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NARCOLEPSY

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Practice Parameters for the Treatment of Narcolepsy

Learning Objectives

● Define what is meant by the term "narcolepsy"

● Identify the ways in which narcolepsy is diagnosed

● Identify the etiology of narcolepsy

● List the various ways in which narcolepsy can be treated

● List the medications most frequently used in association with narcolepsy

● Identify occupational and social accommodations for the disabilities due to or associated with narcolepsy.

● List the various techniques recommended for helping patients "live with" narcolepsy

Abstract

Successful treatment of narcolepsy requires an accurate diagnosis to exclude patients with other sleep disorders, which have different treatments, and to avoid unnecessary complications of drug treatment. Treatment objectives should be tailored to individual circumstances. Modafinil, amphetamine, methamphetamine, dextroamphetamine, methylphenidate, selegiline, pemoline, tricyclic antidepressants, and fluoxetine are effective treatments for narcolepsy, but the quality of published clinical evidence supporting them varies. Scheduled naps can be beneficial to combat sleepiness, but naps seldom suffice as primary therapy. Regular follow up of patients with narcolepsy is necessary to educate patients and their families, monitor for complications of therapy and emergent of other sleep disorders, and help the patient adapt to the disease.

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Introduction
NARCOLEPSY IS CHARACTERIZED BY UNCONTROLLABLE SLEEPINESS (ALSO CALLED EXCESSIVE DAYTIME SLEEPINESS) AND INTERMITTENT MANIFESTATIONS OF REM SLEEP AT TIMES WHEN A PERSON WOULD NORMALLY BE AWAKE**.** Beside sleepiness, the REM manifestations may include cataplexy, sleep paralysis, and hypnagogic hallucinations.
Narcolepsy is not a common disease.

The largest population study estimates the prevalence of narcolepsy at 26 per 100,000 people in Finland, which is similar to the prevalence of myasthenia gravis, Marfan's syndrome, systemic lupus erythematosis, and Crohn's disease. The actual prevalence may be higher in the United States,1 where approximately 5% of patients seen at AASM accredited sleep disorder centers have narcolepsy.2 Narcolepsy has clinical importance which exceeds its prevalence.

A lifelong, often disabling, condition such as narcolepsy demands that many health care providers besides sleep specialists must be familiar with optimum treatments. Sleep attacks associated with narcolepsy can lead to serious accidents or loss of employment, so treatment to reduce excessive sleepiness has clinical and societal value. Nevertheless, many health care providers are overly cautious in approaching treatment of narcolepsy, because stimulant medications, which are the mainstay of narcolepsy treatment, are regulated by government agencies to prevent abuse. Because of the importance of narcolepsy treatment, the American Academy of Sleep Medicine (AASM) sponsored a review paper on the use of stimulants for treatment of narcolepsy in 1994.3 Based on that review, the Standards of Practice Committee (SPC) of the AASM published practice parameters on narcolepsy therapy with stimulants.4 Since publication of the initial review and practice parameters several developments have occurred. Researchers have identified a potential biochemical basis of narcolepsy in dogs and humans.5,6 The genetic defect in canine narcolepsy associated with cataplexy results in a nonfunctional receptor (OX2R) for hypocretin (orexin), a neurotransmitter previously associated with feeding behavior and energy metabolism. In humans, hypocretin is reduced or undetectable in many but not all patients with narcolepsy associated with cataplexy. Also, the United States Food and Drug Administration (FDA) approved modafinil for treatment of narcolepsy. There is optimism that these research and clinical developments will result in better treatment and quality of life for patients with narcolepsy.

In 1999, the Agency for Healthcare Research and Quality in partnership with the American Medical Association (AMA) and the American Association of Healthplans, established the National Guideline Clearinghouse™ (NGC), a comprehensive database of evidence-based clinical practice guidelines and related documents. The clearinghouse provides a central repository of practice parameters from all medical specialties. To be listed, practice parameters must have been developed, reviewed, or revised every five years and must be based on a systematic review of scientific evidence published in peer-reviewed journals. In view of the new treatments, basic research advances, and the NGC protocol, the AASM decided to update the practice parameters for treatment of narcolepsy. This update concerns advances in therapy for narcolepsy since the publication of the expert review; 3 grades the evidence available; and modified and replaced the1994 practice parameters.

Then in December 2007 practice parameters for narcolepsy were updated again and expanded to also address treatment of other hypersomnias of central origin in an American Academy of Sleep Medicine (AASM) report published in the December 1 issue of the journal *Sleep*.

The specific disorders addressed are narcolepsy (with or without cataplexy, from a medical condition, and unspecified), idiopathic hypersomnia (with and without long sleep time), recurrent hypersomnia, and hypersomnia from a medical condition.

The practice parameters were developed by the Standards of Practice Committee of the AASM, which appointed a task force of content experts to perform a comprehensive review of the literature and to develop evidence-based treatment guidelines.

Changes Expected to Have Broad Impact

"The AASM expects these guidelines to have an impact on professional behavior, patient outcomes and possibly, health care costs," Timothy I. Morgenthaler, MD, of the Mayo Clinic in Rochester, Minnesota, a committee member and lead author of the report, said in a statement issued by the AASM. Since the previous treatment guidelines were published in 2000, "there have been significant advances in the treatment of hypersomnia to justify a practice parameters update," he added.

Narcolepsy, a disorder characterized by excessive daytime sleepiness and intermittent manifestations of rapid eye movement sleep during wakefulness is the best characterized and studied central hypersomnia. In 1994, the AASM published practice parameters about the use of stimulants to treat narcolepsy. In 2000, it published an update that included therapies other than stimulants. The scope of the current guidelines has been expanded to include disorders for which alerting medications often represent the primary mode of therapy.

The researchers classified the practice parameters as "standard," "guideline," and "option" recommendations, based on decreasing levels of clinical evidence.

"Standard" Recommendations

The report classifies the following as "standard" recommendations because they are generally accepted patient-care strategies that reflect a high degree of certainty:

- It is important to establish an accurate diagnosis of a specific hypersomnia of central origin and evaluate other possible causes of excessive daytime sleepiness.
- Treatment objectives should include control of sleepiness and other sleep-related symptoms when present.
- Modafinil is effective for the treatment of daytime sleepiness from narcolepsy (unchanged from the previous recommendation and supported by 14 additional studies).
- Sodium oxybate is effective for the treatment of cataplexy, daytime sleepiness, and disrupted sleep from narcolepsy.
- Regular follow-up of patients with hypersomnia of central origin is necessary to monitor response to treatment, to respond to potential adverse effects of medications, and to enhance patients' adaptation to the disorder**.**

"Guideline" Recommendations

The following are classed as "guideline" recommendations because they reflect a moderate degree of clinical certainty:

- Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness from narcolepsy (unchanged from previous recommendations; these generic medications have a long history of use, but limited high-level evidence).

- Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy (unchanged).

- Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and reboxetine may be effective for cataplexy (expanded medication recommendation).

- Modafinil may be effective for the treatment of daytime sleepiness from multiple sclerosis (new recommendation based on 2 studies).

"Option" Recommendations

The following are classed as "option" recommendations because they reflect inconclusive or conflicting evidence, or conflicting expert opinion:

- Sodium oxalate, tricyclic antidepressants, SSRIs, and venlafaxine may be effective for hypnagogic hallucinations and sleep paralysis.

- Selegiline may be an effective treatment of cataplexy and daytime sleepiness.

- Ritanserin may be an effective treatment of daytime sleepiness from narcolepsy.

- Modafinil may be effective for treatment of daytime sleepiness from idiopathic hypersomnia and Parkinson's disease.

- Modafinil or methylphenidate may be effective treatment options for daytime sleepiness from myotonic dystrophy.

Areas for Future Research

Based on their review of the literature, the authors have identified a need for randomized trials to compare newer agents with traditional stimulants for the treatment of hypersomnia from narcolepsy and to compare antidepressants with sodium oxybate for the treatment of cataplexy.

More effective, better-tolerated therapies for hypersomnia from narcolepsy need to be developed because existing therapies only provide, at best, moderate improvement in sleepiness, they write.

More research is needed to address treatment of sleepiness in disorders other than narcolepsy. Lastly, studies are needed for populations such as children, elderly patients, women who are pregnant, and women who are breast-feeding.

The practice parameters were developed by task force content experts who were appointed by the Standards of Practice Committee of the AASM.

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Clinical Context

Excessive daytime sleepiness has a significant detrimental effect on psychological, social, and vocational function and personal safety, adversely affecting quality of life. Hypersomnia of central origin is a category of sleep disorders in which daytime sleepiness is the primary complaint, but the cause is not related to disturbed nocturnal sleep.

This is a practice guideline from a Task Force of the Standards of Practice Committee of the AASM examining the classification of disorders as hypersomnia of central origin and their treatments. A comprehensive review of the literature was conducted on MEDLINE, and evidence was identified and graded before the board of directors of the AASM approved the recommendations, which define the principles of practice meeting the needs of most patients with hypersomnia of central origin.

Study Highlights:

- The revised *International Classification of Sleep Disorders*, *Second Edition*, includes 12 disorders in the category of hypersomnia of central origin.
- The primary pathophysiology is not related to sleep deprivation, medication use, or a psychiatric disorder.
- The primary mode of therapy is alerting medications.
- The specific disorders are narcolepsy (with or without cataplexy, from a medical condition, and unspecified), idiopathic hypersomnia (with and without long sleep time), recurrent hypersomnia, and hypersomnia from a medical condition.
- Idiopathic hypersomnia refers to severe and excessive sleepiness with naps that are nonrestorative with post-sleep confusion or sleep drunkenness.
- Recurrent hypersomnia is rare and is characterized by episodes of hypersomnia with behavioral abnormalities such as binge eating and hypersexuality as in the Kleine-Levin syndrome.
- Hypersomnia from a medical condition refers to hypersomnia without cataplexy secondary to conditions such as Prader-Willi syndrome, myotonic dystrophy, Parkinson's disease, and lesions of the central nervous system such as multiple sclerosis.
- Recommendations for management
    - An accurate diagnosis of a specific hypersomnia disorder of central origin should be established that includes a thorough evaluation to exclude other causes of excessive daytime sleepiness, such as sleep-disordered breathing syndromes, periodic limb movements, and psychiatric disorders.

- Treatment objectives should include control of sleepiness and other sleep symptoms when present with return to normal work, social, or school function.
- Treatment options for daytime sleepiness from narcolepsy include modafinil, amphetamine, methamphetamine, dextroamphetamine, and methylphenidate.
- Scheduled naps can be beneficial but seldom suffice as primary therapy for narcolepsy.
- Modafinil may be effective in addition for idiopathic hypersomnia, daytime sleepiness from Parkinson's disease, myotonic dystrophy, and multiple sclerosis.
- Combinations of short-acting and long-acting forms of stimulants may be indicated and may be effective for some patients.
- Treatment of hypersomnia of central origin in children aged 6 to 15 years with methylphenidate or modafinil seems to be relatively safe.
- Regular follow-up of patients to monitor treatment response and adverse effects of medications will enhance patient adaptation and outcomes.
- Patients with severe sleepiness should avoid potentially dangerous activities at home and work and should not operate a motor vehicle until symptoms are controlled by stimulants.
- Amphetamines are most likely of all the treatments to be associated with tolerance.
- A patient previously stabilized with stimulant medication should be seen regularly by a clinician at least once yearly and preferably every 6 months.
- Clinicians should assist the patient with occupational and social adaptation for disabilities related to hypersomnia of central origin.
- Polysomnographic reevaluation should be considered if symptoms of sleepiness increase significantly or specific symptoms suggest other diagnoses such as sleep apnea or periodic limb movement disorder.
- Recommendations for antidepressant use such as tricyclic antidepressants and SSRIs are for cataplexy and are based on experience rather than on evidence.
- There is limited evidence for conditions other than narcolepsy, and more data are needed for special populations such as children, older adults, women who are pregnant, and women who are breast-feeding.

Highlights for Practice:

- Hypersomnia of central origin includes specific disorders of narcolepsy (with or without cataplexy, from a medical condition, and unspecified), idiopathic hypersomnia (with and without long sleep time), recurrent hypersomnia, and hypersomnia from a medical condition.

- Treatment options for daytime sleepiness from narcolepsy are based on the use of stimulants, which include modafinil, amphetamine, methamphetamine, dextroamphetamine, and methylphenidate**.**

Previous Recommendations
Recommendations that are similar to, or an expansion of, previous ones and new recommendations are noted as such in the text.

1. An accurate diagnosis of narcolepsy should be established which shall include a thorough evaluation of other possible contributing causes, apart from narcolepsy, to the excessive daytime sleepiness {Standard}.

For patients suspected of having narcolepsy, an all-night polysomnogram is done primarily to ascertain the presence of concurrent sleep disorders and is followed immediately by a multiple sleep latency test (MSLT) to help confirm the diagnosis. The MSLT also helps determine the severity of daytime sleepiness.

Other methods to evaluate sleepiness include objective tests such as the maintenance of wakefulness test (MWT), and subjective approaches such as the Epworth Sleepiness Scale.[52] This part of the recommendation is based on committee consensus and is similar to a recommendation made previously.[4] Chronic daytime sleepiness is a nonspecific symptom and conditions that produce such sleepiness may coexist with narcolepsy. For example, the obstructive sleep apnea syndrome (OSAS) and periodic limb movement disorder (PLMD) may be present as determined by the results of the all-night polysomnogram. Insufficient sleep, idiopathic hypersomnia, inadequate sleep hygiene, and circadian rhythm disorders, among others should be considered as possible contributors to sleepiness independent of narcolepsy.[50] Management of other disorders possibly contributing to sleepiness in a patient with narcolepsy may require approaches apart from stimulants to treat sleepiness either directly or as therapy of the underlying condition. This part of the recommendation is new and is based on committee consensus.

2. Individual treatment objectives should be established for each patient with narcolepsy to improve quality of life {Standard}.

One level II, grade B, four level III, grade C, and one level V, grade C, studies, and committee consensus, provide evidence that symptoms of narcolepsy may adversely impact quality of life..

In keeping with the previous practice parameters, a major objective of treatment should be to alleviate daytime sleepiness with stimulants. The goal should be to produce the fullest possible return of normal function for patients at work, at school, at home, and socially. A new recommendation is to control

cataplexy, hypnagogic hallucinations, and sleep paralysis, when present and troublesome. The health care provider should consider the benefit-to-risk ratio of medication for an individual patient, the cost of medication, convenience of administration, and the cost of ongoing care including possible laboratory tests when selecting a medication for treatment of narcolepsy.

3. The following medications are effective treatments for narcolepsy. Comparative safety and efficacy of the stimulant medications are not defined. The rating of the recommendation is based on the grade of evidence for each.

a. Modafinil is effective for treatment of daytime sleepiness due to narcolepsy {Standard}. This conclusion is based on the favorable benefit-to-risk ratio for modafinil established in three level I, grade A studies with confirmation from additional studies. [20-27] This is a new recommendation.

b. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy {Guideline}. These medications are mainstays of narcolepsy treatment. Based on 3 level II, grade B and 4 level V, grade C studies and long clinical practice, they have a long record of efficacy. However, the benefit-to-risk ratio is not well documented, because the published clinical trials include only small numbers of patients. This recommendation is similar to that made previously.

c. Selegiline is an effective treatment for all narcoleptic symptoms {Guideline}. Based on two level II, grade B and one level IV, grade C studies, selegiline is effective, but the cost of the medication is very high, experience with the high doses needed for narcolepsy is limited, and diet-induced hypertension is a danger at effective doses.[28-30] This is a new recommendation.

d. Pemoline is effective for treatment of daytime sleepiness in narcolepsy {Option). Pemoline can produce rare and potentially lethal liver toxicity that may be unpredictable. See the Appendix product alert from Abbott Laboratories for more details and recommendations for ongoing monitoring for liver toxicity. Because of this toxicity, the use of pemoline in patients with narcolepsy is rarely indicated. Based on one level II, grade B study, pemoline may be less potent than amphetamines, but adherence to pemoline therapy may be better than adherence to amphetamines or methylphenidate. This is a modification of a recommendation made previously. In particular, the warning on liver toxicity is emphasized to a greater degree than previously.

e. Tricyclic antidepressants and fluoxetin may be effective treatment for cataplexy, sleep paralysis, and hypnagogic hallucinations {Guideline}. The recommendation for tricyclic agents is based on one level V, Grade C study, long clinical experience and committee consensus. This is a new recommendation. The recommendation for fluoxetine is based on one level II, grade B and one level V, grade C study. This is a new recommendation.

f. Combinations of long- and short-acting forms of stimulants may be effective for some patients {Option}. Some stimulants have a short (3 to 4 hour) effective period (e.g., methylphenidate). Others have longer duration of activity and longer onset of

action (e.g., modafinil, sustained release amphetamine). By combining stimulants with different activity characteristics, it may be possible to achieve alertness quickly and for longer periods of time and alsonot produce insomnia as an unwanted side effect. In addition, combinations of stimulants and antidepressants may be of benefit for treatment of sleepiness and REM-related symptoms such as cataplexy. For example, modafinil appears compatible with antidepressant medications, but published evidence is limited.[54] This recommendation is similar to that made previously and is based on committee consensus.

4. Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy {Guideline}. This recommendation is based on two level II, grade B, one level IV, grade C and one level V, grade C studies and long clinical experience.[42-45] This recommendation is similar to that made previously.

5. Regular follow-up of patients with narcolepsy is necessary to monitor response to treatment, to respond to potential side effects of medications, and to enhance the patient's adaptation to the disorder {Standard}.

a. A patient stabilized on stimulant medication should be seen regularly by a health care provider at least once per year, and preferably once every 6 months, to assess the development of medication side effects, including sleep disturbances, mood changes, and cardiovascular or metabolic abnormalities. This is the same recommendation as made previously and is based on committee consensus.

b. Follow-up is necessary to determine adherence and response to treatment; to monitor for the safety of medications in individual patients; and to assist the patient with occupational and social problems. Adherence to stimulant drug treatment in narcolepsy is impeded by inconvenient dosage, but not by age, educational level, gender, or response to therapy. Of note, many patients with narcolepsy can not be restored to normal levels of daytime alertness, even when adhering to optimum doses of stimulant medications. Most often, response to therapy can be determined by interview of the patient and associates as well as by self-report questionnaires, such as the Epworth Sleepiness Scale. Objective measures, such as the MWT or the MSLT, may play a role when occupational or public safety concerns are at issue. This is an expansion of a similar recommendation made previously and is based on committee consensus.

c. Patients with severe sleepiness should be advised to avoid potentially dangerous activities at home and at work, and should not operate a motor vehicle until sleepiness is appropriately controlled by stimulant medications. This recommendation is the same as that previously and is based on one level II, grade B and one level III, grade B study and committee consensus.

d. Of the stimulants used to treat narcolepsy, amphetamines, especially at high doses, are the most likely to result in the development of tolerance. This is the same recommendation as previously. Reiteration of the discussion and literature cited in the previous review paper [3] are beyond the scope of the current review and the reader is referred for further information.

e. Patients who fail to respond to adequate doses of stimulant medication should be carefully assessed for other sleep disorders such as insufficient sleep, inadequate sleep hygiene, circadian rhythm disorders, obstructive sleep apnea syndrome, or periodic limb movement disorder, that may contribute to excessive sleepiness. This is essentially the same recommendation as previously and is based on committee consensus.

f. For side effects, dosage ranges, use in pregnancy and by nursing mothers, class of medication and use in narcolepsy. The information on stimulants is similar and, in some cases, an expansion of information provided previously. The information on the other classes of medications is new. Note that any of the stimulant medications can be abused.

g. Treatment of narcolepsy with methylphenidate in children between the ages of 6 and 15 appears relatively safe, but caution must be used if other medications are employed. This recommendation is similar to that previously and is based on the considerable experience with use of methylphenidate for treatment of attention deficit disorder.[55]

h. Health care providers should assist the patient with occupational and social accommodation for disabilities due to narcolepsy. The Americans with Disabilities Act provides legal guidance.[56] Patients deserve appropriate help from health care providers to insure that the intent of the law is realized. Because sustained alertness often is difficult to achieve even with optimum treatment, some patients should be advised to avoid potentially dangerous activities, such as driving, climbing, or working in the vicinity of dangerous machinery, which could result in injury to the patient or others. This recommendation is similar to that previously and is based on committee consensus.

i. Polysomnographic reevaluation of patients should be considered if symptoms of sleepiness increase significantly or if specific symptoms develop that suggest new or increased sleep abnormalities as might occur in disorders such as sleep apnea or periodic limb movement disorder. This is the same recommendation as that previously and is based on committee consensus.

Further Research

The preparation of these practice parameters revealed significant weaknesses in the published literature about treatment of narcolepsy. Better studies of diagnostic criteria are needed. Studies which explicitly consider patient preferences about therapeutic objectives should be undertaken.

Further research on
selective serotonin reuptake inhibitors (SSRIs), including ones besides fluoxetine available in the United States, should be undertaken. A large comparative clinical trial of amphetamine, methylphenidate, modafinil, and selegiline for treatment of narcolepsy would be of benefit for patient management. Such a study could establish the relative efficacy, side effects, and patient preferences for treatments. A registry should be established to track the outcome of pregnancy in patients who take modafinil and other stimulants that do not have adequate human data. Treatment of cataplexy needs better assessment, and a clinical trial comparing fluoxetine, tricyclic agents, and placebo would be helpful to clinicians. Research about social interventions to improve function of narcoleptic patients at work and home should be a priority. Gamma hydroxybutyrate is being evaluated experimentally and may have a role to play in treating nocturnal awakenings and cataplexy.[58] However, it is not approved by the FDA. Finally, investigation about whether case management of narcolepsy patients might lead to better patient outcomes is needed.

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Pharmacology Options for Narcolepsy

by Robert A. Whitman, PhD, ABSM, RRT, RPFT

While the search continues for a cure for narcolepsy, researchers are studying hypocretin neurotransmission and treating patients with the latest drug therapies.

Narcolepsy is a central nervous system disorder characterized by excessive daytime sleepiness (EDS) and frequently by rapid eye movement (REM) manifestations during normal awakening. Although not rare, narcolepsy is considerably less common than sleep apnea or periodic limb movement disorder. Its prevalence in the United States is 0.02% to 0.05% and is similar between males and females.[1]

Worldwide, it is been shown to range from 0.02% to 0.18%. Prevalence varies with ethnicity, being more common in Japan and least common in Israel.

Narcolepsy symptoms commence most frequently in the second and third decades. The onset of symptoms is rare after the fourth decade. It has been reported in children as early as 2 years of age. Although symptoms may begin early in life, actual diagnosis may not occur until many years later. Narcolepsy is often mistaken for other disorders characterized by daytime sleepiness and fatigue. A history of symptoms, generally EDS, can in many cases be traced back to puberty.

Clinical Features
Narcolepsy consists of a "tetrad" of symptoms. The most common and most specific features are EDS and cataplexy. EDS usually precedes the onset of cataplexy and then develops and progresses over several weeks or months before it stabilizes. It is the primary clinical feature in all patients. It is generally irresistible and persistent. Although patients may be aware of sudden "sleep attacks" when hypersomnia peaks, they are physiologically sleepy all the time. They report feeling refreshed upon awakening in the morning and daytime naps of 15 to 30 minutes' duration are usually refreshing; however, the benefit from daytime naps is limited, lasting only 2 to 3 hours.

Cataplexy (to strike down in fear) is the abrupt loss of muscle tone precipitated by intense emotion; most commonly, laughter, but emotions such as anger, surprise, excitement, and sexual arousal may also trigger cataplectic attacks. These attacks occur without the loss of consciousness, may be characterized by partial or complete loss of muscle tone (sagging of face, eyelid, or jaw; head drop; blurred vision; or buckling of the knees), and last anywhere from a few seconds to minutes. Cataplexy usually develops within a few months of EDS, but may develop years later. It is specific to narcolepsy and may occur several times a day or only a few times a year. It can be very stressful and socially embarrassing.

The remaining two features of the "tetrad" are sleep paralysis and hypnogogic hallucinations. Sleep paralysis is characterized by the inability to move (loss of muscle tone) for a few seconds or minutes at sleep onset (most common) or sleep offset. The paralysis usually ends spontaneously or after mild sensory stimulation. It is present in 70% to 80% of narcoleptics and varies in frequency throughout life. It can be present in other sleep disorders, most commonly in those disorders causing frequent disruptions in sleep. Hypnogogic hallucinations are vivid dreams that occur during transitions between sleep and wakefulness.

They occur most commonly with sleep onset, but may be experienced upon awakening (hypnopompic). Patients may experience other types of hallucinations including sensory and auditory experiences. Hypnogogic hallucinations are present in about 50% of narcoleptics.

Etiology
The cause of narcolepsy is unknown. It is a neurologic disorder with evidence pointing to altered a-adrenergic receptor functioning.[2] The primary REM generator lies in the rostral pontine reticular formation. There is a reduction of discharge of monoaminergic neurons in the locus ceruleus and raphe nuclei and an enhancement of brainstem cholinergic activity. In cataplexy, there are changes in neurotransmitter levels with emotion. Excessive cholinergic stimulation and reduced noradrenergic activity lead to muscle atonia. Rarely, central nervous system (CNS) lesions are associated with narcolepsy symptoms.

Sleep apnea syndrome
Insufficient sleep
Periodic limb movement disorder
Withdrawal from stimulants
Sedating medications
Circadian rhythm disorders
Idiopathic hypersomnia
Psychiatric disorders
Malingering

Table 1. Differential diagnosis in patients with excessive daytime sleepiness.

Recently, a neurotransmitter named hypocretin has been found to play a role in narcolepsy in dogs. This neurotransmitter has also been found to be undetectable in narcoleptic patients.[3] Reduced numbers of hypocretin-containing neurons have been observed in hypothalamic areas of the human narcoleptic brain.

Human narcolepsy has been strongly associated with positive HLA-DR2 typing. The halotype found to be consistent across most ethnic groups is HLA DQB1*0602. This genotype occurs in 90% to 100% of Japanese and Caucasian patients with narcolepsy, while its occurrence is 12% in the Japanese general population and 22% in the Caucasian general population.[2]

Diagnosis

The diagnosis of narcolepsy is usually made through a detailed clinical history, physical examination, and specific testing. A detailed clinical history and physical examination are required to establish possible differential diagnoses of the patient's EDS (Table 1). The presence of cataplexy is the most specific clinical finding for narcolepsy; however, it may be poorly perceived by the patient and unrecognized by the physician or family members. EDS can be assessed using several approaches. The Epworth Sleepiness Scale is a rating scale assessing the likelihood that a patient would fall asleep in a number of different situations.[4] Each situation is scored on a scale of 0-3 and total scores greater than 10 are suggestive of pathological sleepiness. The scale is limited in that it is a subjective assessment of the patient's degree of sleepiness. It may be useful in following a patient's response to treatment. Specific testing includes polysomnography (PSG) and multiple sleep latency testing (MSLT). These tests are required to substantiate clinical findings as the lifelong management of narcolepsy involves drugs with considerable addictive and abuse potential.

PSG is used to assess the quality and quantity of nighttime sleep. It allows the identification of sleep-related breathing disorders or movement disorders that could result in fragmented sleep leading to the patient's complaint of daytime sleepiness. Narcoleptic patients generally demonstrate a short sleep latency and the early onset of REM sleep, frequently within minutes of turning the lights out. Patients generally have excessive sleep disruption with frequent arousals and awakenings and excessive movements in non-REM and REM sleep.

Protriptyline	**5-60 mg**
Imipramine	**10-100 mg**
Desipramine	**25-100 mg**
Clomipramine	**10-150 mg**
Fluoxetine	**20-60 mg**
Venlafaxine	**75-225 mg**
Reboxetine	**2-10 mg**
Sodium oxybate	**4.5-9 g**

Table 2. Drugs used to treat cataplexy with the usual range of daily dosage.

The MSLT is performed following the nighttime PSG to objectively assess the degree of daytime sleepiness.[5] It consists of polygraphic monitoring of sleep parameters for a period of 20 minutes in a quiet, dark, and comfortable bedroom. The patient is given four or five nap opportunities to fall asleep at 2-hour intervals throughout the day. Both the time to sleep onset and the presence of a sleep onset REM period are documented. REM sleep that occurs within 15 minutes of sleep onset is considered a sleep onset REM period. A mean sleep latency of <8 minutes and the presence of REM sleep in at least two naps are considered diagnostic for narcolepsy. If other sleep disorders are recognized on the PSG, then results of the MSLT are not valid. If, for example, obstructive sleep-disordered breathing is

observed on the PSG, then this disorder must be treated first. If daytime sleepiness persists or if cataplexy is suspected after the effective treatment of other sleep disorders, then an MSLT is indicated. To be clinically relevant, the MSLT must be performed under specific conditions. Patients should be off medications for a period of 2 weeks to avoid possible drug interactions. The patient should fill out a sleep diary for the 2-week period prior to testing to ensure that the patient's sleep schedule has been stable.

Treatment

As there is no cure for narcolepsy, treatment is aimed at reducing the EDS and related REM dissociated features (cataplexy, sleep paralysis, and hypnogogic hallucinations). There are a number of social and economic costs of untreated narcolepsy including poor school performance, avoidance of social interactions, workplace mishaps, automobile accidents, interpersonal difficulty, and depression. Treatment is individualized relative to the presence and degree of symptoms and involves both nonpharmacological and pharmacological interventions. The American Academy of Sleep Medicine has published practice parameters for the treatment of narcolepsy.[6]

Patient Education

Patient education is paramount in maximizing treatment benefit. Patients should be instructed on good sleep hygiene practices, avoidance of irregular sleep patterns, or sleep deprivation. Patients with narcolepsy should avoid working shift work.

It is generally beneficial for the patient to take short naps of 10 to 15 minutes two or three times a day; however, this may be impractical in many settings such as school or work. The patient and family should be aware of the hazards of driving as well as possible hazards in the workplace.

Pharmacological Treatment of EDS

For many years, the mainstay of drug treatment of EDS associated with narcolepsy has been amphetamine-like drugs. These stimulants are indirect sympathomimetics that increase levels of monoamines within the synaptic cleft by enhancing the release of norepinephrine, dopamine, and serotonin, and by blocking their reuptake. These stimulants include dextroamphetamine, methamphetamine, methylphenidate, pemoline, and mazindol. The amphetamine-like drugs have significant side effects including nervousness, headaches, irritability, tremor, insomnia, anorexia, gastrointestinal upset, and heart palpitations. Methylphenidate has been the drug of choice since its discovery in the 1950s. Its efficacy is similar to that of dextroamphetamines and methamphetamines, but with fewer side effects. Pemoline is the weakest of these agents and has a high potential for liver toxicity. If used, it is recommended that liver function tests be performed on a regular basis. The use of pemoline has decreased greatly since the recognition of the potential for liver toxicity. Increasing the dose of stimulant medication is generally done with great caution among physicians who are concerned about inducing tolerance and dependence; however, dependence is acknowledged to be rare among narcoleptics even when using high doses.

Methylphenidate	**10-60 mg**
Dextroamphetamine	**5-60 mg**
Methamphetamine	**5-60 mg**
Pemoline	**20-115 mg**
Mazindol	**0.5-6 mg**
Modafinil	**100-400 mg**

Table 3. Drugs used in the treatment of excessive daytime sleepiness with the usual range of daily dosage.

A new wake-promoting drug, modafinil, has been approved by the Food and Drug Administration (FDA) for the treatment of narcolepsy. Modafinil is structurally unrelated to the amphetamine-like drugs and its mode of action is unknown. It has a half-life of 9 to 14 hours, thus permitting once-daily dosing. It is considered to be less potent than the amphetamine-like drugs, but because it has fewer side effects and a lower abuse potential, it has become the preferred drug for the treatment of EDS in narcoleptics. However, switching patients to modafinil who are stabilized on amphetamine-like stimulants may be difficult.[7] These patients frequently find modafinil to be less effective, especially if they were on high doses of these stimulants. Switching from pemoline to modafinil is generally well tolerated. In addition, amphetamine-like stimulants have a mild anticataplectic effect. Switching to modafinil may be associated with an increase in the frequency of cataplectic attacks requiring the addition of or an increase in anticataplectic medications (see Table 2, page 27). There is a high incidence of headaches with the initiation of treatment with modafinil that can usually be avoided by a progressive increase in dosage over an 8- to 10-day period to the common dosage of 300 mg to 400 mg.

Stimulant medication is best administered in divided doses, generally upon awakening and at noon. A later dose may be given if indicated, but should not be given after 3 pm. Table 3 shows the normal daily range of dosing for the commonly used stimulants.

The combination of long-acting and short-acting stimulants may be possible to achieve alertness quickly and for extended periods of time. Hypnotic medications may be given at bedtime if the patient reports problems with sleep maintenance. Benzodiazepine is the hypnotic of choice, as it generally does not have carry-over sedation the next morning.

Treatment of Cataplexy

When cataplexy is present, it is usually controlled by the use of medications that have a noradrenergic reuptake blocker action (Table 2, page 27). Cataplexy has been traditionally controlled by tricyclic antidepressant medications. Due to the anticholinergic adverse side effects (dry mouth, tachycardia, urinary retention, constipation, and blurred vision) associated with this class of medications, selective serotonin-reuptake inhibitors are gaining in popularity and are less sedating; however, this drug class is believed to have weaker anticataplectic effects.[1] Tricyclic antidepressants are also effective in the treatment of hypnogogic hallucinations and sleep paralysis through their REM-suppressing effects.

A recent FDA-approved treatment for cataplexy is sodium oxybate, a central nervous system depressant. This drug can have serious side effects that include CNS and respiratory depression, confusion, depression, urinary incontinence, and sleepwalking. It is a form of gamma-hydroxybutyrate, which is a known drug of abuse and is generally known as the “date-rape” drug. As a result, it is a schedule class III drug. The manufacturer, in cooperation with the FDA, has established a program to ensure the safe and effective use of sodium oxybate (Xyrem Success ProgramSM). Dosing usually starts at 4.5 g per night given in two equally divided doses to a maximum of 9.0 g. The patient usually takes one dose at bedtime and the second dose 3 hours later.

The Future of Narcolepsy

Although there is no cure for narcolepsy and the treatment of narcolepsy has relied mostly on drug therapies that have been around for decades, the search for new treatments continues. This effort has led to the discovery of modafinil, a wake-promoting drug with fewer side effects than traditional stimulant medications, and sodium oxybate, an effective drug for the treatment of cataplexy. Sodium oxybate also appears to have wake-promoting and sleep-consolidating properties as well and this is currently under investigation.[8] The recent discovery that hypocretin neurotransmission and hypocretin

cells are reduced in patients with narcolepsy may provide future options for the management of narcolepsy.

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All About Narcolepsy: National Sleep Foundation

BASICS:

Narcolepsy is a neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally. The main features of narcolepsy are excessive daytime sleepiness and cataplexy. The disease is also often associated with sudden sleep attacks, insomnia, dream-like hallucinations, and a condition called sleep paralysis. Its prevalence in the developed world is approximately the same as that of multiple sclerosis or Parkinson's disease. However, with increased public education about narcolepsy and physician training in the diagnosis and treatment of sleep disorders, these figures are expected to rise.

In order to understand the basics of narcolepsy, it is important to first review the features of "normal sleep." Sleep happens in cycles. When we fall asleep, we initially enter a light stage of sleep and then progress into increasingly deeper stages. Both light and deep sleep stages are called non-REM (rapid eye movement) sleep. After about 90 minutes, we enter the first stage of REM sleep, which is the dreaming portion of sleep, and throughout the night we alternate between stages of REM and non-REM sleep. For people with narcolepsy, sleep begins almost immediately with REM sleep and fragments of REM occur involuntarily throughout the waking hours. When you consider that during

REM sleep our muscles are paralyzed and dreaming occurs, it is not surprising that narcolepsy is associated with paralysis, hallucinations, and other dream-like and dramatically debilitating symptoms.

Despite the perception that people with narcolepsy are perpetually sleepy, they do not typically sleep more than the average person. Narcolepsy is considered a "state boundary" control abnormality. That is, narcolepsy patients sleep a normal amount but cannot control the timing of sleep.

Narcolepsy affects both sexes equally and develops with age; symptoms usually first develop in adolescence or young adulthood and may remain unrecognized as they gradually develop. The instance of a familial connection with narcolepsy is quite small but a combination of genetic and environmental factors may be at the root of this sleep disorder.

Narcolepsy patients typically endure many years of daytime sleepiness before seeking treatment because sleepiness is not indicative of disease to most people.

Yet the devastating potential of this disorder is reflected in studies showing that narcoleptic patients are more accident-prone and have difficulty with interpersonal relationships.

Researchers believe that narcolepsy may be caused by a deficiency in hypocretin production in the brain. The results of one recent study, in which hypocretin was directly administered to the brain, suggest that using hypocretin derivatives may be an effective way to prevent cataplexy and improve wakefulness.

SYMPTOMS:

The main symptoms associated with narcolepsy are:

- Excessive daytime sleepiness - this is usually the first symptom to appear in people who have narcolepsy. Unless they're being treated for the disorder, the need to sleep can be overwhelming for narcolepsy patients: someone who has narcolepsy is prone to falling asleep while engaged in conversation, driving, eating dinner, or at other inappropriate times. The sleepiness occurs in spite of a full night's sleep and may persist throughout the day.
- Cataplexy - cataplexy is a sudden loss of muscle tone, usually triggered by emotional stimuli such as laughter, surprise, or anger. It may involve all muscles and result in collapse. It may only affect certain muscle groups and result in slurred speech, buckling of the knees, or weakness in the arms. Consciousness is maintained throughout the episode but the patient is usually unable to speak.
- Hypnogogic hallucinations - during transition from wakefulness to sleep, the patient has bizarre, often frightening dream-like experiences that incorporate his or her real environment.
- Sleep paralysis – a temporary inability to move during sleep-wake transitions. Sleep paralysis may last for a few seconds to several minutes and may accompany hypnagogic hallucinations.
- Disturbed nocturnal sleep – waking up repeatedly throughout the night.
- Leg jerks, nightmares, and restlessness.

TREATMENT:

In order to make a determination of narcolepsy, your doctor will ask you for a complete medical and family history and may refer you to a sleep center for evaluation. You should keep a sleep diary as well as a record of your symptoms and their severity for at least a week or two. Bring this information with you when you visit your doctor.

There is currently no widely-accepted cure for narcolepsy but symptoms can be alleviated to the point of near-normal functioning in many patients. Treatment for narcolepsy includes the use of medication as well as behavioral therapy.

Behavioral therapies may help control symptoms, including taking three or more scheduled naps throughout the day. Patients should also avoid heavy meals and alcohol, which can disturb or induce sleep. Also see "Coping" for more information on behavioral remedies for this disorder.

Counseling is very important for people with narcolepsy. The particular symptoms of this disorder are not widely understood by the general public and this may cause patients to feel uncomfortable, alienated, or depressed. The disease can also be quite frightening and the fear of falling asleep inappropriately often significantly alters life for people with narcolepsy.

In treating narcolepsy, doctors typically prescribe stimulants to improve alertness and diminish excessive daytime sleepiness. Antidepressants are also often used to treat cataplexy, hypnagogic hallucinations and sleep paralysis. Finally, sodium oxybate, a strong sleep-inducing agent, may be given at night to improve disturbed nocturnal sleep and reduce daytime sleepiness and cataplexy. All these treatments may have side effects. Stimulants can cause headaches, irritability, mood changes, nervousness, insomnia, anorexia, and irregular heartbeat. Side effects from the use of antidepressants vary and can include nausea, weight gain, anxiety or decreased emotions, drowsiness, sexual dysfunction and changes in blood pressure. Sodium oxybate can induce nausea, excessive sedation, mood changes and enuresis.

The goal in using medications to treat narcolepsy is to achieve normal alertness with minimal side effects.

COPING:

Behavior treatment of narcolepsy includes:

- Several short daily naps (10-15 minutes) to combat excessive sleepiness
- Establish a routine sleep schedule
- Maintain a regular exercise and meal schedule
- Avoid alcohol, caffeine, nicotine

Living With Narcolepsy

What is narcolepsy?

Narcolepsy is a chronic (long-lasting) neurological (affecting the brain or nerves) disorder that involves your body's central nervous system. The central nervous system is the "highway" of nerves that carries messages from your brain to other parts of your body. For people with narcolepsy, the messages about when to sleep and when to be awake sometimes hit roadblocks or detours and arrive in the wrong place at the wrong time. This is why someone who has narcolepsy, not managed by medications, may fall asleep while eating dinner or engaged in social activities - or at times when he or she wants to be awake.

Recent discoveries indicate that people with narcolepsy lack a chemical in the brain called hypocretin, which normally stimulates arousal and helps regulate sleep. They also discovered that there is a reduction in the number of Hcrt cells or neurons that secrete hypocretin. This may be due to a degenerative process or an immune response. How this occurs is unknown.

About one in 2,000 people suffers from narcolepsy. It affects both men and women of any age, but its symptoms are usually noticed after puberty begins. For the majority of persons with narcolepsy, their first symptoms appear between the ages of 15 and 30.

Major symptoms

Excessive daytime sleepiness is usually the first symptom to appear, and often the most troubling. It is an overwhelming and recurring need to sleep at times when you want to be awake. In addition to sleepiness, key symptoms of narcolepsy can include regular episodes of:

- **Cataplexy** - **a** sudden loss of muscle control ranging from slight weakness (head droop, facial sagging, jaw drop, slurred speech, buckling of knees) to total collapse. It is commonly triggered by intense emotion (laughter, anger, surprise, fear) or strenuous athletic activity. Most persons with narcolepsy have some degree of cataplexy**.**
- **Sleep Paralysis -** being unable to talk or move for a brief period when falling asleep or waking up. Many persons with narcolepsy suffer short-lasting partial or complete sleep paralysis.
- **Hypnagogic Hallucinations -** vivid and often scary dreams and sounds reported when falling asleep. People without narcolepsy may experience hypnagogic hallucinations and sleep paralysis as well.
- **Automatic Behavior -** familiar, routine or boring tasks performed without full awareness or later memory of them.

Diagnosing Narcolepsy

In addition to a medical history and physician examination, a diagnosis is made from polysomnogram tests in an overnight sleep laboratory to measure brain waves and body movements as well as nerve and muscle function. A diagnosis also includes the results of the Multiple Sleep Latency Test (MSLT), which measures the time it takes to fall asleep and to go into deep sleep while taking several naps over a period of time.

Many physicians are not familiar with identifying the symptoms and diagnostic procedures specific to narcolepsy. Often, these symptoms are associated with other disorders. Asking for a referral to a sleep specialist or sleep center will avoid the delay in both diagnosis and treatment so often experienced by those who suffer from this serious disorder.

Treatment options

The best treatment plan is the one that works for you. Treatment with medications is the first line of defense.

The goal in using medications should be to approach normal alertness while minimizing side effects and disruptions to daily activities. Changes in behavior combined with drug treatment have helped most persons with narcolepsy improve their alertness and enjoy an active lifestyle.

Common medications and side effects

Doctors generally prescribe stimulants to improve alertness and antidepressants to control cataplexy, hypnagogic hallucinations and sleep paralysis.

Common stimulants include: dextroamphetamine sulfate (DexedrineTM), methylphenidate hydrochloride (RitalinTM), and pemoline (CylertTM). Methamphetamine hydrochloride (DesoxynTM) is prescribed less frequently for narcolepsy.

Some of the most common side effects of stimulants are headache, irritability, nervousness, insomnia, irregular heart beat, and mood changes.

A wake-promoting drug, modafinil (ProvigilTM) was approved by the U.S. Food and Drug Administration (FDA) in 1999 for use in treating the excessive daytime sleepiness associated with narcolepsy. It does not act as a stimulant for other body systems and studies have shown that modafinil is effective in improving alertness with few side effects and low abuse potential.

Several classes of antidepressants are prescribed to treat cataplexy, hypnagogic hallucinations and sleep paralysis. One class, multicyclics, includes imipramine (TofranilTM), desimpramine (NorpraminTM), clomipramine (AnafranilTM), and protriptyline (VivactilTM). Another class are selective serotonin re-uptake inhibitors (SSRIs). These include fluoxetine (ProzacTM), paroxetine (PaxilTM), and sertraline (ZoloftTM).

Side effects vary from one class of antidepressants to another. Those most often reported are drowsiness, sexual dysfunction and lowered blood pressure. In a small percentage of patients, SSRIs cause overexcitement, anxiety, insomnia, nausea and reduced sexual drive.

Sodium oxybate (XyremTM) is the first and only FDA-approved medication for the treatment of cataplexy associated with narcolepsy. It produces consolidation of sleep and improvement of disturbed nighttime sleep characteristic of narcolepsy. It is sedating and should only be used at night. Xyrem is a Schedule III controlled drug substance with abuse potential that is available by prescription.

Narcolepsy patients who have other health conditions (like high blood pressure, heart disease or diabetes) should ask their doctor or pharmacist how medications for those conditions may interact with those taken for narcolepsy. If you take over-the-counter cold and allergy medications, keep in mind that they may make you sleepy.

Sleep hygiene and naps

Doctors generally agree that drug treatment is only one element of narcolepsy symptom management. Changes in behavior to encourage good nighttime sleep are important too.

Try to:

- avoid caffeine, nicotine and alcohol in the late afternoon or evening,
- exercise regularly, but at least three hours before bedtime,
- not use your bed for any waking or unrelaxing activities,
- establish a routine time for going to bed and getting up & and follow it regularly, and
- get enough nighttime sleep - eight hours nightly.

Some sleep specialists recommend several short daily naps along with drug treatment to help control excessive sleepiness and sleep attacks. Others report that a single, long afternoon nap works well to improve a patient's alertness. If naps help you, set aside at least 20-40 minutes for sleep. Be sure you have time to wake up fully.

Living with narcolepsy

The symptoms of narcolepsy can often be effectively managed so that you do not miss the normal activities of life. NSF experts recommend the following:

- Discuss any changes in your symptoms and possible side effects of medications with your doctor.
- Develop your own ways to cope with symptoms and cataplexy triggers. Looking for safe situations, places and supportive persons when cataplexy is likely may prove helpful to avoid injury from falls.
- Schedule regular nap times.
- Join a well-informed support group where you can share experiences and coping strategies (See resources at end of brochure).
- Help others by supporting research or lobbying for legislation.
- Seek out counseling, alone or with your family. A mental health professional, familiar with disabilities, can be helpful when you need to discuss personal, family and employment matters.

Learning with narcolepsy

Because symptoms of narcolepsy may appear as early as age ten, some persons with narcolepsy must learn early on how to deal with the disorder while in school. With a good treatment plan and support from family, friends, and teachers, persons with narcolepsy can do well in school. Educating teachers and classmates can help. The school nurse or health center should know about narcolepsy symptoms

and medications as well. Many schools have strict guidelines for where a student may keep his or her medications (in the school nurse's office rather than in a student locker or backpack) and when he or she may take them (only under supervision).

All schools that receive federal funds must, by law, offer the same basic programs and services to all students. Young people with narcolepsy can enjoy the same advantages as their peers while receiving any needed special assistance. The Individuals with Disabilities Education Act (IDEA) directs schools to plan for "disabled" students' success in school.

It requires public schools to focus on improving rates of secondary school graduation, college attendance and job placement of students with special needs.

Parents can help by bringing their child's needs to the attention of school personnel (teachers, principal, school nurse or guidance counselor) as needed. The special education services available to children with narcolepsy differ from state to state and, in many cases, from school to school.

Many of the same academic challenges that gradeschoolers face apply to students at the high school and college level. At these levels, however, peer pressure and questions about the future multiply. To manage narcolepsy and school better:

- **speak with your instructors so they will understand if you experience symptoms of narcolepsy during class,**
- **schedule classes to avoid most sleepy periods of the day and nap just before classes,**
- **find a reliable classmate to share notes,**
- **audiotape classes to review later (ask permission first!),**
- **choose small classes over larger ones in lecture halls, and**
- **study in a group to help you retain more knowledge and increase your circle of friends.**

Working with narcolepsy

Persons with narcolepsy can find career success and job satisfaction. Treated persons with narcolepsy can work in almost all areas of employment from unskilled to professional. Look for jobs that will allow you to manage your symptoms.

For many, a job requiring regular driving and/or long commutes is troublesome. Also, look for jobs that keep you active and busy, let you interact with others, keep you on the move, and allow a flexible schedule.

Thanks to federal laws including the Americans with Disabilities Act (ADA), your employer must make reasonable accommodations for you at work so you can adequately do your job - modifying your schedule, changing your work location or job duties and providing permission for short naps, for example. And while it is not necessary to inform your employer of your narcolepsy, you must do so before your symptoms begin to interfere with your duties or if you take prescriptive medications on a job with required drug testing. (An uninformed employer cannot be said to discriminate.) The ADA

applies to all aspects of employment, including hiring, promotion, leave, termination, and compensation.

If you work for a company employing more than 50 people, the Family and Medical Leave Act may allow you up to 12 weeks away from work without pay to care for your own health condition or that of an immediate family member.

If you are unable to work at all, you (and sometimes children under age 18) may qualify for Social Security Disability Insurance or Supplemental Security Income. The former is based on age, number of years worked, and salary during those years.

The later is for those without sufficient prior earnings. Your doctor, lawyer, and/or company personnel administrator can help you determine which laws, if any, apply to your situation, as well as when and how to file claims.

Narcolepsy and driving

You may need to drive to school or work, or as part of your job. The good news is that diagnosed and medically treated persons with narcolepsy appear no more at risk for crashes than the general public. If your state restricts driving by people with narcolepsy, proving that you can remain alert may help you get (or keep) your driver's license. This may require a letter from your doctor, whom you should keep informed about your ability to drive safely.

All drivers should be concerned about sleepiness behind the wheel and plan ahead for proper breaks as follows:

- **Stop driving**
- **Find a safe place to stop for a break or for the night.**
- **Pull off into a safe, well-lighted (if at night) area away from traffic and take a brief nap: 15-20 minutes is best.**
- **Drink coffee or other type of caffeine drink to promote short-term alertness if needed. Caffeine is also available in soft drinks, chewing gum and tablets. Caffeine and a nap together offer short-term benefits.**
- **Get off the road if you hit shoulder rumble strips. These are deep grooves that are placed on high-speed roads to alert you when you are leaving the road.**

Narcolepsy and personal life

The symptoms of (and some of the drugs taken for) narcolepsy may affect your sex life. Sexual problems, such as low sex drive and impotency, may result from severe sleepiness, depression, medications or cataplectic attacks. These problems, especially any resulting from a new medication or changed dosage, should be discussed with your doctor.

The risk of having a child with narcolepsy has been reported to be 1 to 2% or a 10-40 fold higher risk than the general population. A woman with narcolepsy who is pregnant (or is thinking about becoming pregnant) should speak to her doctor about the possible effects of her medication on the fetus. Although the emotional, physical and psychological demands of having a child should be considered, many parents with narcolepsy do have healthy children and manage parenting successfully.

Narcolepsy symptoms can also result in a change or loss of employment, physical restrictions and social withdrawal. Loss of self-esteem, learning difficulties and depression can result.

Developing a combination of medical and behavioral treatments with your doctor is the key to successful management of your narcolepsy. Selecting a knowledgeable and compatible doctor that best meets your individual needs, explores options and with whom you can communicate effectively will help you manage your particular symptoms and achieve a quality of life. Many people also benefit from support groups. Together, a healthy physical routine, ongoing medical treatment, and sharing your concerns can help you be one of the thousands of Americans coping and living well with narcolepsy.

Sharing information about narcolepsy

Since narcolepsy is often misunderstood and is considered a rare disorder, many people you encounter are unfamiliar with its symptoms. To help yourself in a variety of situations, you should be prepared to educate others including:

- **Family members**
- **School officials**
- **Teachers**
- **Doctors**
- **Counselors**
- **Employers**
- **Supervisors**
- **Co-Workers**
- **Police**
- **Judges**
- **Lawyers**
- **Friends**

- **Neighbors**

From Faithful Dogs and Difficult Fish, Insight Into Narcolepsy

By INGFEI CHEN- October 23, 2007

On a sun-drenched morning this month, a small, black, bushy-haired dog trotted out from the animal care center at Stanford. The Belgian schipperke, Bear, soon veered off to lift a hind leg over a shrub.

He was, clearly, oblivious to the gravitas of the day. Bear had spent nearly seven years in the underground kennels as part of a colony of narcoleptic dogs studied by Dr. Emmanuel Mignot, director of the Stanford Center for Narcolepsy.

Dr. Mignot had just signed papers to adopt the dog, the last of the colony. Bear's freedom ended 30 years of investigations that led to the discovery of the importance of a neurochemical called hypocretin in human and animal narcolepsy, and in normal sleep.

Bear will now be a pet. And Dr. Mignot has turned to less huggable research subjects, like wet, cold-blooded and, unexpectedly, less cooperative zebrafish.

Investigators now understand that narcolepsy arises from a deficiency of the brain cells that make hypocretin, similar to the way that Parkinson's is caused by the loss of dopamine-producing neurons.

Dr. Mignot, who has devoted his career to studying narcolepsy, has been "a real pioneer in this," said Giulio Tononi, a sleep researcher at the University of Wisconsin, Madison. Pivotal contributions also came independently from scientists in Dallas and Los Angeles.

The normal boundaries between wakefulness and slumber fray in narcolepsy, which plagues 135,000 Americans. Symptoms include overwhelming sleepiness during the day, insomnia at night and hallucinations or muscle paralysis while dozing off. Laughter or strong emotions like elation and anger can set off sudden muscle weakness. One good joke, and patients can find their knees buckling or heads sagging. But they remain awake.

In the early 1970s, a sleep scientist at Stanford, William C. Dement, diagnosed narcolepsy in a French poodle. He tracked down Doberman pinschers and Labrador retrievers with an inherited form of the disorder, establishing a breeding colony in 1976. The dogs shared a striking trait: collapsing in attacks of muscle weakness when excited by their favorite food.

Dr. Mignot began studying the colony in 1986. Born in Paris, he received his M.D. from the René Descartes School of Medicine in 1984, in tandem with doctorate pharmacology studies at Pierre and Marie Curie University. After a psychiatry residency, he faced a year of mandatory military training, or he could practice medicine for 16 months in Africa or Asia.

Dr. Mignot, who said he was "a nerd of the greatest dimension," sought a different path. Intrigued by the enigma of sleep, he persuaded a French company to send him to Stanford to test its experimental narcolepsy drug on the dogs. Dr. Mignot arrived in Palo Alto, Calif., in 1986.

The medication, modafinil, reduced sleepiness but had no effect on paralysis attacks, Dr. Mignot found. In 1988, he became head of the Center for Narcolepsy and decided to hunt for the canine narcolepsy gene. “At that time,” he recalled, “there were no maps of the dog genome.”

It took 10 years and breeding nearly 200 Doberman and Labrador puppies to succeed, working with a psychiatry professor, Dr. Seiji Nishino, and others. (Animals were later put up for adoption.)

In August 1999, Dr. Mignot’s team announced the culprit: a flawed gene for a receptor protein that binds to hypocretin. In a surprise, Dr. Masashi Yanagisawa, a geneticist at the University of Texas Southwestern Medical Center, reported that month that deleting the gene for hypocretin caused narcolepsy in mice.

Those genes are normal in most human narcoleptics but they still lack hypocretin, according to separate studies by Dr. Mignot’s group and a team led by Jerome Siegel, a neuroscientist at the University of California, Los Angeles. The reason is that patients have lost 90 percent of the brain cells that make hypocretin.

In a report in May, Dr. Siegel said that in late-stage Parkinson’s disease, as well, the hypocretin-producing cells were missing, 62 percent of them. Daytime drowsiness and poor night sleep are common in Parkinson’s patients. “Long before they’re diagnosed,” Dr. Siegel said, “these individuals are sleepy.”

Hypocretin was the first protein directly linked to a true sleep disorder, and many labs jumped into deciphering its role in normal sleep. “I think hypocretin is a key molecule that helps you stay awake when you start to be sleep deprived,” Dr. Mignot said.

Scientists know that a small set of hypothalamus neurons secrete hypocretin, activating brain circuits to promote wakefulness. Research also suggests that hypocretin is involved in regulating muscle tone, metabolism and feelings of pleasure.

Initial hopes for improved narcolepsy medicines that replace hypocretin have faded, because studies showed that the molecule did not readily cross the blood-brain barrier. It may be possible to find an oral hypocretinlike drug, Dr. Mignot said. Many patients rely on modafinil, approved in 1999, and other stimulants. To suppress paralysis, patients take antidepressants or sodium oxybate, found in the date-rape drug. None of the medicines influence the hypocretin system.

Dr. Mignot is now asking why hypocretin neurons die in narcoleptic people. The best hypothesis is that the immune system destroys the cells, but no one has direct evidence of that, Dr. Mignot said.

His group has been studying rodents, tinkering with genes in their hypocretin cells to see whether damage or symptoms result. But diagnosing narcolepsy in mice is tricky. “Sometimes,” he said, “they collapse, but you don’t really know why.”

He has turned to zebrafish, which possess hypocretin and hatch rapidly. Computer analyses of fish videos convinced him that the animals do sleep. Snoozing fish drift to the tank bottom and stop. “Their tail kind of droops,” he said.

In a study published last week in PLoS Biology, the researchers reported on an effort to breed a colony of narcoleptic zebrafish by obtaining mutant fish that lacked hypocretin receptors. “I was hoping that they would collapse, like the dogs,” Dr. Mignot said. But the fish did not flop over. They were no sleepier during the day, and they were evening insomniacs.

Their hypocretin cells, it turns out, are not wired like those in mammals. Dr. Siegel concluded that zebrafish would not open major insights into hypocretin's role in narcolepsy; the sleep system “is just very different.”

Although disappointed by the findings, Dr. Mignot mused that one could learn as much from negative results as from positive. He still plans to explore the cell biology of zebrafish hypocretin neurons.

By studying fish and other animals, Dr. Mignot said and Dr. Siegel agreed, researchers could reap knowledge about the evolution of sleep across species.

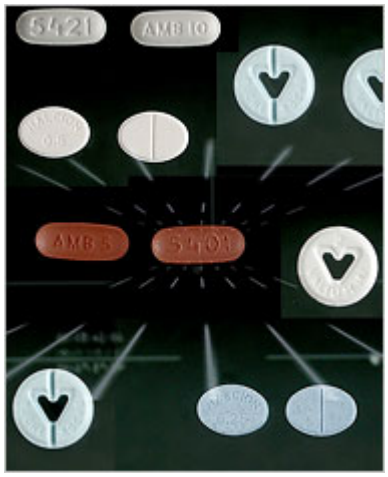
Dr. Mignot is optimistic about cracking the immune-system connection in narcolepsy soon. “I don’t care actually even if it’s going to take a long time,” he said. “I’m ready to cross deserts.”

Dr. Tononi said Dr. Mignot was ideally suited for that, adding: “This is what is good about Mignot. He is relentless.”

Sleep Drugs Found Only Mildly Effective, but Wildly Popular

Your dreams miss you.

By **STEPHANIE SAUL**
Published: October 23, 2007



Or so says a television commercial for Rozerem, the sleeping pill. In the commercial, the dreams involve Abraham Lincoln, a beaver and a deep-sea diver.

Not the stuff most dreams are made of. But if the unusual pitch makes you want to try Rozerem, consider that it costs about $3.50 a pill; gets you to sleep 7 to 16 minutes faster than a placebo, or fake pill; and increases total sleep time 11 to 19 minutes, according to an analysis last year.

If those numbers send you out to buy another brand, consider this, as well: Sleeping pills in general do not greatly improve sleep for the average person.

American consumers spend $4.5 billion a year for sleep medications. Their popularity may lie in a mystery that confounds researchers. Many people who take them think they work far better than laboratory measurements show they do.

An analysis of sleeping pill studies found that when people were monitored in the lab, newer drugs like Ambien, Lunesta and Sonata worked better than fake pills. But the results were not overwhelming, said the analysis, which was published this year and financed by the National Institutes of Health.

The analysis said that viewed as a group, the pills reduced the average time to go to sleep 12.8 minutes compared with fake pills, and increased total sleep time 11.4 minutes. The drug makers point to individual studies with better results.

Subjects who took older drugs like Halcion and Restoril fell asleep 10 minutes faster and slept 32 minutes longer than the placebo group. Paradoxically, when subjects were asked how well they slept, they reported better results, 52 extra minutes of sleep with the older drugs and 32 minutes with the newer drugs.

“People seem to be getting a lot of relief from sleeping pills, but does getting 25 minutes of sleep really give you all that relief?” asked Dr. Wallace B. Mendelson, the former director of a sleep disorders unit at the University of Chicago. “A bigger aspect of this is that they change a person’s perception of their state of consciousness.”

Dr. Mendelson is semiretired and is a consultant for pharmaceutical companies.

Dr. Karl Doghramji, a sleep expert at Thomas Jefferson University in Philadelphia, agreed. “Sleeping pills do not increase sleep time dramatically, nor do they decrease wake time dramatically,” he said. “Despite those facts, we do find patients who, when they take them, have a high level of satisfaction.” Dr. Doghramji has disclosed in the past that he is a consultant to pharmaceutical companies.

Most sleeping pills work on the same brain receptors as drugs to treat anxiety. By reducing anxiety, the pills may make people worry less about not going to sleep. So they feel better.

Another theory about the discrepancy between measured sleep and perceived sleep involves a condition called anterograde amnesia. While under the influence of most sleep medications, people have trouble forming memories. When they wake up, they may simply forget they had trouble sleeping.

“If you forget how long you lay in bed tossing and turning, in some ways that’s just as good as sleeping,” said Dr. Gary S. Richardson, a sleep disorders specialist at Henry Ford Hospital in Detroit who is a consultant and speaker for pharmaceutical companies and has conducted industry-sponsored research.

Sleep, after all, causes a natural state similar to amnesia, one reason toddlers often forget their violent nightmares by the next morning. If you stay in bed, as most people taking sleeping pills do, amnesia is not a bad thing.

Even some people who sleepwalked while taking Ambien, which was implicated in cases of odd, sometimes dangerous behavior while sleeping, believed they were having a good night’s sleep. Rosemary Eckley, a graphic artist in New London, Wis., said she thought she was sleeping well on

Ambien but woke to find her wrist broken, apparently in a fall while sleepwalking, she wrote in an e-mail exchange.

Reports of sleep-eating and sleep-driving on Ambien are reminiscent of problems nearly 20 years ago with Halcion. Some people who took that drug to sleep on airplanes developed a condition known as traveler's amnesia. They landed at their destinations, then got lost or forgot where they were, prompting the authorities in several countries to withdraw Halcion from the market.

Reports show that Ambien and similar drugs, advertised as safer than benzodiazepines like Halcion, can cause similar problems. The reports prompted the Food and Drug Administration to ask manufacturers to develop warning guides for distribution with virtually all sleep drugs. Despite such problems, most specialists say sleeping pills are generally safe. Dr. Mark W. Mahowald, director of the Minnesota Regional Sleep Disorders Center, which is involved in documenting cases of sleep-eating under the influence of Ambien, said serious side effects were rare and should not discourage the use of the pills.

The class of drugs known as nonbenzodiazepines, sometimes called "Z" drugs, includes Ambien, Lunesta and Sonata. Ambien and its generic equivalent, zolpidem, are the most widely used, together accounting for 40 percent of the market.

Newer drugs like Lunesta and Ambien CR, a controlled-release formula, cost about $4 a pill. Zolpidem recently sold for $2 a pill on walgreens.com.

Of the three drugs in the class, Sonata, which also retails for about $3.50 a pill, remains in the body the shortest time and, therefore, is normally used by people who have trouble falling asleep but no problem staying asleep. The advocacy organization Public Citizen's Health Research Group says its benefits are so minimal it should not be used. King Pharmaceuticals, the maker of Sonata, did not respond to several messages seeking comment.

A study by an Oregon State University group that reviews the safety and effectiveness of drugs found that Lunesta offered little benefit over generic Ambien or older benzodiazepines, but cost more. Jonae Barnes, a spokeswoman for Lunesta's maker, Sepracor, said the company strongly disagreed and added that the Oregon group did not adequately consider waking time after falling asleep, an area in which Lunesta performed better.

Users also sometimes report that Lunesta leaves a bad taste in their mouths, according to studies of the drug. Dr. Mahowald said the older drugs, including Halcion, also known as triazolam, offered better value than the newer ones.

"We tend to use the old benzodiazepines," he said of his practice. "They appear to be as effective as some of the newer ones, and they're infinitely less expensive."

Dr. Mahowald said that his center participated in industry-sponsored clinical research, but that he did not personally work as a consultant or adviser to pharmaceutical companies. Such drugs, which include flurazepam, brand name Dalmane, and temazepam, Restoril, sell in generic versions for 30 to 50 cents each.

Another inexpensive alternative, and one of the most widely used sleep medications in this country, is the antidepressant trazodone. It works well in many patients, but some people say it leaves them groggy the next day, according to Dr. Daniel Carlat, a psychiatrist in Newburyport, Mass., who

publishes The Carlat Psychiatry Report and declines industry financing. In men, trazodone has been linked to rare cases of priapism, prolonged and painful erections.

Some patients who fear using sleeping pills turn to over-the-counter remedies like Tylenol PM and Advil PM. Those contain the painkillers acetaminophen and ibuprofen combined with an antihistamine, diphenhydramine, the ingredient in the allergy medication Benadryl.

Antihistamines are known to make people sleepy, but there is little evidence that they improve sleep. They can also cause next-day sedation that impairs driving, as well as racing heartbeat and constipation. The Medical Letter, which reviews drugs, recommends against using antihistamines for sleep. Some doctors say users of Tylenol PM may be taking acetaminophen they do not need. Acetaminophen overdoses can cause liver failure.

Rozerem, with its unusual advertising campaign, has at least one benefit over other medications. Because it works by a different mechanism from the others, it is not a controlled substance and apparently does not affect the ability to form memories. It may be the sleeping pill of choice for elderly people who have trouble falling asleep, but suffer memory problems.

Still, researchers and drug companies have yet to find a holy grail. “The problem is, there is no ideal hypnotic,” said Dr. Manisha Witmans, a sleep medicine specialist at the University of Alberta’s Evidence-Based Practice Center. “The magic pill for sleep has not been invented yet.

Overview of the Diagnosis and Treatment of Narcolepsy

by Roza Hayduk, M.D.

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The role of primary care physicians in the evaluation and diagnosis of narcolepsy is extremely important, as they may be the first contact for the patient suffering from this disorder. Careful history taking, physical examination, the use of specific questionnaires and sleep laboratory tests are valuable tools in the evaluation valuable tools in the evaluation overview addresses the clinical manifestations, diagnostic criteria and treatment of narcolepsy.

Description, Prevalence and Etiology

Narcolepsy is a **chronic neurological disorder** characterized by excessive daytime sleepiness (EDS) and associated features including cataplexy, hypnagogic hallucinations and sleep paralysis.

Additional symptoms associated with narcolepsy are disturbed nocturnal sleep and automatic behavior. EDS is the main symptom present in 100% of patients with narcolepsy. The other symptoms may be present in various combinations and degrees of severity.

Narcolepsy affects both sexes equally. The onset of the disease is usually in teenage years or young adulthood. The first symptom to appear is daytime sleepiness; it may remain unrecognized for a long time as it develops gradually over time. The other symptoms could follow by months or years.

The prevalence of narcolepsy is similar to Parkinson's disease and multiple sclerosis (0.03 -0.09%for North America and Western Europe). It is estimated that approximately 125,000-200,000 Americans suffer from narcolepsy; however, fewer than 50,000 are properly diagnosed (Nishino and Mignot,1997).

Narcolepsy often remains undiagnosed or misdiagnosed for several years. In part, this may occur because physicians may not include narcolepsy in the differential diagnosis of other diseases with complaints of fatigue, tiredness, problems with concentration, attention, memory and performance, and other illnesses (e.g.seizures, hallucinatory states).

Rapid advances in determining the etiology of narcolepsy have been made. Recent findings in canine narcolepsy (a mutation on hypocretin (Hcrt)receptor 2 gene)and murine form (a null mutation on preprohypocretin gene), implicate the hypocretin system in the etiology of narcolepsy (Lin et al.,1999,Chemelli et al.,1999). Additional recent reports of a decreased level of Hcrt in the cerebral spinal fluid of narcoleptic patients (Nishino et al.,2000) and markedly decreased number of Hcrt neurons in the hypothalamus of narcoleptic patients (Payron et al., 2000,Thannickal et al., 2000) further confirmed the involvement of Hcrt system in the etiology of human narcolepsy. It is postulated that the loss of Hcrt neurons may be due to an autoimmune reaction (Honda et al.,1988,Mignot et al.,1997) initiated by environmental factors (Van den Pol et al.,2000).

Clinical Manifestations

Excessive daytime sleepiness

(EDS) is the primary and often the most disabling symptom of narcolepsy; it is manifested as a propensity to fall asleep or doze off easily in relaxed situations, but also at inappropriate times and places (e.g. watching TV, reading a book, driving a motor vehicle, during a meeting, while engaged in a conversation). The daytime sleepiness is present even after normal nighttime sleep. Patients may refer to this symptom as being tired, fatigued, sleepy or feeling lazy, with low energy. EDS is present throughout the day and the patient may be able to resist the sleepiness with extreme effort until it becomes overwhelming, ending in a sleep episode of varied duration (seconds to minutes).In addition, repetitive, irresistible and unintentional sleep attacks may occur. EDS usually has a negative impact on patient functioning as it reduces motivation and vigilance, interferes with concentration and memory, and increases irritability.

Cataplexy is a sudden, reversible loss of muscle tone, usually triggered by emotional stimuli such as laughter, excitement, surprise, or anger. Contributing factors could be physical fatigue, stress, or sleepiness. Severe attacks of cataplexy may involve all skeletal muscles, resulting in complete body collapse with a fall to the ground and risk of injury. Milder forms of cataplexy are more common and involve focal muscle groups resulting in symptoms such as a dropping head, sagging jaw, slurred speech, buckling of the knees, or weakness in the arms.

Consciousness is maintained throughout the episodes; however, the patient is usually unable to speak. The cataplectic attacks may last from a few seconds to several minutes and may vary from a few per year to numerous attacks per day, which could render the patient disabled.

Cataplexy is present in 65-70%of patients with narcolepsy. The onset of cataplexy may coincide with the onset of EDS, but often develops years later. Clinicians should inquire carefully about muscle weakness. The absence of cataplexy should not rule out the diagnosis of narcolepsy.

Hypnogogic hallucinations are dream-like experiences, which occur during transition from wakefulness to sleep. These sensory experiences may be auditory, visual, tactile, or kinesthetic and often incorporate images of the patient 's environment with the dream-like images. They are often vivid, bizarre, frightening and disturbing for the patients who may become apprehensive of mental illness. The hallucinations may be present in up to 60% of narcoleptic patients.

Sleep paralysis is a temporary inability to move or talk occurring during sleep/wake or wake/sleep transitions. The duration of these episodes may be from seconds to minutes and can occur simultaneously with hypnagogic hallucinations. Respiration is maintained although some patients may experience a frightening sensation of "not being able to breathe." Sleep paralysis may be present in up to 60%of patients with narcolepsy.

Disturbed nocturnal sleep with frequent awakenings and increased body movements may develop after the onset of the primary symptoms as an additional symptom of narcolepsy.

Automatic behavior refers to performance of routine activities with reduced awareness, or semipurposeful behavior often with unusual verbalization (irrelevant words, lapses in speech).The patient is unaware of this behavior while fluctuating between sleep and wakefulness. Other diseases with amnesia should be considered in the differential diagnosis (partial complex seizures or psychogenic states). Automatic behavior may be present in 60-80% of narcoleptic patients.

Additional complaints associated with narcolepsy may include ocular disturbances such as blurred vision, diplopia and ptosis (droopy eyelids due to the sleepiness).

Assessment Tools

In addition to the clinical evaluation, several questionnaires may be used in the assessment of patients with symptoms of narcolepsy.

The Stanford Narcolepsy Questionnaire is a very extensive questionnaire, which can provide the physician with valuable information on all symptoms of narcolepsy, but especially on cataplexy.

The Epworth Sleepiness Scale is a brief self-administered scale, which provides an estimate of the degree of daytime sleepiness. Visit NSF's website to take the test and get results: www.sleepfoundation.org

The use of **sleep logs or sleep diaries** for 2-3 weeks is recommended in the evaluation of ANY patient with EDS. Sleep diaries provide the physician with information about usual sleep patterns (sleep deprivation, irregular sleep/wake pattern, interrupted sleep), common waking behaviors ("Internet syndrome," poor sleep hygiene), or alcohol and/or drug use, all of which may be useful in the differential diagnosis of EDS.

Standard sleep laboratory tests for narcolepsy include polysomnography (PSG) followed by a multiple sleep latency test (MSLT). These procedures provide objective measures of sleepiness and REM sleep abnormalities, and aid in ruling out other causes of daytime sleepiness. In some cases, repeat PSG and MSLT may be recommended if there is worsening of the symptoms of narcolepsy despite the treatment and/or additional sleep disorders are suspected (e.g. sleep apnea syndrome).

Even though a very high association of narcolepsy and Class II Human Leukocyte Antigen (HLA) (DQB1*0602/DRB1*1501) was described years ago (Honda et al., 1988),this test is not specific and

should not be used for the diagnosis of narcolepsy. There are familial forms of narcolepsy without the HLA marker and sporadic forms, which may have the HLA marker (Hayduk et al.,1996,1997).

Diagnostic Criteria

The diagnostic criteria for narcolepsy described in the International Classification of Sleep Disorders indicate that the diagnosis may be based on clinical symptoms alone, if EDS and cataplexy are present, or on the clinical manifestations and polysomnographic findings, if there is no cataplexy. However, most experts agree that it is advisable to confirm the diagnosis of narcolepsy with sleep laboratory procedures (PSG and MSLT) before the start of the treatment.

Treatment

Treatment of narcolepsy includes pharmacological and non-pharmacological/behavioral therapies. Treatment options should be individualized depending on the severity of the symptoms, life conditions of the patients, and the specific goals of therapy. Optimal management usually takes weeks to months to achieve and requires continued communication among the physician, narcoleptic patient, family members, employer, teachers and others. Good treatment management typically produces significant improvement of the symptoms, rather than resolution of all symptoms.

Pharmacological treatment of narcolepsy is determined by the number and severity of the symptoms. Severe daytime sleepiness may require treatment with high doses of stimulant medication, and sometimes a combination of stimulants may be needed. Rare or infrequent cataplexy and other auxiliary symptoms may not require drug treatment, or a prn regimen may be adequate. Insomnia and depression may also require treatment. The treatment should be catered to the individual needs of the patient. For example, improved alertness throughout the day may be critical for students and working adults, but only at certain times of the day for others (e.g., driving times).

Alerting medications are used for treatment of EDS. Amphetamines (e.g., Dexedrine, Desoxyn, DextroStat, Adderall) and Methylphenidate (Ritalin) are generalized CNS stimulants, which decrease sleepiness and improve alertness, but also increase sympathetic activity and may produce undesirable side effects, such as elevations in blood pressure, nervousness, irritability, and rarely, paranoid reaction. These medications can also produce dependency due to the euphorogenic effects caused by increased dopaminergic activity, although this has rarely been described in narcoleptic individuals.

Pemoline (Cylert) is also used as an alerting medication but with less effectiveness. There is a potential risk of hepatotoxicity, and if used, requires frequent liver function tests.

Modafinil (Provigil), approved by FDA in 1999, has alerting effects similar to those of traditional stimulants, but with a much lower risk for cardiovascular and psychiatric side effects associated with these medications, due to a different mechanism of action. Modafinil is not a generalized CNS stimulant; it does not have significant effects on the sympathetic nervous system and it does not cause mood changes and euphoria, dependence and tolerance. Headache and nausea are the most commonly reported side effects and they are usually mild and transient. Modafinil has a longer half-life, which allows single daily dosing for many patients. It could be the drug of choice for newly diagnosed narcoleptic patients or for patients with significant side effects from other stimulant medications.

Although relatively new in the US, modafinil has been used for narcolepsy for many years in France and other countries. (US Modafinil in Narcolepsy Multicenter Study Group,1998).

Cataplexy and other auxiliary symptoms are treated with anticataplectic medications. Tricyclic antidepressants (TCAs), used in lower than antidepressant doses, are often effective in controlling cataplexy.

In some cases, anticholinergic side effects limit their use, although in most cases, these side effects may be temporary. Sedating TCAs should be prescribed for evening use, whereas the alerting ones should be used during the day. Significant rebound cataplexy could be seen upon abrupt discontinuation of these medications.

Selective serotonin reuptake inhibitors (SSRIs) are also useful in treatment of cataplexy, at doses comparable to those used for the treatment of depression. They may not be as effective as TCAs (comparative data are lacking), but they have a more favorable side effect profile.

Sodium oxybate (Xyrem), also known as gamma-hydroxybutyrate or GHB, is another medication with anticataplectic effects. This medication is usually administered in two doses, at bedtime and 4 hours later. It produces consolidation of sleep and improvement of disturbed nocturnal sleep characteristic of narcolepsy. This improvement may contribute to decreased daytime drowsiness and diminished cataplexy (Broughton and Mamelak, 1980; Scharf et al.,1985). Although Xyrem is unrelated to other known hypnotic drugs and is not indicated for insomnia, it is sedating and should only be used at night. It has been used in Europe for treatment of narcolepsy. Xyrem is approved by the US FDA for the treatment of cataplexy and daytime sleepiness in narcolepsy patients.

Non-pharmacological treatment encompasses the disease-specific education of the patient and family members and modification of behavior patterns. Understanding the symptoms of narcolepsy may relieve some of the frustrations, fears, anger, depression and resentment of the patients and family members caused by the unusual symptomatology and social ignorance of this disease. National organizations and local narcolepsy support groups are additional sources of information.

Behavioral approaches include the establishment of a regular, structured sleep-wake schedule. Planned naps of 15-30 minutes or longer are usually refreshing and may be beneficial in reducing patient's daytime sleepiness. Dietary restrictions should be observed (avoidance of alcohol, large meals). Regular exercise and exposure to bright light could improve alertness. Occupational/ marriage/ family counseling may be beneficial in improving patient's quality of life (special consideration for school schedules, avoidance of occupations which require shift work or changes in work schedule, driving, disability). The danger of driving while sleepy and/or experiencing cataplexy should be addressed and the patients should be advised to avoid driving under such circumstances. Many patients with narcolepsy would be able to continue to drive for short distances, at certain parts of the day and after taking their stimulant medications. Reporting requirements differ from state to state.

Conclusion

The role of the primary care physician is to recognize narcolepsy symptoms, initiate proper evaluation, and manage treatment usually in collaboration with a sleep medicine specialist. In addition, the primary care physician has an important role in managing the impact of narcolepsy on a patient's quality of life, just as for any other complex, chronic condition.

Narcolepsy and Pregnancy

"When you are pregnant and have narcolepsy you will have to make sacrifices, surrendering some independence."

Pregnancy is a time of immense joy and a time of numerous life-altering challenges. Imagine how these challenges are intensified when narcolepsy is added to the picture.

Collene Dugan, mother of two (ages 15 and two) and narcolepsy sufferer, understands the demands of having a sleep disorder and being pregnant all too well. "While I was pregnant, I was sleeping 10 or 11 hours a night and took a couple of two-hour naps in the afternoon," she says. "It was exhausting."

Narcolepsy is a chronic neurological sleep disorder. It is characterized by excessive daytime sleepiness, often accompanied by cataplexy, a sudden loss of muscle control in response to strong emotional reactions that often cause the body to collapse suddenly during waking hours. Other symptoms of narcolepsy include sleep paralysis (difficulties that occur when falling asleep such as being unable to speak or move for a brief period), and hypnagogic hallucinations (vivid and often scary dreams).

Narcolepsy must be treated with medication; however it is the symptoms of narcolepsy that are treated, not the disease itself. "People with narcolepsy are commonly prescribed stimulants such as Provigil®, Ritalin®, or Dexedrine&reg to treat daytime sleepiness," says Emmanuel Mignot, MD, PhD, director of the Stanford Center for Narcolepsy. "Anti-depressants such as Effexor XR® and Zoloft&reg are often prescribed to treat cataplexy. The newly approved Xyrem® treats both cataplexy and can help relieve daytime sleepiness."

Since the long-term effects of these drugs on a developing fetus are unknown, Mignot says that he always advises his patients that it is better to stop taking their medication. For many women with narcolepsy an extended time without medication, which can begin with the decision to become pregnant and last until birth, can be quite miserable. This can lead to very difficult choices. "The decision to go off medication is obviously a very personal one," explains Michelle Hemingway, who has narcolepsy and is in her first trimester of pregnancy. After weighing the risks,

Hemingway is off her medication. "I've decided that if I have to be housebound for nine months, then so be it. I don't want to have cataplexy while I'm out running errands," she adds. "I'm not taking any chances, for the baby or myself."

Joyce Walsleben, PhD, director of the Sleep Disorders Center at the NYU School of Medicine and author of *A Woman'sGuide to Sleep*, notes: "Before conception, women with narcolepsy need to first talk with their physician and evaluate their individual situation. A woman with narcolepsy needs to consider the health of the baby as well as her own health and safety."

There are risks associated with going off narcolepsy medication, though the degree of risk may vary by drug. The most serious effects are felt when the cataplexy treating anti-depressants are not taken. "To abruptly stop taking anti-depressants can lead to a very bad cataplexy rebound," says Dr. Mignot. "Going off short acting stimulants like Dexedrine® also causes rebound sleepiness. However, when Xyrem® and Provigil® are stopped, the change is less dramatic. The best thing to do is gradually come off medication," he advises.

Dugan's narcolepsy is treated with Dexedrine® for alertness and imipramine for cataplexy. Due to the seriousness of her condition, she was unable to completely stop taking the Dexedrine®, although the dosage was dramatically reduced. She did stop taking the imipramine. "As a result, I couldn't do my job as a systems engineer," she said. "I couldn't even drive or go to the grocery store by myself. When you are pregnant and have narcolepsy you will have to make sacrifices, like surrendering some independence."

There are resources available for narcolepsy and pregnancy. Bob Cloud, executive director of the Narcolepsy Network, notes that their Web site, www.narcolepsynetwork.org, has a "Medications and Pregnancy" question and answer board. He also recommends the section titled "Investigating your local support groups."

Dugan offers the following advice, "It's important that you also work closely with your doctors, your OB/GYN and sleep specialist. Do your research and consider your best course of action." "I urge anyone with narcolepsy who is considering motherhood to make sure that you have a support network in place," says Dugan. "Work with your family, friends, and neighbors. Educate them! Teach them what narcolepsy is and give them the signs to recognize when you need help." As Dr. Walsleben says in her book: "Don't ask for help, demand it!" "To be a mother, especially a narcoleptic mother, is a calling— a profession—for the brave of heart," adds Dugan. "The journey of living and sacrificing for your child is a gift from God to parents, which teaches us what life is really all about, and what makes life so full and meaningful. My children warm my heart. Narcolepsy teaches us to look at the things we can do, rather than what we cannot."

Narcolepsy and the ADA: Lessons Learned

By Robert L. Cloud, Attorney, Executive Director, Narcolepsy Network

Is Narcolepsy a Disability?

A simple question, but the answer can be complex. It will depend on how a particular law defines disability, the severity of one's symptoms and evidence that can be submitted. Under the Americans With Disabilities Act (ADA), the answer can vary with one's type of work, company size, an employer's knowledge, and with developing case law.

The ADA (42 United States Code 12101) became law in 1990. The purpose is to prohibit companies (with at least 15 employees) from discriminating on the basis of disability. Its key provision requires employers to make reasonable accommodations to the known physical or mental limitations of an otherwise qualified employee with a disability, unless the accommodation would impose an undue hardship on the business.

Now let's look at some important definitions under the ADA:

- A Qualified Individual with a Disability **is one who has the required skills, experiences, and education and who, with or without reasonable accommodation, can perform the essential functions of the job.**

- A Disability **is a physical or mental impairment that substantially limits one or more major life activities.**
- A Physical Impairment **includes any physiological disorder, condition or disfigurement.**
- Major Life Activities **include performing manual tasks, walking, seeing, hearing, learning, sitting, climbing, reaching, and working, and basic activities that the average person in the general population can perform with little or no difficulty, and which may affect fundamental job duties.**
- A Reasonable Accommodation **is one that does not cause undue hardship, which an employer can make to the application process, customary work procedures, or job environment in order to provide an opportunity for a qualified individual with a disability to perform the essential functions of a job.**
- An Undue Hardship **would include accommodations that are so costly, extensive, substantial or disruptive as to fundamentally change the nature or operation of a business.**

One might ask, why aren't sleep and/or maintaining wakefulness included as major life activities under the ADA?

Perhaps because they are so basic to life that they are presumed to qualify as "major life activities." Or perhaps they aren't included because the law was drafted 13 years ago, before fundamental research this past decade regarding sleep, sleep disorders, and narcolepsy.

Narcolepsy Network, Inc. is a national nonprofit patient organization. Our mission includes support and advocacy on behalf of our members. We often send written and audiovisual materials to a member who wishes to further educate his/her employer. (These often include NSF publications regarding narcolepsy.)

The purpose and spirit of the ADA appear to be of much greater benefit than the enforcement remedies to employed persons with narcolepsy. Most employers, like the general public, are unaware of narcolepsy. And many, upon learning of it, are willing to attempt reasonable and sometimes creative accommodations, particularly for a valued employee.

Such accommodations might include allowing space and/or time for brief naps, changes to work hours or shift requirements, modification of job duties, implementing a more wake promoting environment, or even allowing more work at home. On the other hand, some jobs, by their nature, are more difficult to save for one with less controlled narcolepsy. These include jobs requiring extensive or commercial driving, operating heavy machinery, and others.

Narcolepsy

Although people with the disorder do not fall face-first into their soup as in the movies, narcolepsy is still a mysterious disease. But science has new leads

by Jerome M. Siegel

After hearing the punch line of the joke, the teenager falls to the floor, almost as if actually punched. She remains there, completely unable to move. She hears her parents reassure her friends that they need not worry about her because she will be all right in a few minutes. She is embarrassed and frustrated as the episode continues, and her friends begin to leave. They bid her goodbye, but she is unable to respond. Although she cannot talk or move, she is otherwise in a state of high alertness, feeling, hearing and remembering everything that is going on around her. The episode lasts for five minutes, longer than her typical cataplexies--which often last only seconds--but shorter than her longest episode, which lasted 25 minutes. Then it ends, almost as abruptly as it began. She gets up from the floor, and her everyday life resumes.

Cataplexy, the loss of skeletal muscle tone without loss of consciousness, is one of the defining symptoms of a puzzling neurological disorder called narcolepsy. The cataplectic attacks of narcolepsy are frequently prompted by laughter; other times, embarrassment, social interactions with strangers, sudden anger, athletic exertion or sexual intercourse may trigger an episode.

Another characteristic symptom of narcolepsy--and usually the most incapacitating one--is persistent daytime sleepiness. If you have ever gone without sleep for 48 hours, you have experienced the sleepiness that a narcoleptic lives with every day. In spite of being so sleepy, they tend to sleep poorly at night. And although they feel refreshed after a short nap, the sleepiness soon returns. As a result, narcoleptics fall asleep at dangerous or inappropriate times, as illustrated by the cartoon above. Untreated, they are therefore at high risk for motor vehicle accidents and often have trouble reaching their potential in school and the workplace.

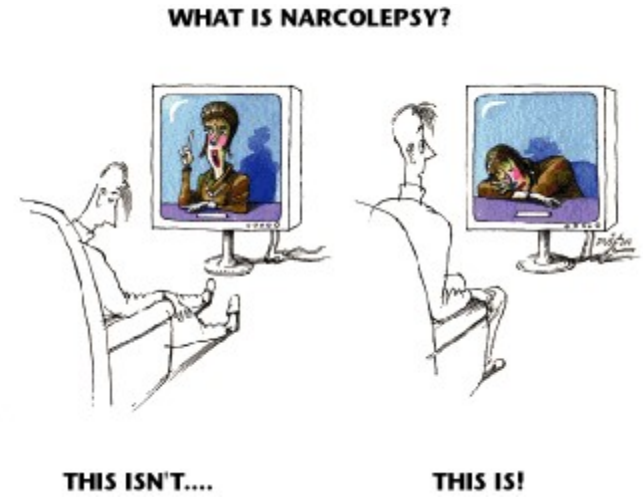

Image: Dusan Petricic, after a cartoon from the American Narcolepsy Association

OVERWHELMING SLEEPINESS **is a symptom that best characterizes narcolepsy.**

Within the past several years, researchers have begun to unravel the mysteries of this debilitating--but surprisingly common--disease.

My colleagues and I have identified the specific regions of the brain that appear to be affected in cataplexy and have discovered that they are the same regions that normally prevent us from moving in synchrony with our dreams (for example, thrashing our legs when we dream we are in a race). We have also found the first evidence of neuronal degeneration in narcolepsy. Other scientists have isolated a gene that when mutated can cause narcolepsy in dogs. Perhaps most intriguingly, there are hints that narcolepsy might be an autoimmune disease, in which the immune system attacks normal brain tissue as foreign.

This disorder has a number of extraordinary features. Besides cataplexy and sleepiness, two other classic symptoms are sleep paralysis and so-called hypnagogic hallucinations. Sleep paralysis is an inability to move when falling asleep or awakening. Although normal individuals may have short periods of sleep paralysis a few times in their lives, it is a daily occurrence for many narcoleptics. Hypnagogic hallucinations are dreamlike experiences during waking that often incorporate elements of the environment. They usually occur when narcoleptics are most sleepy. Not every patient suffers in exactly the same way, however. For instance, the severity of cataplexy and sleepiness varies among individuals.

Narcolepsy is also surprising in its wide range of incidence. It affects between one in 1,000 and one in 2,000 people in the U.S. Rates in other countries range from one in 600 in Japan to one in 500,000 in Israel. Genetic factors linked to ethnicity or possibly environmental conditions may be responsible for this variation. The overall incidence of narcolepsy in the U.S. is about 10 times that of amyotrophic lateral sclerosis (Lou Gehrig's disease), half that of multiple sclerosis, five times that of cystic fibrosis and about one quarter that of Parkinson's disease. The first signs of narcolepsy typically begin in the teens or 20s. Symptoms worsen for a few years and then plateau.

Sleep and Narcolepsy

Narcolepsy is linked to a disruption of the sleep control mechanism. The sleep cycle normally consists of two primary phases: so-called rapid eye movement (REM) sleep and non-REM sleep.

Non-REM sleep is a quiet sleep state. The muscles are relaxed but maintain some tone, breathing is regular, the cerebral cortex generates high-voltage waves, and consumption of energy by the brain is minimal. Although REM sleep shares the loss of consciousness of the environment seen in non-REM sleep, it is physiologically quite different. Breathing and heart rate are irregular; characteristic rapid eye movements occur; the cortex generates fast, irregular, low-voltage waves similar to those present in alert waking; vivid dreams take place; and brain metabolism often exceeds levels seen when the subject is awake. Tone in the postural muscles, such as those in the back and legs, is absent during REM sleep, although twitches occasionally break through the motor quiescence.

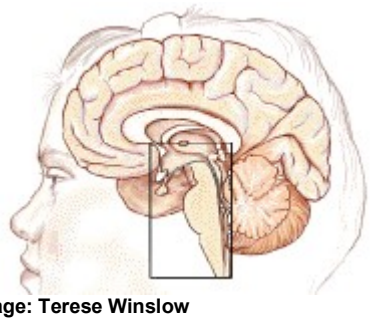

Image: Terese Winslow

THE NEURAL CIRCUITRY OF NARCOLEPSY

People who are not narcoleptic begin their nighttime rest with non-REM sleep, with REM sleep following roughly 90 minutes later. But narcoleptics frequently go straight into REM sleep. Because of this trait--and because narcoleptics experience loss of muscle tone and dreamlike hallucinations that normally occur only during REM sleep--researchers have hypothesized that these symptoms of narcolepsy result from the inappropriate triggering of some aspects of REM sleep.

Although sleep problems are the most common symptoms of narcolepsy, much of the basic research on the disease has used cataplexy as a starting point. Sleepiness is a normal phenomenon; it is the amount of sleepiness that is abnormal in narcolepsy. Therefore, it is difficult to know if particular episodes of sleepiness seen in narcoleptics are abnormal. Cataplexy, however, never occurs in normal individuals. It is easily quantified and has an abrupt onset that allows scientists to determine the time course of the neural events that trigger it. By observing and manipulating cataplexy, we hope to gain a clear insight into the pathology of narcolepsy.

Narcoleptic Dogs

A major advance in narcolepsy research occurred in the early 1970s, when investigators observed that some dogs display symptoms very similar to those of human narcoleptics. William C. Dement of Stanford University was given a litter of Doberman pinschers (and later a litter of Labrador retrievers), all of which were narcoleptic. The disease was transmitted as a recessive trait, which means that a particular dog developed the disease only if it inherited the trait from both its mother and its father. Accordingly, when Dement bred two narcoleptic dogs, all the offspring were narcoleptic. The dogs experienced cataplexy during vigorous play or when they were excited by being offered their favorite foods. My colleagues and I have conducted electrophysiological studies on such dogs to try to elucidate the causes of the strange symptoms of narcolepsy. We use tiny electrodes to record the electrical impulses from nerve cells, or neurons, in the brain stem as they communicate with cells in other areas of the brain and spinal cord.

We began our studies with recordings from the brain stem because of experiments conducted in the 1940s by Horace W. Magoun of Northwestern University. Magoun discovered that when he electrically stimulated the medial medulla (a part of the brain stem), muscle tone vanished, almost as if he had thrown a switch for preventing movement. At the time of this discovery, the polio epidemic was sweeping the U.S. Magoun hypothesized that damage to the medulla could be responsible for some of the increases in muscle tone seen in the acute phase of polio and could also be responsible for increased tone seen in other neurological diseases.

Magoun did not connect his observation to sleep, because his finding was made before the 1953 discovery of REM sleep and the subsequent discovery of its associated muscle paralysis. Studies in animals now suggest that although the main function of the muscle-tone control system in the medulla is in suppressing muscle activity in REM sleep, it also has a role in regulating the general level of muscle tone in waking. This region is inactive when animals are moving, moderately active when animals sit or lie down, further activated during non-REM sleep and maximally active in REM sleep.

When you try to relax or "turn off" your muscles, you are actually trying to "turn on" this brain region.

Based on Magoun's findings, we wondered whether unusual activity in the medial medulla might be responsible for the cataplectic episodes experienced by narcoleptics. In 1991 we found that this was indeed the case: neurons in this region fired when narcoleptic dogs had a cataplectic attack. What is more, we observed that in normal animals, cells in this part of the medial medulla fired at high rates only when the animals were in REM sleep. Our discovery made sense because we knew from other studies that REM sleep is the only time when normal individuals lose all muscle tone.

Extending this line of research, Elizabeth Schenkel in my laboratory demonstrated that otherwise normal animals whose medial medullas were damaged moved around during REM sleep, instead of being completely relaxed. Other studies by Michel Jouvet of Claude Bernard University in Lyon, France, and Adrian R. Morrison of the University of Pennsylvania had shown that damage to higher levels of the brain stem that connect with the medulla produced animals that raised their heads, walked and appeared to attack imaginary adversaries during REM sleep. For some reason, in narcolepsy a group of neurons that is supposed to be active only during REM sleep to suppress muscle tone and protect us from the elaborate motor programs that accompany our dreams is being triggered during waking [see box].

Another series of studies carried out in my laboratory by Frank Wu indicates that a second group of nerve cells in an area of the brain stem called the locus coeruleus also plays a role in REM sleep and narcolepsy. These cells release norepinephrine, a molecule called a neurotransmitter that neurons use to communicate with one another. When norepinephrine is secreted into the bloodstream, it participates in the body's "fight-or-flight" response during emergencies. Norepinephrine-producing neurons in the locus coeruleus have been shown in normal animals to be active throughout waking but to be inactive when the animals are in REM sleep. Our experiments in narcoleptic dogs indicate that cells in the locus coeruleus become completely inactive before and during cataplexy, just as they do during REM sleep.

The cessation of activity in norepinephrine-containing cells removes a source of excitation from motor neurons just as the parallel system in the medulla responsible for inhibiting motor neurons becomes active. The loss of excitation and concurrent increase of inhibition together are responsible for greatly reducing the activity and excitability of motor neurons. When motor neurons cease discharging, the muscles that they control relax. In REM sleep the reduction of motor neuron excitability prevents them from responding to the motor signals that accompany dreams. In cataplexy the same reduction in excitability prevents the motor neurons from responding to a narcoleptic's attempts to move.

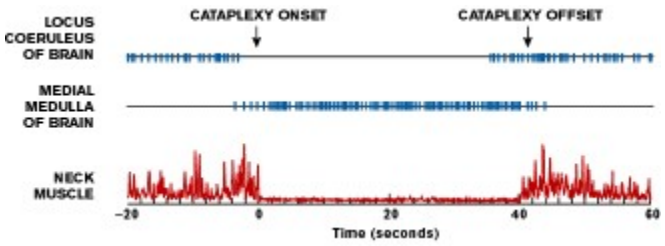

Image: Laurie Grace

ELECTRICAL RECORDINGS **taken from the brain and neck muscles of a dog with narcolepsy show that cells in the locus coeruleus are inactive during the muscle paralysis of a cataplexy attack, whereas those in the medial medulla are active. The brain recordings (blue) were obtained using tiny electrodes; the muscle ones (red), with an electromyograph.**

Recording the activity of neurons in narcoleptic dogs has given us an insight into how cataplexy is triggered. But why do these inhibitory events occur during waking in narcoleptics? Why are they not confined to REM sleep, as in healthy individuals?

There are no clear answers to these questions, but two genetic studies have recently yielded clues that might help solve the mystery. Emmanuel Mignot of Stanford and his co-workers have identified the gene responsible for narcolepsy in dogs. His research group has determined that the dogs carry a mutation in the receptor for a neurotransmitter variously called hypocretin or orexin.

Neurotransmitter receptors sit on the surfaces of neurons like molecular locks. When a neurotransmitter "key" binds to its receptor, it sets off a chain reaction of chemical processes within the receiving cell that prompts the cell to take some action, such as sending its own neurotransmitter signal to a third cell. Mignot's group found that the mutation harbored by the narcoleptic dogs produces hypocretin/orexin receptors that are missing a critical part, so that they cannot respond normally to the messages they receive.

In a complementary study, researchers led by Masashi Yanagisawa of the Howard Hughes Medical Institute at the University of Texas Southwest Medical Center in Dallas have generated mice whose neurons cannot send the hypocretin/ orexin message in the first place. They have observed that such mice also have some symptoms of narcolepsy, including REM sleep at sleep onset.

Hypocretin/orexin is made only in a region deep in the brain called the hypothalamus, which besides regulating body weight also controls water balance, pituitary functions, body temperature and many other processes. Hypocretin/orexin producing neurons in the hypothalamus connect to other brain

neurons that produce arousal, such as to the forebrain and brain-stem neurons that release acetylcholine and to other neurons that release histamine and serotonin. They are also linked up to brain-stem neurons, such as those in the locus coeruleus, that play an important role in the control of muscle tone.

Mutations that affect the hypocretin/orexin system might be responsible for some cases of narcolepsy in humans, but it is unlikely that most human narcoleptics have mutations in the genes responsible for synthesizing hypocretin/ orexin or its receptor. Most narcoleptics have no narcoleptic relatives, and the disease does not arise until the second or third decade of life. In addition, in 75 percent of cases in which narcolepsy occurs in an identical twin, the other twin is unaffected. These findings indicate that environmental conditions are important in human narcolepsy. These environmental conditions may cause damage to the hypocretin/orexin system, mimicking the symptoms caused by mutations, or may prompt damage to closely linked systems of neurons.

An Autoimmune Disease?

Some scientists have proposed that narcolepsy arises when unknown agents in the environment spur an autoimmune reaction that winds up damaging neurons in the brain circuits that control arousal and muscle tone. In 1984 Yutaka Honda and his colleagues at Seiwa Hospital in Tokyo found that all members of a group of 135 Japanese narcoleptics had one aspect of their tissue type in common, which meant their immune systems used the same molecule, one of the human leukocyte antigens (HLAs), to tell friend from foe. The molecule the narcoleptics shared was found in approximately 35 percent of nonnarcoleptic Japanese. Whereas the HLA type was clearly not sufficient to induce narcolepsy, Honda's finding indicated that HLA type greatly affected susceptibility to the disease.

HLA molecules are pitchfork-shaped structures that cells of the body use to show pieces of the proteins they contain to the immune system. Cells of the immune system ordinarily attack foreign substances and cells infected by viruses, which hijack cells into making viral proteins instead of normal ones.

Someone's HLA type is often referred to as their tissue type because people with the same HLA profile can receive tissue or organ transplants from one another. Certain autoimmune diseases tend to afflict those with particular HLA types, most likely because those HLA types when linked to particular antigens may look like naturally occurring proteins in the body, thereby causing the immune system to become confused and to damage normal cells.

The obvious next step will be to determine whether the immune systems of narcoleptics are mistakenly targeting the hypocretin/orexin receptors in their own brains as foreign. Because the body would continue to regenerate the receptors, such an autoimmune response would be expected to continue for the duration of the disease, but no such response has yet been detected in people with narcolepsy.

In another scenario the autoimmune response might be destroying the neurons or the parts of neurons that bear the hypocretin/orexin receptors, so that the autoimmune response would cease. Alternatively, the deficit in human narcolepsy could occur farther along the neuronal circuits regulating sleep than those cells involved in the hypocretin/orexin system. Autoimmune damage to neurons or receptors in the locus coeruleus or in other sleep-related regions of the brain might produce the syndrome even though the hypocretin/orexin neurons and their receptors were functioning normally.

Evidence for an autoimmune cause of narcolepsy will most likely come from studies of the brains of people who had the disorder. Ever since French physician Jean Baptiste Edouard Gélineau named narcolepsy as a distinct syndrome in 1880, researchers have examined the brains of patients in a futile search for neurological damage that could explain the symptoms of the disease. In a series of studies in the 1980s and 1990s, Mignot, Dement and their Stanford colleagues Ted L. Baker and Thomas S.

Kilduff observed that the brains of narcoleptic dogs had more than the usual number of receptors for the neurotransmitters acetylcholine, dopamine and norepinephrine and higher levels of some of the neurotransmitters themselves.

In the early 1990s Michael S. Aldrich of the University of Michigan noted similar changes in the brains of human narcoleptics. Such alterations in neurotransmitter and receptor levels, however, can result from behavioral changes--including sleep disturbances--so it has been unclear if they are the cause or the result of the disease.

My colleagues and I considered this issue and wondered whether pathologists had failed to find consistent evidence for brain damage in narcoleptics because they had been looking at the wrong time in the disease process. Narcolepsy is a chronic disease but not a progressive one. After symptoms are fully established, narcoleptics do not get progressively worse or markedly better. This suggests that the damage might occur during a short time, roughly during the period in which a patient first develops signs of the illness. Debris left over from degenerative processes that occurred at the age of 20 would be removed by the brain's support cells long before most patients died, and any remaining clues would be obscured by the normal degeneration of aging. A loss of neurons would be undetectable unless the dead cells were concentrated in a particular area, as in Parkinson's disease, or unless many, many neurons died, as in Alzheimer's disease.

Accordingly, my co-workers and I examined the brains of narcoleptic dogs shortly after their symptoms had begun.

Using a stain that detects damaged neurons, we found clear evidence that neurons in certain areas of the dogs' brains were degenerating between one and two months of age--just before and during the onset of symptoms. Evidence of the degeneration largely disappeared by the time the dogs were six months old.

The degeneration in the dogs was most pronounced in the amygdala, a brain structure known to be involved in emotion and in inducing sleep, and adjacent regions at the bottom of the forebrain. Remarkably, although the brain stem mediates some of the symptoms of narcolepsy, it showed no clear signs of degeneration. We hypothesize that damage to the amygdala and adjacent forebrain areas can cause the motor symptoms of narcolepsy by inappropriately activating brain-stem circuits that are undamaged, just as a properly functioning car can run out of control if the person inside steps on the accelerator at the wrong time.

As usual in science, our findings answered one question but generated even more. What causes the damage we observed in the amygdala and other forebrain regions in the young dogs? Is it the result of an autoimmune process, as suggested by the human study? Does the abnormality in the hypocretin/orexin receptor trigger the damage? Is it possible to prevent or even reverse the damage?

Until we can find answers, all we can offer people with narcolepsy are drugs to control their symptoms. We can counteract some of the sleepiness experienced by narcoleptics using stimulants such as Ritalin and Cylert or amphetamines, which activate dopamine receptors to increase the overall level of arousal. Another drug, Provigil, whose mechanism of action is not clear, may act by stimulating hypocretin/orexin neurons and other neural populations in the hypothalamus that in turn activate brain arousal systems. The downside is that such drugs are effective only for short periods and can cause unpleasant side effects, such as agitation, dry mouth and anxiety.

To prevent the cataplectic attacks of narcolepsy, physicians can prescribe agents that increase the availability of norepinephrine in the brain. These include monoamine oxidase inhibitors--which block

the enzyme that destroys norepinephrine after it is released by neurons--and drugs such as Prozac, whose breakdown products activate norepinephrine receptors. Gamma hydroxybutyrate (GHB), whose mode of action is unclear, can also be effective against cataplexy. Our newfound understanding of the processes underlying narcolepsy gives us reason to hope that new treatments that restore the imbalance in the hypocretin/orexin, norepinephrine and other neurotransmitter systems that control the sleep-wake cycle will improve treatment of this disease. We are entering a promising era in narcolepsy research.

A Review With Emphasis on Narcolepsy-related Excessive Daytime Sleepiness and Cataplexy.

Narcolepsy is a chronic and substantially disabling medical condition characterized by overwhelming daytime sleepiness. It is difficult to put together an all-inclusive definition of narcolepsy due to its protean and evolving clinical presentation. The disorder can be difficult to recognize and treat, especially if the physician involved in the case is not updated on the appropriate diagnostic and therapeutic steps to reach optimal control of this condition. Narcoleptics endure the daunting challenge of living with their condition in the setting of insufficient resources and lack of understanding from the lay community.

Recent developments in the field of sleep medicine make it imperative to produce updated guidelines for the diagnosis and treatment of narcolepsy. The goal of this article is to provide practicing physicians with a brief overview of narcolepsy and an updated review of its pharmacotherapy.

CLINICAL PICTURE

In 1880, Dr Jean-Baptiste-Edouard Gelineau[1] published the first case of a rare, sudden, and undeniable urge to sleep. Gelineau named this condition “narcolepsy.”

The patient with narcolepsy is caught in a vicious cycle of overwhelming sleepiness perpetuated by a disrupted nocturnal sleep architecture that is not conducive to restful sleep. Daytime functioning is severely affected by sleepiness, and this is further complicated by intrusion of rapid eye movement (REM) sleep phenomena in the awake state, making the patient literally “trapped in a land of bad dreams.”

The classic tetrad of narcolepsy symptoms includes:

1. Excessive daytime sleepiness (EDS).
2. Cataplexy: a sudden, partial, or complete loss of voluntary muscle tone in response to strong emotion.
3. Sleep paralysis during the transition from wakefulness to sleep or vice versa.
4. Hypnagogic or hypnopompic hallucinations: hallucinations occurring during the transition from wakefulness to sleep (hypnagogic) or from sleep to wakefulness (hypnopompic).

However, about 30% to 50% of patients with narcolepsy do not have all the above-mentioned symptoms at presentation. Patients can show nocturnal sleep disruption, insomnia, nightmares, REM behavior disorder, periodic limb movements during sleep, and automatic (“absent-minded”) behavior. Narcolepsy may present in a variety of forms or syndromes that include:

1. Narcolepsy with cataplexy.
2. Narcolepsy without cataplexy.
3. Familial narcolepsy.
4. Human leukocyte antigen (HLA) narcolepsy with normal cerebrospinal fluid (CSF)

hypocretin-1.
5. Symptomatic narcolepsy.
6. Psychogenic narcolepsy.

EPIDEMIOLOGY

According to The International Classification of Sleep Disorders. Diagnostic & Coding Manual,[2] narcolepsy with cataplexy affects 0.02% of the populations of the United States and Western Europe. Both sexes are affected with a slight preponderance of males. Cases of narcolepsy without cataplexy are seen in 10% to 50% of the narcoleptic population.

DIAGNOSTIC TESTS

Careful documentation of clinical information from the patient and the patient's close contacts, along with an array of diagnostic tests, will increase the chance of a correct diagnosis and minimize the risk of treatment mismanagement.[3]

The following three tests are used in diagnosis:

1. Nocturnal polysomnogram (PSG)[4] with a minimum of 6 hours of uneventful sleep, followed by a **multiple sleep latency test** (MSLT)[5] where the mean sleep latency is £ 8 minutes and the sleep onset REM periods (SOREMPs) are ≥ 2. The PSG should be preceded by a 2-week sleep log (and/or actigraphy) to avoid running the test in the setting of sleep deprivation. This log will also help in establishing the right timing of PSG lights on/lights off. The standard four two five MSLT nap opportunities should begin 1.5 to 3 hours after the final wake-up from the PSG.

2. A CSF hypocretin-1 test with a £ 110 pg/mL or a third of mean normal control values.[6] Only a limited number of centers in the United States can test this marker locally; one of them is the Center for Narcolepsy at the Stanford University School of Medicine in California (www.med.stanford.eduschool/Psychiatry/narcolepsy/).

3. A genetic test for the HLA subtype DQB1*0602, which is the HLA subtype most specifically associated with narcolepsy. However, this HLA subtype can also be found in 12% to 38% of the general population. Typing of HLA is at best useful to exclude the diagnosis of narcolepsy in very selected cases or when a secondary etiology is suspected.[2]

NARCOLEPSY THERAPY

Narcolepsy diagnosis and therapy are truly a blend of science, art, and compassion. Therapy must be comprehensive and should not be limited only to the pharmacologic approach. On the contrary, a number of other issues must also be addressed to successfully treat or prevent the devastating consequences of narcolepsy.[7-9] Supporting the patient's emotional, familial, and social dimensions, and advocating for medical insurance and occupational issues, should be part of the treatment plan. Physicians should encourage their patients to be actively involved in their own disease management, and both physicians and patients should be proactive in engaging in legislation initiatives and community awareness about narcolepsy.

Some medications for narcolepsy-related excessive daytime sleepiness

NARCOLEPSY PHARMACOTHERAPY

The latest published American Academy of Sleep Medicine (AASM) guidelines for the treatment of narcolepsy date back to 2001.[10] Since then, significant advances have been accomplished, and an

updated consensus on the pharmacotherapy recommendations should be expected in the near future. A number of excellent reviews[11-15] and editorials[16] on the topic have been published over the last few years by experts in the United States and abroad. With the current developments in the field, no narcolepsy patient should be left treated with suboptimal regimens. It is also imperative to conduct adequately powered head-to-head clinical and cost-effectiveness studies comparing different wake-promoting medications to determine which agent(s) has the best safety and efficacy profile for narcolepsy symptoms.[17] The "superior" psychostimulant should effectively promote wakefulness, have minimum impact on sleep, and show minimal tolerance, dependence, and withdrawal/rebound effect.

NARCOLEPSY-RELATED EDS RX

The treatment of EDS uses psychostimulants, which are drugs that produce a behavioral activation that is accompanied by an increase in arousal, motor activity, and alertness. They can be regarded as sympathomimetic (amphetamine, methylphenidate, dextroamphetamine, selegiline, pemoline) and non-sympathomimetic drugs (caffeine, modafinil).

Traditional sympathomimetic psychostimulants were for a long time the mainstay of therapy for narcolepsy-related EDS, even though there have been only a few randomized placebo-controlled trials with these drugs. They improve EDS and sleep onset latency time. Sympathomimetic drugs enhance monoamine neurotransmission (dopamine, noradrenaline, and serotonin) by increasing release and inhibiting reuptake of these neurotransmitters. Methylphenidate[18] is the most frequently prescribed stimulant for narcolepsy in the United States, followed by dextroamphetamine (Disomer of amphetamine). Both have comparable effectiveness. Pemoline is a milder stimulant with a lower potency compared to the amphetamines. However, due to reported liver toxicity, it is now rarely used in clinical practice. Fortunately, the potential for abuse with sympathomimetic drugs is uncommon in patients with narcolepsy.

Caffeine is a natural alkaloid that acts as an adenosine receptor antagonist promoting wakefulness. There is evidence that activation of a subgroup of adenosine receptors causes an inhibition of cortical acetylcholine release, which may also contribute to promoting wakefulness. Caffeine is an inexpensive drug that may play a role in narcolepsy treatment, particularly in maintaining wakefulness between the daily dosing of other wakefulness promoters.[13] However, there is little scientific data on the effect of caffeine on narcolepsy-related EDS[19] as there have been no placebo-controlled trials of caffeine therapy in narcolepsy.

Modafinil (Provigil®) is an alertness-promoting agent of unclear mechanism of action. It is most likely involved in dopamine reuptake inhibition. Modafinil was approved by the Food and Drug Administration (FDA) in 1998, and has been shown to improve objective (MSLT and mean wakefulness test or MWT sleep onset latency) and subjective (Epworth Sleepiness Scale) measures of EDS in patients with narcolepsy.[20,21] Modafinil is less potent than traditional sympathomimetic stimulants in promoting alertness, but it does not have their numerous side effects.[22] Modafinil has no effect on cataplexy and has limited potential for abuse.[23] It is considered first-line treatment for narcolepsy-related EDS. However, there is no data yet comparing the efficacy of modafinil to sympathomimetic psychostimulants in human narcolepsy. If necessary, changing therapy from sympathomimetic drugs to modafinil is safe and feasible.[24]

Sodium oxybate (Xyrem®), the sodium salt of gamma-hydroxybutyrate, was first approved for treatment of cataplexy. However, it has also shown beneficial effects on EDS in narcolepsy patients, and received additional FDA approval for this indication in November 2005.[25,26] Further evidence of effectiveness in EDS has been recently published or is about to be published.[27,28] Due to its potential for diversion and abuse, a centralized pharmacy (The Xyrem Success Program)[29] distributes and monitors the medication. The program can be contacted at (866) 997-3688 or accessed through www.xyrem.com. It supplies physicians who prescribe sodium oxybate with educational materials and enrolls them into a registry. Specialized prescription forms are then provided, and, upon approval, the patient is contacted for delivery of the medication and counseling.

If treatment of EDS with modafinil or sodium oxybate alone is unsatisfactory, combining both of them or supplementing with "as needed" or appropriately scheduled traditional sympathomimetic psychostimulants is generally effective.

Armodafinil (Nuvigil®), the longer half-life enantiomer of modafinil, received an "approvable letter" from the FDA on May 1, 2006. Actual approval is contingent upon finalizing the product label. It is formulated to be effective over a shorter period,[30] which should allow for multiple dosing during the day. Besides its effectiveness in treating EDS, preliminary data indicates that armodafinil does not affect intended sleep in narcoleptics and other patients with EDS.[31]

To date, there have been no head-to-head trials between sympathomimetic drugs, caffeine, modafinil, and sodium oxybate that look at the efficacy and long-term safety of these medications in narcolepsy.

NARCOLEPSY-RELATED CATAPLEXY RX

While narcolepsy-related EDS can be managed with stimulant drugs, these medications often do not provide significant relief from cataplexy. Consequently, additional drugs have to be used to reduce the frequency and severity of cataplexy. Drugs that increase aminergic signaling decrease cataplexy. Sodium oxybate is also effective in cataplexy by an unknown mechanism. The most frequently recommended anticataplectics include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), sodium oxybate, and non-selective serotonin reuptake inhibitors/non-tricyclic antidepressants (NSSRI/NTCAs).

TCAs potentiate the activity of endogenous amines by blocking their reuptake into presynaptic neurons. In addition, TCAs have varying degrees of anticholinergic activity, blocking primarily muscarinic acetylcholine receptors and causing familiar side effects such as dry mouth. They are generally active on cataplexy at doses at or below usual antidepressant dose range efficacy. Imipramine was the first reported TCA with anticataplectic activity.[32] Numerous case series but no double-blind studies have shown the effectiveness of protriptyline[33] and several other TCAs on cataplexy (desipramine, clomipramine, etc).

SSRIs enhance the effect of endogenous monoamines and catecholamines by blocking their uptake into presynaptic neurons, which terminates their activity. They are relatively more selective toward the serotoninergic transporter. These agents are generally effective on cataplexy, although higher doses were needed and effects less pronounced than with classic TCAs. However, fluoxetine[34] seems as effective in control of cataplexy as clomipramine, a TCA. Other SSRIs include paroxetine, fluvoxamine, etc.

Sodium oxybate is effective for controlling cataplexy[35] and received FDA approval for this indication in July 2002. Further studies confirmed this effectiveness,[36,37] but its mechanism of action is unknown. It may act through its own receptors and via stimulation of GABA-B receptors, with major effects on silencing dopaminergic neurons. It provides a slow and continuous improvement of cataplexy over long periods of time, and patience is required to obtain full efficacy. It has beneficial effects on insomnia, a major complaint in patients with narcolepsy, and has immediate beneficial effects on disturbed nocturnal sleep. Of note, contrary to antidepressant therapy for cataplexy, sodium oxybate interruption does not abruptly result in a rebound of cataplexy.

When used with antidepressants for cataplexy or with stimulants for EDS, it often leads to slowly reducing and occasionally stopping conventional therapy using those medications. Clinicians consider sodium oxybate as a first-line therapy for all narcolepsy patients.

Sodium oxybate is typically administered twice during the night, with the patient lying in bed both times because the drug causes immediate initiation of sleep. Patients take the first dose at the beginning of the night of sleep and the second 3 to 4 hours later when they awake either spontaneously or with the help of an alarm clock.

NSSRI/NTCAs are a group of drugs that proved effectiveness in the treatment of cataplexy. (See figure 2 on page 50.) Venlafaxine is an atypical antidepressant that blocks the reuptake of both norepinephrine and serotonin. It is effective decreasing frequency of cataplexy attacks at doses at or below the antidepressant effect,[16] especially when the extended release form is used. In another study, reboxetine decreased cataplexy frequency, improved sleepiness, and reduced sleep-onset REM periods (SOREMPs) in MSLT.[38] Other medications in this group include duloxetine, atomoxetine, and viloxazine.

SOME NOVEL THERAPIES

Immune-based therapy. New-onset narcolepsy with cataplexy in an 8-year-old boy failed to respond to immunosuppression with prednisone at 1 mg/kg/day for 3 weeks.[39] However, four patients with new-onset narcolepsy with cataplexy successfully received therapy with intravenous immunoglobulin at 1 mg/kg/day over 2 days, repeated three times at 4-week intervals (cataplexy resolved, but EDS did not show a clear improvement).[40]

Hypocretin cells transplantation. Though cell transplantation still yields disappointing results in several diseases,[41] it may someday provide a cure for narcolepsy.

SUMMARY

Narcolepsy is a chronic and potentially devastating medical condition, especially if unrecognized and undertreated. Recent advances in the field mandate that the physician keep up-to-date with new research and treatment developments. Likewise, an update on consensus guidelines for pharmacotherapy is needed. Narcolepsy patients deserve a comprehensive approach for their treatment that addresses the medical, psychological, and social issues involved (including family, school, workplace, insurance, and legislation aspects). Non-pharmacologic interventions should also play an important role in the treatment plan, including structured nocturnal sleep and daytime naps, avoidance

of irregular sleep-wake schedules, adequate diet and exercise, and driving caution for patients with EDS or cataplexy. Patients with narcolepsy should consider enrolling in the Narcolepsy Network Inc as a support and advocacy group.

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Narcolepsy

Introduction

Narcolepsy is a chronic neurological disorder that involves the body's central nervous system. People with narcolepsy experience sudden, overpowering attacks of sleepiness lasting from a few seconds to half an hour. They might suffer dozens or even hundreds of these attacks each day. This can happen at any time, and is often accompanied by a loss of muscle tone or partial paralysis, a condition called cataplexy that is triggered by the experience of a strong emotion, usually laughter or anger. These cataplexy episodes occur during the day, sometimes many times a day. Then, at night, people with narcolepsy may suffer from sleep paralysis, a condition of being unable to speak or move even though fully aware of external events.

For people with narcolepsy, the most important and debilitating effect of the disorder is that they are unbearably sleepy all the time. Their struggle to stay awake is relentless, and whenever they let down their guard, sleep immediately overcomes them. Even when they are on guard, they are often overtaken by sleep-in the middle of a sentence, while eating, or even during sex. Such unintended sleep "attacks" may last up to 10 or 20 minutes, and then victims wake up feeling somewhat refreshed. Soon afterward, they become sleepy again. The attacks may be triggered by excitement or other intense emotions.

It is nearly impossible for people with narcolepsy to lead normal lives. Relationships are often damaged irreversibly when patients fall asleep during a conversation--or even during sex. It is difficult for mates to understand that it is narcolepsy, a disease, not boredom, that causes their mate to fall asleep at emotionally charged moments. The sufferers find it very difficult to function socially. They often withdraw completely from active social life to minimize embarrassment.

Narcolepsy is a genetic disorder. The cause or causes of narcolepsy are unknown, but brain infection, head trauma, or brain tumors maybe behind some cases. It is known that narcolepsy is almost never the result of insomnia or sleep deprivation. Sleep lab studies show that narcolepsy results from a severe disturbance in the normal architecture of sleep. Specifically, people with narcolepsy go into the REM stage first, instead of at the end of a sleep cycle as in healthy people.

Narcolepsy affects both men and women of any age. It has been identified in children as young as three and has first emerged as late as 50 in a few adults. The peak time of onset is during adolescence.

Typically, the first symptoms of narcolepsy appear between the ages of 15 and 30. Often 10-15 years pass between the onset of symptoms and diagnosis.

It's particularly harmful when narcolepsy occurs in children and isn't recognized. Parents often mistake the behavior of a narcoleptic child as from being uncooperative, lazy, and liar.

According to the American Narcolepsy Association, 1 out of every 1000 Americans is afflicted with this disorder. Yet, between 50 and 80 percent of them remain undiagnosed.

Diagnosis/ Symptoms of Narcolepsy

Narcolepsy is characterized by:

- **Sleepiness or excessive daytime sleepiness that is often profound.**
- **Sleep on-set REM sleep**
- **Cataplexy**
- **Hypnagogic hallucinations or hypnopompic hallucinations**
- **Sleep paralysis**
- **Automatic behavior**
- **Disrupted nocturnal sleep**

Surveys on people with narcolepsy have found that they often suffer from:

- **Double vision**
- **Memory problems**
- **Balance disturbances**
- **Personality changes**
- **Getting involved in frequent rear-end automobile accidents.**

Symptoms most often first occur during adolescence or young adulthood; however, narcolepsy symptoms may also occur earlier in childhood or not until the third or fourth decade of life.

Hazards Of Narcolepsy

People who have narcolepsy but don't know it represent a serious safety hazard to themselves and others when they drive. They may doze off while waiting for a traffic signal to change, or they may drive to destination and be completely unable to recall how they got there. At least one in every 500 drivers is estimated to be suffering from narcolepsy. Many of them get involved in fatal traffic accidents.

Individuals with excessive daytime sleepiness are at a much greater risk than normal for motor vehicle accidents caused by falling asleep at the wheel. If you have narcolepsy, refrain from driving long distances. Stop driving immediately when sleepy.

Yet, narcolepsy is a major traffic safety problem with a low-cost and easy solution: proper diagnosis and medical care.

Diagnosed patients who understand their symptoms appear to be very safe drivers, and their driving can be coordinated with the use of medication. Some people can sense the imminent sleepiness.

Others don't. If you are able to adequately sense sleepiness, you can drive safely provided you immediately pull over and take a nap when sleepy or turn over the wheel to someone else.

Those who cannot predict or sense sleepiness or who are unwilling to avoid driving when sleepy should not drive. Persons with cataplexy can potentially experience cataplectic episodes while driving. They must refrain from driving until the cataplexy has been adequately medically treated.

Conventional Treatment of Narcolepsy

At present, there is no cure for narcolepsy. The focus of treatment is on treating the symptoms.

Narcolepsy is often treated by providing stimulants to counter patients' excessive daytime sleepiness. Cataplexy, hypnagogic hallucinations, and sleep paralysis are pure manifestations of REM sleep and must be treated with different medications. Most often antidepressants are used because they block REM paralysis (the source of cataplectic paralysis).

Drug therapy is often the first line of defense. However, drug therapy alone is not sufficient in most cases. Non-pharmacological strategies are used to complement drug therapy to develop an effective program to manage narcolepsy.

Sleepiness in Narcolepsy

Jed E. Black MD., Director, Stanford University Sleep Disorders and Research Clinic recommends the following treatment strategy for sleepiness in Narcolepsy:

1. Provide nonpharmacologic treatment education and begin modafinil. Start at 100 mg/day for 3 days. Titrate to 200-400 mg/day as required to reduce sleepiness. (Occasionally, higher doses may be useful.)

2a. If sleepiness is improved but still remains a problem, then add traditional stimulant (e.g., methylphenidate, dextroamphetamine) and adjust dose as required. Or switch to traditional stimulant and add modafinil if needed.

2b. If sleepiness is not improved after the modafilnil treatment, then switch to traditional stimulant and adjust dosage as needed.

Dr. Black recommends the following treatment strategy for cataplexy in Narcolepsy:

1. **Option 1**

Begin with low dose (25 mg) of one of the following:

- **protriptyline (Vivactil, Merck)**
- **clomipramine (Anafranil, Novartis)**
- **desipramine (or other Tri Cyclic Antidepressant)**

or venlafaxine extended- release (Effexor ER, Wyeth-Ayerst) 37.5 mg

Titrate as needed to adequately control symptoms.

Option 2

Try SSRI in antidepressant dose range (may require maximum doses)

OR Give nightly divided doses (at bedtime and 3-4 hours later) of sodium oxybate (GHB) starting with 3 g total dose and titrating to 9 g as needed. (FDA approval for this medication is pending.)

If cataplexy remains inadequately treated after any one of the options above, then he recommends a careful, combined treatment with a medication from 2 of the above classes.

Nonpharmacolegic Strategies

The non-pharmaceutical strategies for narcolepsy include:

Structured nocturnal sleep

Maintain a structured bedtime and arising time, despite the quality or continuity of the nocturnal sleep. If you wake up during the night, and find it difficult to go back to sleep, you can take a short break and do a sedentary activity such as reading for a brief time. But you should return to bed and attempt to sleep. The time scheduled for nocturnal sleep should be 8 hours or more.

Structured daytime naps

Daytime naps provide a critical part of treatment for the daytime sleepiness associated with narcolepsy. Naps may range from 15 to 20 minutes to longer than one hour. Many find a short nap (<30 minutes) refreshing, but others require longer naps. At least one nap, and usually two, proves very beneficial for almost all persons with narcolepsy.

Avoidance of irregular sleep-wake schedules

If you are suffering from narcolepsy, you should maintain regular sleep-wake schedules. Most narcoleptics will find shift work or changes in work schedule extremely difficult. Daytime work is strongly recommended.

Counseling or other assistance

A recent study of more than 500 narcoleptics revealed that they suffer decrease in quality-of-life measures similar to those experienced by patients with Parkinson's disease. Most victims of narcolepsy require special considerations at work or school. They should have access to marriage or family assistance/counseling, and some require full-time disability.

Medications Used in the Treatment of Narcolepsy

Alerting Agents

Anticataplectic Agents

Alerting Agents (wake-promoting therapeutics and stimulants)

Occasionally, patients prefer to avoid medications and to take extra naps during the day instead. This approach may not provide enough daytime alertness to people suffering from excessive sleepiness associated with narcolepsy function adequately. In these cases, medications classified as alerting agents provide substantial improvements in their daytime alertness. However, for most patients with narcolepsy, alerting agents will not yield a normal degree of daytime alertness. Optimal improvement usually requires scheduled naps.

Modafinil (Provigil, Cephalon)
Modafinil is a novel wake- promoting medication. It is comparable to traditional stimulants in promoting alertness, but without a number of negative side effects commonly associated with stimulant therapy. The effect may last longer. It is now considered first-line therapy for all newly diagnosed narcolepsy patients or for patients currently demonstrating inadequate response to, or bothersome side effects from, traditional stimulant therapy.

Modafinil is well tolerated, effective, and extensively studied in narcolepsy. It is often the first-line treatment for narcolepsy.

See Modafinil datasheet for information on dosage and side reactions

If treatment with modafinil alone is not sufficient, traditional stimulants are given with it.

Traditional stimulants

Commonly used traditional stimulants for narcolepsy include methylphenidate and dextroamphetamine. Other amphetamines, amphetamine-analog agents, and sustained-release preparations are available.

Many people experience negative effects with these stimulants. It also may exacerbate sleepiness (rebound hypersomnia) as the dose wears off. The patient may develop tolerance (tachyphylaxis) to the alerting effect with repeated dosing.

Amphetamines

Common Side effects are: headache, gastrointestinal disturbance, anxiety, irritability, increased pulse, increased blood pressure

Amphetamines are frequently used for narcolepsy and are generally very effective.

See drug information for amphetamines for information about dosage, side effects and warnings.

Methylphenidate

Side effects: headache, gastrointestinal disturbance, anxiety, irritability, increased pulse, increased blood pressure - The side effects are often characterized as not as prominent as in amphetamines.

Commonly used agent for narcolepsy, effective.

See drug information for methyphenidate for information about dosage, side effects and warnings.

Pemoline (Cylert. Abbott)

Pemoline in normal doses is less effective in improving daytime sleepiness than methylphenidate, dextroamphetamine, or methamphetamine. This medication also has the potential for hepatotoxicity. Because of these reasons, it is used only when modafinil or traditional stimulants cannot be used. If you use this, regular liver function evaluation is recommended.

Side effects: hepatotoxicity, amphetamine-Iike side effects are generally less pronounced.

This medication was previously used frequently in narcolepsy. But potential for hepatic failure renders pemoline a second- or third-line agent.

See drug information for pemoline for information about dosage, side effects and important safety warnings.

Mazindol

Dosage

Common initial dose - 1-2 mg once or twice daily
Usual maximal dose (carefully monitored higher doses may sometimes be required) - 8 mg in divided doses

Mazindol is generally considered less effective as a stimulant.

See drug information for Mazindol for information about dosage, side effects and important safety warnings.

Medications for Cataplexy (Anticataplectic Agents)

Medications useful in the treatment of cataplexy usually also improve hypnagogic/hypnopompic hallucinations and sleep paralysis. In general, tricyclic antidepressants (TCAs) are effective in ameliorating or eliminating symptoms of cataplexy. Dosage required is much less than that for depression. Disadvantage is the side effects.

Selective serotonin reuptake inhibitors (SSRIs) have also proven useful in treating cataplexy. Doses comparable to that required for depression are required. Also, SSRIs are not as effective as TCAs in some patients. SSRIs, however, may be better tolerated by some than TCAs.

Sodium oxybate (also known as gamma-hydroxybutyrate or GHB) had been used in Europe. It is now undergoing clinical trials in the US.

It appears to be an effective anticataplectic agent, even in individuals with inadequate responses to other agents. GHB is highly effective in reducing nocturnal sleep disruptions and consolidating nocturnal sleep. It also exhibits an alerting effect during the day.

See Gamma-Hydroxybutyrate (GHB) for more information

Antidepressants with central nervous system noradrenergic activity have been reported in individual cases to provide effective treatment for cataplexy. Venlafaxine extended-release (Effexor ER) has been found to be particularly effective for cataplexy by a number of clinicians.

Tricyclic antidepressants

Dosage

Common initial dose - 25 mg once or twice daily
Usual maximal dose - 150-300 mg divided (doses this high are rarely required)

Side effects: orthostatic hypotension, sedation, anticholinergic effects

TCAs are often more effective, but less tolerable than SSRls

See drug information for TCA for information about dosage, side effects and important safety warnings.

SSRI antidepressants

Dosage

Common initial dose - 20 mg (Prozac and Paxil), 50 mg (Zoloft), daily
Usual maximal dose
fluoxetine (Prozac) - 80 mg
paroxetine (Paxil)- 60 mg
sertraline (Zoloft)- 200 mg

Side effects: nausea, insomnia, anxiety, decreased appetite

SSRIs may be less effective than TCAs. But they are often better tolerated than TCAs.

More Info about side effects, interactions and safety concerns of Prozac, see: drug information for fluoxetine

More Info about side effects, interactions and safety concerns of Paxil, see: drug information for paroxetine

More Info about side effects, interactions and safety concerns of Zoloft, see: drug information for sertraline

Sodium oxybate (Xyrem, Orphan Medical)

Dosage

Common initial dose - 1.5g at HS and 3-4 h later
Usual maximal dose (carefully monitored higher doses may sometimes be required) - 4.5g at HS and 3-4 h later

Side effects: sedation, nausea, lightheadedness, dizziness

Remarks: usually well tolerated with time; improves nocturnal sleep disruption and can improve daytime sleepiness, FDA approval pending

Venlafaxine (Effexor XR, Wyeth Ayerst)

Dosage

Common initial dose - 37.5 mg once daily
Usual maximal dose - unknown, but maximum recommended dose for depression is 225 mg

Side effects: nausea, dizziness, sedation

Venlafaxine is not well studied in cataplexy, but clinical reports are promising. It is generally better tolerated than TCAs.

For more Info about side effects, interactions and safety concerns of Venlafaxine, see: drug information for venlafaxine

5-HTP

5-HTP (5-hydroxytryptophan) is a compound produced by the body from tryptophan. It is naturally found in many foods and most commonly extracted from the seeds of the Griffonia plant.

In Europe, 5-HTP has been used for decades as an approved treatment for depression, sleep problems, and other medical complaints. It is now starting to be used in the USA.

Clinical trials show that 5-HTP is a safe, natural way to boost the brain serotonin levels. Use of 5-HTP has been shown to produce results equal to or better than those of standard synthetic drugs used in the problems arising from serotonin deficiency syndrome.

Some evidence exists to suggest that taking 5- HTP may help some people with narcolepsy. In one study, a dose of 600 mg was found to have no effect on the number of sleep attacks. However, it reduced the amount of time narcoleptics spent asleep during a daytime attack. More importantly, it lengthened the amount of time they slept at night.

Narcolepsy Post Test

Select the best answer to each of the following items. Mark your responses on the Answer Form.

1. Narcolepsy is a sleep disorder characterized by uncontrollable sleepiness (also called excessive daytime sleepiness) and _____.

a. lack of energy
b. intermittent manifestations of REM sleep at times when a person would normally be awake

c. dizziness
d. All of the above

2. For patients suspected of having narcolepsy, an all-night polysomnogram is done primarily to ascertain the presence of _____ and is followed immediately by a multiple sleep latency test.

a. concurrent sleep disorders
b. narcolepsy
c. mental illness
d. All of the above

3. Successful treatment of narcolepsy requires an accurate diagnosis to exclude patients with other sleep disorders, which have different treatments, and to avoid unnecessary complications of drug treatment.

a. True
b. False

4. _____is (are) effective treatments for narcolepsy.

a. Modafinil
b. methamphetamine
c. dextroamphetamine
d. All of the above

5. Many health care providers are overly cautious in approaching treatment of narcolepsy, because stimulant medications, which are the mainstay of narcolepsy treatment, are _____.

a. expensive and not always covered by insurance
b. regulated by government agencies to prevent abuse
c. often misunderstood by the patient
d. All of the above

6. One of the first standards of care listed for narcolepsy states that "An accurate diagnosis of narcolepsy should be established which shall include a thorough evaluation of other possible contributing causes, apart from narcolepsy, to the excessive daytime sleepiness."

a. True
b. False

7. The treatment goal in the treatment of narcolepsy should be to produce the fullest possible return of normal function for patients at_____.

a. work
b. socially
c. home
d. All of the above

8. Human narcolepsy has been strongly associated with positive HLA-DR2 typing. The halotype found to be consistent across most ethnic groups is HLA DQB1*0602. This genotype occurs in 90% to 100% of Japanese and Caucasian patients with narcolepsy, while its occurrence is 12% in the Japanese general population and _____% in the Caucasian general population.

a. 8
b. 12
c. 22
d. 44

9. A new recommendation for treatment goals regarding narcolepsy is to control _____ when present and troublesome.

a. cataplexy
b. sleep paralysis
c. hypnagogic hallucinations
d. All of the above

10. The presence of _____ is the most specific clinical finding for narcolepsy; however, it may be poorly perceived by the patient and unrecognized by the physician or family members.

a. RLS
b. cataplexy
c. sleep apnea
d. None of the above

11. Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy.

a. True
b. False

12. In the treatment of narcolepsy patients, Follow-up is necessary to _____.

a. determine adherence and response to treatment
b. monitor for the safety of medications in individual patients
c. assist the patient with occupational and social problems
d. All of the above

13. Patients with severe sleepiness should be advised to avoid potentially dangerous activities at home and at work, and should not operate a motor vehicle until sleepiness is appropriately controlled by stimulant medications.

a. True
b. False

14. Patients who fail to respond to adequate doses of stimulant medication should be carefully assessed for other sleep disorders such as _____.
a. insufficient sleep
b. inadequate sleep hygiene
c. obstructive sleep apnea syndrome
d. All of the above

15. Cataplexy (to strike down in fear) is the abrupt loss of muscle tone precipitated by intense emotion; most commonly, laughter, but emotions such as _____ may also trigger cataplectic attacks.

a. anger
b. surprise
c. excitement
d. All of the above

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