes naps whenever she has the opportunity and feels a bit better for a little while afterward. Because of the “tiredness” (sleepiness), the patient has not been able to complete much of her homework and has fallen behind in her classes. She is regarded as a poor student. As an explanation for this, the patient’s mother says that the patient is lazy and does not eat properly; she also expresses concern that her daughter might be depressed. The mother mentions that the patient’s brother has had similar tiredness problems. The patient scores 19 on the ESS, indicating severe sleepiness (TABLE 1).

EDS: A symptom of many disorders

EDS is a very common complaint in primary care and is a symptom of many disorders. Some of the most

FIGURE 2

Negative effect of narcolepsy on quality-of-life domains



SF-36, Medical Outcomes Study Short-Form 36 Health Status Survey.

Negative effect of narcolepsy on quality-of-life domains. Health-related quality of life was assessed by the SF-36 questionnaire for 77 Norwegian patients who had narcolepsy with cataplexy and compared with data from the general population. Men and women with narcolepsy had lower scores in all SF-36 domains except vitality. Most profoundly affected were bodily pain (men, $P = .0001$; women, $P = .0001$), social function (men, $P = .0001$; women, $P = .0001$), and general health (men, $P = .04$; women, $P = .0001$).

With permission from Evik S, et al. *Acta Neurol Scand.* 2006;114:198-204.

common are listed in TABLE 2, and these should be considered when interviewing a patient. Sleep disorders that may cause EDS fall into 3 broad categories: insufficient sleep (in which self-induced sleep deprivation is the most common cause); erratic or nonphysiologic sleep patterns (circadian rhythm disorders); and poor quality sleep, such as sleep fragmentation (mainly obstructive sleep apnea or periodic limb movements during sleep). Less common causes of EDS are idiopathic hypersomnia and recurrent hypersomnias, such as Kleine-Levin syndrome and menstrual-related hypersomnia.^{16,17} EDS also is common in patients with some neurologic illnesses, such as Parkinson disease, affecting up to 50% of patients.¹⁸ Interestingly, the dopaminergic agents used to treat Parkinson disease can further increase EDS in these patients; removal or replacement of dopamine agonists can offer some relief.¹⁸ Patients with a variety of other neurologic disorders, including head trauma, encephalitis, and Alzheimer disease, also can present with EDS. Other

TABLE 2

Differential diagnoses for excessive daytime sleepiness

Disorder	Distinguishing characteristics	Diagnostic tools
Sleep-disordered breathing	Middle age; male sex; obesity; history of loud snoring, hypertension, or cardiac arrhythmias	Interview with bed partner for description of patient's sleep behavior (loud snoring, pauses in breathing); physical examination; polysomnography
Narcolepsy	EDS plus other symptoms of the narcoleptic tetrad	Interview with patient about cataplexy; referral for MSLT to screen for rapid onset of REM sleep
Sleep deprivation or circadian misalignment	Altered sleep-wake cycle owing to job, activity schedule, jet lag, or shift work	Thorough history; referral for polysomnography (should be normal)
Restless legs syndrome (Ekbom syndrome)	Compulsion to move the legs; reports of various leg sensations; possible vasculopathies, neuropathies, iron deficiency anemia, or metabolic abnormalities	Thorough history; physical examination; interview with bed partner for reports of leg movement
Substance use or abuse	History of substance dependency or signs of current drug abuse or dependence	Thorough history and drug screening
Depression	Severe mood disturbance; indecisiveness; somatic preoccupations; changes in appetite, weight, bowel habits, or the capacity to experience pleasure	Thorough history; referral for physical examination; referral to sleep center to rule out narcolepsy (the disorder should respond to antidepressants)
Kleine-Levin syndrome (rare)	Male sex (M/F ratio, 3:1); adolescence; compulsive overeating; hallucinations; sexual hyperactivity	Thorough history
Idiopathic hypersomnia	Prolonged nocturnal sleep times; absence of multiple brief sleep attacks; absence of nocturnal insomnia; few alert periods; relative lack of wakefulness; severe lethargy on awakening in the morning	Thorough history; possible referral to sleep center for MSLT
Infection	Hypersomnia only; signs of infection	Diagnosis of infection (EDS should resolve with treatment of underlying disease)

EDS, excessive daytime sleepiness; MSLT, Multiple Sleep Latency Test; REM, rapid eye movement.
 With permission from Green PM, Stillman MJ. *Arch Fam Med*. 1998;7:472-478.

medical disorders associated with EDS include fibromyalgia, rheumatoid diseases, congestive heart failure, cancer, and hypothyroidism.¹⁶

In most patients, EDS is the first symptom of narcolepsy to become apparent, usually between the ages of 10 and 25 years.^{8,19} However, there may be age-related differences in the appearance of symptoms. One study found that cataplexy appeared first in 47% of patients 60 years or older, but manifested first in only 21% of younger patients ($P < .05$).¹⁹

Understanding the “tired” patient

It is important to distinguish EDS from fatigue. Both symptoms are highly prevalent, have overlapping presentations, and can be easily confused by patients. The examiner may also become confused because

most patients use the term “tiredness” for both, so clinicians must elicit additional information to facilitate a diagnosis. A patient with fatigue may be experiencing listlessness or lethargy—possibly due to insomnia—rather than a tendency to fall asleep.¹⁶ In contrast, sleepiness is the propensity to fall asleep (drowsiness), especially in low-stimulus situations. When EDS is due to narcolepsy, a short nap of 10 to 15 minutes will reduce “tiredness” and leave patients feeling a bit refreshed afterward.⁹ However, this effect does not last long.

The Multiple Sleep Latency Test (MSLT) can help to distinguish fatigue from EDS.¹⁶ As the name implies, the MSLT is a sleep test done in the sleep laboratory at multiple times during the day, usually consisting of 4 to 5 sessions lasting 20 minutes each and recorded

several hours apart. The patient is placed in a dark, quiet room and asked to try to fall asleep. It is considered an abnormal result when a patient falls asleep within 8 minutes.

CASE STUDY (continued)

After scoring the ESS, the clinician asks the patient whether she experiences anything funny or unusual when she becomes emotional. The clinician further clarifies by asking if anything unusual happens when she laughs or becomes excited or when she feels something pleasurable. The patient responds that she feels weak in her arms and legs prior to sex. The clinician asks her to tell a joke that she thinks is funny. When she starts to laugh, the clinician observes a minor loss of muscle tone in the patient's legs. The patient responds positively when asked about sleep paralysis, stating that she has experienced it for years while going to sleep and waking up. She denies hallucinations.

Narcolepsy with cataplexy

The 4 classic symptoms that define narcolepsy—EDS, cataplexy, sleep paralysis, and hypnagogic hallucinations—are sometimes called the “narcoleptic tetrad.”^{8,10,11} Cataplexy occurs in most cases of narcolepsy but is not common in other sleep disorders; its presence in combination with EDS is definitive for narcolepsy.¹²

The sudden drop in muscle tone that characterizes cataplexy is triggered by emotional factors, usually positive emotions such as laughter or a pleasant surprise, or sometimes by anger, but almost never by stress, fear, or physical exertion.¹⁴ All striated muscles except the diaphragm can be affected. Cataplexy may be partial or generalized and is usually bilateral. Cataplectic attacks are sometimes limited to the facial muscles or to the arms or legs, resulting in dysarthria, facial flickering, jaw tremor, head or jaw drooping, dropping of objects, or unlocking of the knees.¹⁴ Though rare, generalized attacks can lead to collapse.^{8,9,17} The patient is usually conscious and aware during cataplectic attacks and might not see them as pathological.¹⁴ Irregular twitching of the limbs or face during attacks of cataplexy can easily be mistaken for epilepsy.¹⁷ Cataplectic attacks can last from a split second to several minutes; their frequency varies from several episodes a day to less than 1 episode a year.¹⁴

Careful, indirect questioning of the patient can be used to either elicit or confirm the presence of cataplexy. The goal is to make the patient laugh and to

observe for signs of cataplexy when they do. Clinicians also should ask specifically about the incomplete or limited forms of cataplexy described above.¹⁴ However, it should be remembered that muscle weakness in response to emotion is not uncommon (eg, “became weak in the knees”), and the observation of such mild responses should be confirmed with other tests before making a diagnosis of cataplexy.

CASE STUDY (continued)

After observing potential signs of cataplexy, the clinician discusses the possible diagnosis of narcolepsy with the patient. Long-term management of narcolepsy is discussed, including, most valuably, information on sleep hygiene and the need to take strategic naps. The patient is referred for polysomnography to rule out other causes of daytime sleepiness. This is followed by an MSLT the next day to assess the time to sleep onset and to verify the presence of sleep onset rapid eye movement periods (SOREMPs).

Based on a history and the physical exam, the patient's headaches are diagnosed as migraines. A triptan is prescribed, to be taken immediately at the onset of migraine symptoms.

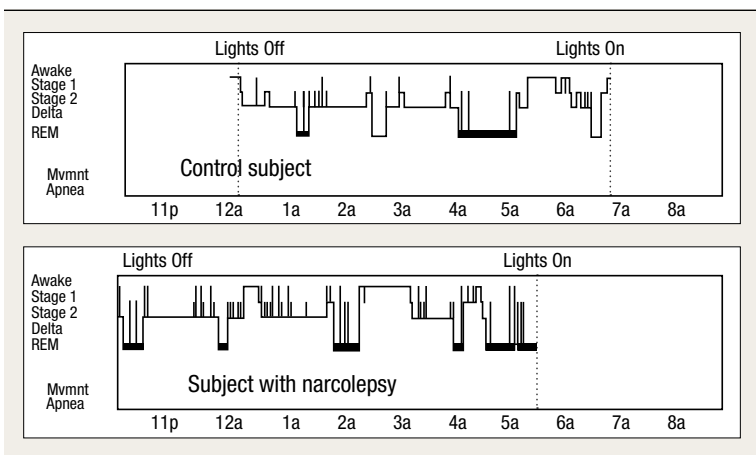
Sleep architecture and narcolepsy

Narcolepsy results from the dysregulation of sleep-wake cycles.^{8,9} During the sleep cycle, restorative sleep is divided into 2 distinct states: rapid eye-movement (REM; representing about 20-25% of sleep time in adults) and non-REM (NREM) sleep.¹ REM and NREM sleep may have separate homeostatic mechanisms.²⁰

NREM sleep is divided into 4 stages (S1, S2, S3, and S4), based on characteristic electroencephalogram signals. The slow frequency (<4 Hz) S3/S4 cortical waves, known as slow-wave or delta sleep, provide an indication of sleep depth.¹ Normal human sleep alternates between NREM stages S1 to S4 and REM sleep approximately every 90 minutes; this cycle is repeated 5 to 6 times a night (FIGURE 3, top trace).¹ During the course of normal sleep, the 90-minute sleep cycle changes from a predominance of NREM, slow-wave sleep during the first sleep cycle to a predominance of REM sleep during the final sleep cycle (FIGURE 3, top trace).¹ REM sleep is the period during which most dreams occur. Muscle tone is greatly suppressed during REM sleep (REM sleep atonia). Cataplexy in narcolepsy shares common neurophysiologic mechanisms with REM sleep atonia.¹⁴

FIGURE 3

Polysomnographic findings



REM, rapid eye movement.

Comparison of a polysomnography from a control subject (top tracing) and a subject with narcolepsy (bottom tracing). In the control trace, the subject cycles through the 4 slow wave sleep stages (stage 1, stage 2, and the Delta stages S3 and S4) before entering REM sleep; REM sleep occurs more than 1 hour after the subject falls asleep. In the bottom trace, the subject with narcolepsy enters the REM stage almost immediately upon falling asleep. The subject with narcolepsy also spends more of the night in the awake state than does the control subject.

Sleep dysregulation in narcolepsy

Patients with narcolepsy enter REM sleep more rapidly than do people without narcolepsy (FIGURE 3, lower trace). Sometimes this transition to REM sleep can occur immediately upon falling asleep (called SOREMPs) without ever entering NREM sleep,¹⁷ leading to the occurrence of hypnagogic hallucinations and sleep paralysis.^{9,10,21,22}

In some cases of narcolepsy, REM sleep and atonia may become dissociated. This can result in REM sleep behavior disorder, in which patients physically enact vivid dreams due to the lack of paralysis.

Dysregulation results in a disturbed nocturnal sleep, and most narcoleptic patients experience frequent awakenings unrelated to REM sleep (FIGURE 3, lower trace).^{8,9,17} Despite falling asleep during the day, patients with narcolepsy do not spend a greater amount of time in sleep than people without narcolepsy.⁸

Use of sleep studies in diagnosis

Formal sleep studies, such as the MSLT, can be used to document sleepiness and SOREMPs and to support a diagnosis of narcolepsy. However, SOREMPs do occur in people without narcolepsy. A recent study found that 4% of a population-based sample experienced 2 or more SOREMPs measured using nighttime polysomnography and daytime MSLT.²³ Of the variables assessed in this study, objective sleepiness, as determined by the

MSLT, was the only measure significantly associated with 2 or more SOREMPs. The authors concluded that subpopulations with excessive sleepiness (eg, shift workers, young adults, patients with apnea) are likely to have a greater prevalence of SOREMPs than the general population.²³ Therefore, results from the MSLT must be considered in the context of the patient's medical history.

Diagnostic criteria have been published by the American Academy of Sleep Medicine to distinguish between narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to another underlying condition.^{12,24} A diagnosis of narcolepsy in the absence of cataplexy should be cautiously evaluated because formal sleep studies are not 100% sensitive or specific.¹²

Narcolepsy and psychiatric disorders

The symptoms of narcolepsy overlap with symptoms of some psychiatric illnesses and can lead to a misdiagnosis of narcolepsy as depression or schizophrenia. EDS has been associated with a number of psychiatric illnesses (TABLE 2), and distinguishing narcolepsy has remained problematic.²⁵ Between 10% and 20% of patients with major depressive disorder (MDD) have EDS; EDS has been reported in up to 36% of patients with atypical MDD.²⁶ Although there are fewer reports of misdiagnosis between narcolepsy and bipolar disease, bipolar disorder may also present with psychotic symptoms and hypersomnia during the depressive stage.²⁵

Hypnagogic hallucinations in narcolepsy are similar to the hallucinations associated with REM sleep intrusions that occur during periods of wakefulness in some schizophrenia patients, possibly resulting in misdiagnosis.²⁷ The patient's illness history, along with the clinical features and a careful psychopathologic assessment, can help to distinguish these disorders.²⁷ The nature of the reported hallucinations also can help to distinguish between narcolepsy and schizophrenia²⁷: most of the hallucinations in patients with narcolepsy are sleep related and dependent on body posture, whereas in patients with schizophrenia, they are not.²⁷

CASE STUDY (continued)

The polysomnogram is unrevealing. During the MSLT, the mean latency-to-sleep onset is less than 1 minute; SOREMPs

occur during the fourth and fifth naps. The patient has difficulty staying awake between the naps. There are no instances of obstructive or central apnea and no hypopnea. The results confirm the presence of severe daytime sleepiness, and the SOREMPs are highly suggestive of narcolepsy with cataplexy. A prescription is given for modafinil, 200 mg per day, to be taken in the morning. The patient is asked to call weekly for updates and the opportunity to endorse or fine tune management. A follow-up visit is scheduled in 1 month.

Neuropathology of narcolepsy

Identification of the neurologic pathways involved in the sleep-wake cycle has advanced in the last decade. Currently, it is hypothesized that the control of sleep involves the interactions of mutually inhibiting sleep and arousal centers in the brain.^{1,20,28} Wakefulness is promoted by brainstem and hypothalamic neurons^{1,20}; neurons that produce acetylcholine, norepinephrine, dopamine, serotonin, histamine, and hypocretin (also called orexin) may be involved.^{17,28} Counteracting these arousal networks are a group of sleep-active cells in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus.^{1,20} These cells are active during sleep and contain the inhibitory neurotransmitters galanin and γ -aminobutyric acid (GABA). They innervate wake-promoting brain regions and produce sleep by coordinating the inhibition of the major ascending monoaminergic arousal systems.^{1,20,28} Narcolepsy represents a major neurologic malfunction of this control system, and central to the pathology of narcolepsy is impairment of hypocretin neurotransmission.^{9,29}

Hypocretin peptides are produced by a cluster of neurons in the posterior half of the lateral hypothalamus.²⁰ The hypocretin neurons are mainly active during wakefulness and especially during motor activity.^{9,14,20} They have ascending projections to the cerebral cortex, as well as descending projections to all of the monoaminergic and cholinergic cell groups of the arousal systems.^{9,14,20} There are also mutual projections between the VLPO neurons and the hypocretin neurons. Thus, the hypocretin neurons appear to reinforce the arousal systems, but probably do not directly inhibit the sleep-active cells in the VLPO.²⁰

Narcolepsy has been associated with a loss of hypocretin activity in the brains of narcoleptic patients.^{9,14,20} Postmortem examination of brain tissue of patients with narcolepsy found undetectable levels of pre-hypocretin RNA, loss of hypocretin peptides, and a selective loss of hypocretin neurons.^{14,30-32} The loss of

hypocretin function was not the result of a generalized neuronal dysfunction in these brain regions, because melanin-concentrating hormone neurons that are normally located within the same region as the hypocretin neurons were intact.¹⁴

Patients with narcolepsy with cataplexy have low concentrations of hypocretin in the cerebrospinal fluid (CSF); CSF hypocretin 1 concentrations lower than 110 ng/L have a high positive predictive value (94%) for narcolepsy with cataplexy.^{14,29} In controls or individuals with other sleep and neurologic disorders, hypocretin 1 concentrations in the CSF were almost always found to be above 200 ng/L.²⁹ In rare instances, low CSF hypocretin concentrations in the absence of narcolepsy were indicative of Guillain-Barré syndrome or head trauma.¹⁴

Together, these results indicated that hypocretin neurons and function are selectively damaged in narcoleptic patients, although perhaps only in patients with associated cataplexy.¹⁴ The cause of this neural loss is not well understood, but it has been hypothesized to result from an autoimmune process.¹⁴ The human leukocyte antigen (HLA) DQB1*0602 is found in 95% of narcoleptic patients with cataplexy and 41% of patients with narcolepsy without cataplexy, but only in 18% to 35% of the general population.^{17,33}

CASE STUDY (continued)

At the follow-up visit, the patient reports that although her drowsiness has improved, it is still troublesome. The prescription for modafinil is increased to 400 mg daily. She is provided with more information about narcolepsy and reinforcing instructions on sleep hygiene. Another follow-up visit is scheduled, and the patient is given information about support groups.

Pharmacologic management of narcolepsy

Although the central hypocretin system plays a prominent role in narcolepsy with cataplexy, there currently are no treatments available to target this system. Management of the disorder relies on symptomatic therapies; the particular symptom that needs the most pharmacologic emphasis varies from patient to patient.¹⁴ Stimulants (mostly dopaminergic) are given to counter patients' excessive sleepiness and sleep attacks. REM suppressants, primarily antidepressants, are used to target cataplexy and other REM-associated

TABLE 3

Currently available narcolepsy treatments and their pharmacologic properties

Compound	Pharmacologic properties
Stimulants	
Amphetamines	Increases monoamine release (DA>NE>>5-HT). Primary effects due to reverse efflux of DA through the DAT. Inhibition of monoamine storage through the VMAT and other effects occur at higher doses. The D-isomer is more specific for DA transmission and is a better stimulant compound. Some effects on cataplexy (especially for the L-isomer) secondary to adrenergic effects occur at higher doses. Available as racemic mixture or pure D-isomer; various time-release formulations available.
Methamphetamines	Profile similar to amphetamine but more lipophilic with increased central penetration.
Methylphenidate	Blocks monoamine (DA>NE>>5-HT) uptake. No effects on reverse efflux or on VMAT. Short half-life. Available as racemic mixture or as pure D-isomer and in various time-release formulations.
Selegiline (L-deprenyl)	MAO-B inhibitor with in vivo conversion into L-amphetamine and L-methamphetamine.
Modafinil	Mode of action debated but probably involves relative selective DA reuptake inhibition. Fewer peripheral side effects. Low-potency compound. Available as a racemic mixture. Little if any addictive potential, but less efficacious than amphetamine or methylphenidate. The R-isomer has a longer half-life and is in development.
Anticatataplectic compounds	
Protriptyline	Tricyclic antidepressant. Monoaminergic uptake blocker (NE>5-HT>DA). Anticholinergic effects. All antidepressants have immediate effects on cataplexy, but abrupt cessation of treatment can induce very severe rebound in cataplexy.
Imipramine	Tricyclic antidepressant. Monoaminergic uptake blocker (NE=5-HT>DA). Anticholinergic effects. Desipramine is an active metabolite.
Desipramine	Tricyclic antidepressant. Monoaminergic uptake blocker (NE>>5-HT>DA). Anticholinergic effects.
Clomipramine	Tricyclic antidepressant. Monoaminergic uptake blocker (5-HT>NE>>DA). Anticholinergic effects. Desmethylclomipramine (NE>>5-HT>DA) is an active metabolite. No specificity in vivo.
Venlafaxine	Dual serotonin and adrenergic reuptake blocker (5-HT>NE). Very effective but some nausea. May have fewer sexual side effects than other antidepressants. Slight stimulant; short half-life; extended-release formulation preferred.
Atomoxetine	Specific adrenergic reuptake blocker (NE) normally indicated for attention-deficit hyperactivity disorder. Slight stimulant; short half-life; reduces appetite.
Fluoxetine	Specific serotonin uptake blocker (5-HT>>NE=DA). Active metabolite norfluoxetine has more adrenergic effects. High therapeutic doses are often needed.
Other	
Sodium oxybate (GHB)	May act via GABA(b) or specific GHB receptors. Reduces DA release. Need 2 doses per night with immediate effects on disturbed nocturnal sleep; therapeutic effects on cataplexy and daytime sleepiness often delayed.

5-HT, serotonin; DA, dopamine; DAT, dopamine transporter; GHB, γ -hydroxybutyric acid; MAO, monoamine oxidase; NE, norepinephrine; VMAT, vesicular monoamine transporter. With permission from Mignot E, Nishino S. *Sleep*. 2005;28:754-763.

symptoms. Hypnotics are used to consolidate sleep.³⁴ At this time, sodium oxybate (γ -hydroxybutyric acid [GHB]) is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of both cataplexy and EDS in patients who have narcolepsy with cataplexy.¹⁴ A list of currently available narcolepsy agents and their pharmacologic properties is presented in **TABLE 3**.³⁴

Although narcolepsy itself is not fatal, uncontrolled EDS and cataplexy can lead to accidents that result in serious injury or death.⁸ Patients with untreated narcoleptic symptoms are involved in automobile accidents about 10 times more frequently than the general population; accident rates are normal among fully managed patients.⁸ Currently available medications do not allow patients with narcolepsy to maintain a consistent,

TABLE 4

FDA-approved narcolepsy medications that treat EDS

Drug	Schedule	FDA-approved indications	FDA-approved dosages
Methylphenidate	C-II	ADHD, narcolepsy	5-60 mg/day
Dextroamphetamine	C-II	Narcolepsy, ADHD with hyperactivity	5-60 mg/day
Modafinil	C-IV	EDS associated with narcolepsy, OSA, and SWSD	200-400 mg/day
Sodium oxybate	C-III	EDS and cataplexy in patients with narcolepsy	4.5-9.0 g Total nightly dose

ADHD, attention-deficit hyperactivity disorder; EDS, excessive daytime sleepiness; FDA, US Food and Drug Administration; OSA, obstructive sleep apnea; SWSD, shift work sleep disorder.

Physicians' Desk Reference. Montvale, NJ: Medical Economics Company; 2005. With permission from Roth (in press).

normal state of alertness, so pharmacologic management should be supplemented with nonpharmacologic approaches.⁸

Nonpharmacologic approaches and behavioral strategies

Patients should be given realistic expectations for therapy and must understand that even with treatment they are not going to be as fully alert as people without narcolepsy. They should avoid over-the-counter and prescription drugs that may cause sleepiness. Proper sleep hygiene is important. Patients should avoid activities that alter sleep schedules, such as shift work. Other simple measures that the patient can take to enhance sleep quality include maintaining a regular sleep schedule, avoiding alcohol and caffeine-containing beverages for several hours before bedtime, avoiding smoking, maintaining a comfortable and adequately warmed bedroom environment, and engaging in relaxing activities before bedtime.⁸

Exercising, except during the 4 to 5 hours prior to bedtime, can improve sleep quality and help patients avoid gaining the excess weight that is associated with narcoleptic patients.⁸ Short naps often can temporarily refresh patients with narcolepsy and should be encouraged.⁹ Four 15-minute naps scheduled across the day may be more beneficial for narcolepsy patients than a longer nap once a day. Patient support groups also can be important in helping patients cope with their symptoms.⁸

Treatment of EDS

Stimulants such as amphetamines and methylphenidate have traditionally been the primary treatment options for EDS¹¹; however, pharmacologic options have in-

creased in recent years. Four drugs have been approved by the FDA for the treatment of EDS in narcolepsy: methylphenidate, dextroamphetamine, modafinil, and sodium oxybate (TABLE 4).

Methylphenidate has been used to treat narcolepsy for more than 50 years.³⁵ It acts by blocking monoamine uptake and is available either as a racemic mixture or as a pure D-isomer.^{34,36} Evidence for the efficacy of methylphenidate in treating EDS is based largely on clinical experience because only 3 case studies totaling fewer than 200 patients have been published (evidence level V-C).^{36,37} The approved dose is 5 to 60 mg methylphenidate per day. However, clinical reports indicate that the dose should be titrated to as much as 200 mg methylphenidate per day to reach maximal efficacy.³⁵ Methylphenidate is a schedule II substance.

Amphetamines are believed to improve sleepiness through presynaptic stimulation of dopaminergic transmission.³⁴ They inhibit the vesicular monoamine transporter, causing the emptying of vesicular dopamine stores into the cytoplasm and a reverse flux of dopamine through its reuptake site.^{34,38,39} This results in a net increase in dopamine release and an associated reduction of presynaptic dopamine stores.³⁴ Dextroamphetamine is the dextrorotary stereoisomer of the amphetamine molecule; its properties are similar to methylphenidate. The dextroamphetamine dosage for narcolepsy is 5 to 60 mg daily. Amphetamines are schedule II substances, and evidence for their use comes from 3 level II-B studies and 2 level V-C studies.³⁶

Modafinil promotes wakefulness in both normal and hypocretin-deficit narcolepsy in humans and animal models (evidence level I-A).³⁶ This suggests that the sites of action of this compound are downstream

or independent of the hypocretin system.⁴⁰ Modafinil has lower abuse potential and is likely to have fewer cardiovascular side effects than the older stimulants.³⁶ The mechanism of action of modafinil is still debated but it may involve dopamine reuptake inhibition.³⁴ It has recently been demonstrated that modafinil activates the hippocampus, which receives afferent innervation from the sleep-wake center of the hypothalamus.^{41,42} In addition to sleepiness, modafinil has been found to improve subjective feelings of vigor and cognitive functioning and also to reduce fatigue.^{42,43} It is available as a racemic mixture, and the dosage range is 200 to 400 mg daily. The FDA has recently approved the R-isomer of modafinil, armodafinil, for treating excessive sleepiness. Modafinil is a schedule IV substance.

The long-term efficacy and safety of modafinil in patients with EDS associated with narcolepsy was examined in 2 open-label, 40-week extension studies; 478 patients were enrolled and data from the 2 studies were combined.⁴³ The majority of patients (approximately 75%) received 400 mg of modafinil daily. Disease severity improved in more than 80% of patients throughout the studies. The mean (\pm SEM) ESS score improved significantly from 16.5 ± 0.2 at open-label baseline to 12.4 ± 0.2 at week 2, and remained at that level through week 40 ($P < .001$). Quality-of-life scores were measured using the Clinical Global Impression of Change and the Medical Outcomes Study Short-Form 38 Health Status Survey (SF-36). Scores in 6 of the 8 SF-36 domains were significantly improved compared with open-label baseline scores ($P < .001$).⁴³ The most common treatment-related adverse events were headache (13%), nervousness (8%), and nausea (5%). Most adverse events were mild to moderate in nature. The authors concluded that modafinil is effective for the long-term treatment of EDS associated with narcolepsy and significantly improves perceptions of general health.⁴³ Other studies have also reported that modafinil is safe and effective for treating EDS associated with narcolepsy.⁴⁴⁻⁴⁶

Sodium oxybate is the most recent drug approved for treating narcolepsy with cataplexy (evidence level I-A).^{34,48} It reduces daytime sleepiness and has an effect on disturbed nighttime sleep.³⁴ Although the exact mechanism of action is unknown, it has been suggested that sodium oxybate may act by stimulation of GABA(b) receptors, and possibly other GHB-specific receptors.^{34,48} It has strong effects on dopamine transmission that may be mediated through GABA(b) receptors on dopamine cells.³⁴ Sodium oxybate acutely reduces nerve cell firing, but does so while uncoupling of dopamine synthesis.^{34,48}

This results in increased dopamine stores.³⁴ Thus, sodium oxybate appears to reduce dopamine release at night, while causing a secondary dopamine increase during the day. Studies of the effects of sodium oxybate for the treatment of narcolepsy have indicated that it improves fragmented nighttime sleep and EDS.^{47,49} Unlike stimulants, it is taken at nighttime, half at bedtime and half 2.5 to 4 hours later, for a total dose of 4.5 to 9 g per night.^{34,36}

The efficacy of sodium oxybate for treatment of EDS associated with narcolepsy was assessed in an 8-week, multicenter, double-blind, placebo-controlled trial.⁵⁰ Two hundred twenty-eight adults with narcolepsy with cataplexy were enrolled in 42 sleep clinics in the United States, Canada, and Europe. Patients were randomly assigned to receive 4.5 g, 6 g, or 9 g of sodium oxybate nightly or placebo for 8 weeks. Doses of 6 g and 9 g were titrated in weekly 1.5-g increments. After 8 weeks, patients displayed dose-related decreases in median ESS scores and in frequency of weekly inadvertent naps, which were significant at the 6-g and 9-g doses (for each, $P < .001$).⁵⁰ Adverse events with greater than 5% incidence included nausea, dizziness, and enuresis, which appeared to be dose related. The authors concluded that sodium oxybate was efficacious in managing daytime sleepiness associated with narcolepsy.⁵⁰ Sodium oxybate was also found to reduce EDS significantly compared with baseline in long-term studies up to 1 year (FIGURE 4).⁵¹ Distribution of sodium oxybate is tightly controlled; prescription information is available at: www.fda.gov/cder/drug/infopage/xyrem/xyrem_qa.htm#4. Sodium oxybate is a schedule III substance.

Head-to-head studies of EDS treatment. Limited data are available comparing the efficacy of similar doses of methylphenidate, dextroamphetamine, modafinil, and sodium oxybate. A 1991 survey of the literature on modafinil, methylphenidate, and dextroamphetamine found that only the latter 2 drugs increased sleep latencies to 70% or more of normal values.⁵² However, the doses of methylphenidate and dextroamphetamine were at or above the high range of recommended doses, whereas modafinil was in the middle range of prescribed doses; the total number of patients examined in each study surveyed ranged from 5 for dextroamphetamine to 21 for modafinil.⁵²

On the other hand, modafinil and sodium oxybate have been compared directly in the same study and were found to have similar efficacies in treating EDS (TABLE 5).⁴⁷ The study examined 270 adult patients with narcolepsy taking 200 to 600 mg of modafinil daily for

the treatment of EDS. Patients received unchanged doses of modafinil during a 2-week baseline phase. Patients were randomly assigned to 1 of 4 treatment groups: placebo, sodium oxybate plus placebo, modafinil plus placebo, or sodium oxybate plus modafinil. Sodium oxybate, 6 g, was administered nightly for 4 weeks and then increased to 9 g nightly for 4 additional weeks. In the sodium oxybate group, there was no decrease in sleep latency from the modafinil treatment run-in period, suggesting that this drug was as efficacious in treating EDS as modafinil. In contrast, the sodium oxybate/modafinil group demonstrated an increase in daytime sleep latency from 10.43 to 13.15 minutes ($P < .001$), suggesting that this combination of drugs produced an additive effect. The sodium oxybate group also demonstrated a decrease in median average ESS scores, from 15.0 to 12.0, whereas the sodium oxybate/modafinil group decreased from 15.0 to 11.0 (for both, $P < .001$; TABLE 5). The authors concluded that sodium oxybate and modafinil are both effective for treating EDS in patients with narcolepsy, producing additive effects when used together.⁴⁸

Treatment of cataplexy

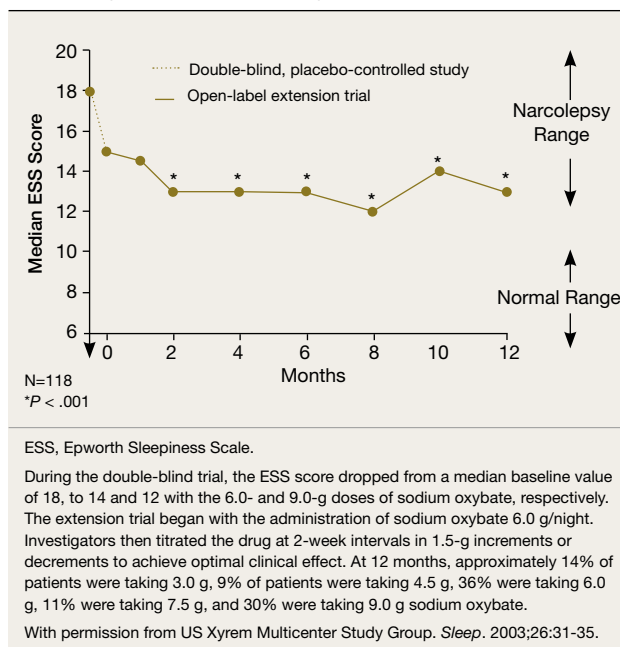
The only drug approved for the treatment of cataplexy in the United States and Europe is sodium oxybate.¹⁴ Tricyclic antidepressants have been used for decades to treat cataplexy, and more recently, the selective serotonin and norepinephrine reuptake inhibitors have been prescribed for this use. However, the effect of these antidepressants on cataplexy has never been examined in randomized clinical trials.¹⁴ Monoamine oxidase inhibitors also may be effective, but are less commonly used. The anticataplectic effects of the antidepressants occurs much more rapidly than their antidepressant effects (less than a week), but rebound cataplexy can occur if their use is abruptly interrupted.^{14,53} Drugs that treat cataplexy also reduce hypnagogic hallucinations and sleep paralysis.¹⁴

Fluoxetine is a selective serotonin reuptake inhibitor with minimal antihistaminic and anticholinergic effects that is used to treat depression.³⁶ The therapeutic doses needed to treat cataplexy are much higher than those needed to treat depression: 60 mg/d fluoxetine for cataplexy treatment versus 20 to 40 mg/d fluoxetine for depression.³⁴ It can take time to wean a patient off the medication because of the long half-life of its active metabolite.

Venlafaxine is another antidepressant used to treat cataplexy. It has less stimulant effect than fluoxetine, as well as a shorter half-life. An extended-release formu-

FIGURE 4

Improvement in EDS with sodium oxybate over 1 year of treatment



lation is available and it may be preferred for cataplexy over fluoxetine.³⁴ The usual dosage of venlafaxine is between 75 and 375 mg/d.

Tricyclic antidepressants used to treat narcoleptic cataplexy include clomipramine, desipramine, imipramine, and protriptyline.¹⁴ Adverse effects occur frequently, especially anticholinergic effects.¹⁴ Other potential adverse effects include orthostatic hypotension, anorexia, diarrhea, weight gain, tiredness, and decreased libido.

Sodium oxybate, administered nightly, results in significant improvements in daytime cataplexy attacks, as well as sleepiness (evidence level I-A).^{50,51,54} The exact mechanism of action of sodium oxybate in cataplexy remains unknown.

In a multicenter, double-blind, placebo-controlled trial, 136 narcolepsy patients with 3 to 249 (median, 21) cataplexy attacks weekly were studied.⁵⁴ Subjects were randomized in double-blinded fashion to receive 3-, 6-, or 9-g doses of sodium oxybate or placebo taken in equally divided doses upon retiring to bed and 2.5 to 4 hours later for 4 weeks. Compared with placebo, weekly cataplexy attacks were decreased by sodium oxybate at the 6-g dose ($P = .0529$) and significantly at the 9-g dose ($P = .0008$). This effect was maintained for more than 44 months, and patients showed no evidence of tolerance.^{14,55} Unlike the antidepressants, there was

TABLE 5

ESS scores: Comparison of modafinil, sodium oxybate, and placebo

	Placebo (n=55)	Sodium oxybate (n=50)	Modafinil (n=63)	Sodium oxybate/ modafinil (n=54)
Visit 3	16.0 (n=54)	15.0 (n=48)	14.0 (n=61)	15.0 (n=54)
Visit 4	17.0 (n=53)	13.0 (n=48)	15.0 (n=62)	11.5 (n=50)
Significance	—	$P < .001$	$P = .071$	$P < .001$
Visit 5	16.0 (n=53)	12.0 (n=49)	15.0 (n=63)	11.0 (n=53)
Significance	—	$P < .001$	$P = .767$	$P < .001$

ESS, Epworth Sleepiness Scale.

Median ESS scores, last observation carried forward. Visit 3 followed 2 weeks of single-blind modafinil at previously established doses (200-600 mg/d). Visit 4 followed 4 weeks of placebo or sodium oxybate, 6 g nightly, and/or modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate, 9 g nightly, and/or modafinil at previously established doses (200-600 mg/d). Significance was as compared with placebo.

With permission from Black J, Houghton WC. *Sleep*. 2006;29:939-946.

no evidence of rebound cataplexy upon abrupt discontinuation of treatment.⁵⁵ Nausea, headache, dizziness, and enuresis were the most commonly reported adverse events. The authors concluded that sodium oxybate significantly improved cataplectic symptoms in patients with narcolepsy.^{54,55}

CASE STUDY (continued)

At the next follow-up, the patient complains that even though she feels better than ever, she continues to have trouble waking up in the morning and still feels significantly drowsy during the day; she also continues to experience 1 or 2 episodes of cataplexy daily. She has become frustrated. The clinician enrolls her in a sodium oxybate program and continues her modafinil prescription of 400 mg daily.

Summary

Pharmacologic management of patients with narcolepsy is usually based on treating separate symptoms, primarily cataplexy and EDS. Treatment options for cataplexy include the antidepressants fluoxetine, venlafaxine, imipramine, and protriptyline, and sodium oxybate. For treating daytime sleepiness, FDA-approved medications include methylphenidate, dextroamphetamine, modafinil, and sodium oxybate. Sodium oxybate is the only drug approved for treating both cataplexy and EDS. Modafinil and sodium oxybate have similar, long-term efficacies in treating EDS at prescribed doses and may have additive effects when used together. ■

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Statements of credit will be awarded upon successful completion of assessment questions (70% or better) and completion of program evaluation. If a score of 70% or better is not achieved, no credit will be awarded and the participant will be notified.

I AM REQUESTING 1.5 CME CREDITS _____

STAY AWAKE! CME POSTTEST *Circle correct answer*

1. Symptoms of narcolepsy usually first appear between the ages of

- a) Birth and 10 years c) 25 and 50 years
b) 10 and 25 years d) 50 and 70 years

2. All of the following are classic symptoms of narcolepsy, except:

- a) Cataplexy c) Spending much more time asleep than people without narcolepsy do
b) Excessive daytime sleepiness d) Sleep paralysis

3. How is the sleep pattern of patients with narcolepsy disturbed?

- a) REM sleep is absent c) REM sleep is entered almost immediately upon falling asleep
b) NREM sleep is unusually prolonged d) NREM sleep is absent

4. Hypnagogic hallucinations and sleep paralysis in narcolepsy may be manifestations of:

- a) REM sleep c) Cataplexy
b) NREM sleep d) Too much sleep

5. Hallucinations that are sleep related and posture related are more characteristic of hallucinations described in which one of the following disorders?

- a) Narcolepsy c) Bipolar disorder
b) Schizophrenia d) Parkinson disease

6. Which neurotransmitter is found in abnormally low concentrations in the central nervous system of patients with narcolepsy?

- a) Acetylcholine c) Dopamine
b) Norepinephrine d) Hypocretin

7. The loss of hypocretin function is the result of a generalized neuronal dysfunction in certain brain regions.

- a) True b) False

8. Antidepressants are used to treat which symptom of narcolepsy?

- a) EDS c) Sleep paralysis
b) Cataplexy d) Antidepressants are not used in the treatment of narcolepsy

9. Compared with amphetamine, modafinil:

- a) Does not have the cardiovascular side effects associated with the older stimulants
b) Does not have the abuse potential associated with the older stimulants
c) Does not cause nausea
d) Both a and b

10. Which of the following has been approved for treating both cataplexy and EDS in narcolepsy?

- a) Sodium oxybate c) Fluoxetine
b) Modafinil d) Dextroamphetamine

PROGRAM EVALUATION *Please complete the evaluation*

1. Please indicate your level of agreement with the following statements:

	Strongly Agree	4	3	2	1	Strongly Disagree
The newsletter adequately addressed the following objectives:						
• Describe the clinical and diagnostic features of narcolepsy	5	4	3	2	1	
• Evaluate the similarities and differences between narcolepsy and other sleep disorders related to other psychiatric or medical diagnoses	5	4	3	2	1	
• Explain the neurobiological mechanisms that currently are believed to bring about narcolepsy and cataplexy	5	4	3	2	1	
• Differentiate the pharmacologic management of cataplexy and excessive daytime sleepiness and explain why narcolepsy is treated symptomatically	5	4	3	2	1	

	Strongly Agree	4	3	2	1	Strongly Disagree
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As a result of reading this newsletter, I am better able to:

• Describe the clinical and diagnostic features of narcolepsy	5	4	3	2	1
• Evaluate the similarities and differences between narcolepsy and other sleep disorders related to other psychiatric or medical diagnoses	5	4	3	2	1
• Explain the neurobiological mechanisms that currently are believed to bring about narcolepsy and cataplexy	5	4	3	2	1
• Differentiate the pharmacologic management of cataplexy and excessive daytime sleepiness and explain why narcolepsy is treated symptomatically	5	4	3	2	1

2. Do you plan to make improvements in how you diagnose and treat narcolepsy (with or without associated excessive daytime sleepiness) in your practice based on new knowledge gained from this activity? (Check one answer.)

- Yes I am considering it No (please explain)

3. If yes, what new strategies are you likely to try for diagnosing and treating narcolepsy (with or without associated excessive daytime sleepiness) in your practice that you have not used before? (Check all that apply.)

- Different or new patient interview questions Different or new nonmedication interventions
 Different or new diagnostic tests Other
 Different or new medication choices

4. Do you have recommendations or suggestions to improve future continuing education programs?

NAME _____ DEGREE(S) _____

STREET _____

CITY _____ STATE _____ ZIP CODE _____

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