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Approach to a Patient with Narcolepsy

Ravichand Madala, MD and Rodney A. Radtke, MD

Department of Neurology, Duke University Medical Center, USA

Introduction

Narcolepsy is one of the most common hypersomnias of central nervous system origin. Its primary symptom is that of excessive daytime sleepiness (EDS). The clinical tetrad of narcolepsy includes EDS, cataplexy, hypnogogic hallucinations, and sleep paralysis.[1] Fragmented nocturnal sleep is often part of the clinical syndrome as well. Sleepiness and cataplexy represent the primary sources of disability of this disorder. Treatment is focused on use of stimulants and other wake-promoting agents to promote alertness. Rapid eye movement (REM)-suppressant medications are used to suppress cataplexy and the other associated auxiliary symptoms of narcolepsy. The recent identification of the loss of hypothalamic hypocretin-containing neurons as the cause of most cases has opened up additional research endeavors to explore how treatment may be more specifically targeted to the underlying pathophysiology of the disorder.

Epidemiology

Narcolepsy is estimated to occur in 0.002–0.18% of the general population. The prevalence is higher in Japanese subjects (0.18%) and lowest in Israeli Jews and Arabs (0.002%).[2] The US prevalence is estimated as between 0.03% and 0.07%, with the condition estimated to occur in 1 in 2000 of Americans.[3] The male-to-female prevalence is equal. The symptoms usually appear in the teens and 20s but in many cases there is a 10-year period between onset and diagnosis. Approximately 50% of adults with the disorder retrospectively report symptoms beginning in their teenage years. Rare cases of onset have been reported in infants and in the elderly.

Clinical symptoms

Excessive sleepiness is often the first reported symptom, followed by cataplexy. Excessive daytime sleepiness alone or in combination with hypnogogic hallucinations and/or sleep paralysis is the presenting symptom in approximately 90% of patients. Using clinical criteria, corresponding to the criteria of the *International Classification of Sleep Disorders*,[1] only 10–15% of patients experience the full tetrad. Approximately 70% of patients have cataplexy, 30% have hypnogogic hallucinations, and 25% have sleep paralysis.[4]

Major symptoms

Excessive sleepiness

The excessive sleepiness seen in narcolepsy is usually characterized by repeated episodes of naps or lapses into sleep of short duration. The typical narcoleptic sleeps for 10–20 min and then awakens refreshed, but with the return of overwhelming sleepiness in the next few hours. Compared to other disorders of excessive sleepiness, the sleepiness is less continually present throughout the day, but episodically becomes overwhelming, leading to what are sometimes described as "sleep attacks." There is no increase in total sleep time per 24 hours, as can be seen in other hypersomnias, such as idiopathic hypersomnia. The excessive sleepiness in narcolepsy often interferes with daytime functioning and work performance. It may also interfere with memory, concentration, and cognitive abilities.

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Cataplexy

This is a sudden decrement in muscle tone leading to muscle weakness, paralysis, or postural collapse. These symptoms are variable in severity, and are often subtle, primarily affecting the knees or face (droopy face, slurring of speech). There is usually bilateral loss of muscle tone. Cataplexy is usually triggered by a sudden emotion such as laughter or anger. Other triggering emotions include embarrassment, sexual arousal, or startle. Some patients may report cataplexy to only specific idiosyncratic stimuli. Episodes generally last for seconds to minutes with a frequency ranging from daily to monthly. The loss of muscle tone is due to the intrusion of the atonia normally seen during REM sleep into wakefulness. The diaphragm and ocular muscles are unaffected. During the episode the patient is awake initially, but can fall asleep if it is a prolonged episode. The patient is aware of the surroundings and can remember details of the event, which differentiate this from other episodic disorders such as epileptic seizures. Cataplexy, when severe, may be the most disabling feature of narcolepsy due to falls and injuries. A rare complication of cataplexy is *status cataplecticus* in which repeated cataplectic attacks last for hours to days. It can occur spontaneously but usually is seen with abrupt discontinuation of REM-suppressant medications.

☆ TIPS AND TRICKS

During cataplexy, respiration and voluntary eye movements are not compromised. Consciousness is preserved during the episode. On examination, deep tendon reflexes are absent.

Hypnagogic hallucinations

These are vivid sensory images that occur during the transition from wakefulness to sleep. They are particularly vivid with sleep-onset REM periods. They can be visual, auditory, or tactile in nature. They are remarkably real in character, often perceived as threatening to the individual, and difficult for the individual to differentiate from reality. As such, the patient will often act on the hallucinatory content, e.g. run out of the house due to the perception that the house is on fire.

Sleep paralysis

Immobility of the body or inability to speak that occurs in the transition between sleep and wakefulness. Episodes of sleep paralysis are thought to be due to the intrusion of the muscle atonia of REM sleep into wakefulness. These episodes end spontaneously after seconds to minutes, but often can be abruptly terminated with the touch of a bed partner. Patients often report feeling unable to breathe. Initially these events may be quite disturbing but with time they become less concerning unless associated with hallucinatory content. Isolated sleep paralysis, not associated with narcolepsy, varies among ethnic groups and may occur in up to 5–30% of the normal population.[5]

☆ TIPS AND TRICKS

Isolated sleep paralysis is common, particularly during periods of sleep deprivation or stress. In the absence of any other symptoms of narcolepsy, the patient should be reassured as to the benign nature of the symptom and that no additional testing is likely warranted.

Associated symptoms

Nocturnal sleep disruption usually is not present early on but in well-established narcolepsy, sleep disruption is common. Patients fall asleep readily but wake up every 60–90 min with periods of sustained wakefulness. Also, acting out dreams (REM behavior disorder), vivid dreams, and automatic behaviors (a manifestation of EDS) can be associated with narcolepsy. Automatic behaviors, such as completing a mundane task without remembering it, is commonly seen in patients with severe sleepiness but is not specific for narcolepsy as it can be seen in other disorders such as sleep apnea or severe sleep deprivation.

Pathophysiology

The pathophysiology is unclear. There is some evidence that genetic predisposition, abnormal neurotransmitter functioning, and abnormal immune modulation may all play a role in the development of narcolepsy. HLA DQB1*0602 is positive in 85% of patients with narcolepsy with cataplexy. Loss of hypocretin-1 secreting cells in the hypothalamus

secondary to an autoimmune mechanism has been postulated.[6] Hypocretin neurons project onto monoaminergic and cholinergic neurons which are involved in the regulation of sleep. A dysfunction of the central sleep regulation leads to inappropriate transitions between sleep and wake, throughout the entire 24-hours period. In narcolepsy, patients have been shown to have a decreased level of hypocretin in the cerebrospinal fluid. The absence of hypocretin causes an imbalance of the motor excitation and inhibition. Emotional stimuli may precipitate this state, causing inactivation of motor excitation and activation of the inhibitory system.

Differential diagnosis

History is important in evaluating other possible causes of EDS. Diagnostic testing with a polysomnogram and next-day Multiple Sleep Latency Test (MSLT) helps to eliminate other causes of EDS such as sleep apnea, periodic limb movements of sleep, and idiopathic hypersomnia. Narcolepsy can be differentiated from idiopathic hypersomnia by many key features (see Table 5.1). There is an increased incidence of sleep apnea in narcoleptics which complicates the diagnosis.

Diagnosis

The diagnosis can be made by history alone, when the history of EDS is accompanied by definite cataplexy. Cataplexy is essentially pathognomonic of narcolepsy. Even in other disorders where cataplexy is described (multiple sclerosis, Prader–Willi, etc.), the cataplexy is not as abrupt and not as consistently associated with emotion. Sleep paralysis and hypnogogic hallucinations, while suggestive of narcolepsy, are seen in the normal population and therefore are less useful in the clinical diagnosis of narcolepsy.

Table 5.1 Differentiating narcolepsy and idiopathic hypersomnia

	Narcolepsy	Idiopathic hypersomnia
Naps restorative?	Usually yes	Usually no
Cataplexy?	Yes	No
REM intrusion?	Yes	No
Disrupted nocturnal sleep?	Usually yes	Usually no
Prolonged sleep need?	Usually no	Usually yes
MSLT results?	MSL <8 min SOREM >=2	MSL <8 min SOREM <2

MSL, mean sleep latency; MSLT, Multiple Sleep Latency Test; SOREM, sleep-onset rapid eye movement.

The physical and neurological examination is usually normal and there is really no finding on physical examination that adds to the diagnostic evaluation. An abnormal neurological exam should raise the suspicion of a different etiology and would likely warrant an imaging study of the brain. Of note, if the examiner has a chance to witness an attack of cataplexy, the examination would show a decreased tone in the extremities and a transient loss of deep tendon reflexes.

CAUTION

Neurological exams in patients with narcolepsy are normal and brain imaging studies are not usually indicated. If neurological exam is abnormal, brain imaging may be warranted to exclude central nervous system (CNS) abnormalities such as multiple sclerosis, stroke, or brainstem tumor that can rarely give rise to narcolepsy.

Several sleepiness scales are available to help assess excessive sleepiness. The most commonly used is the Epworth Sleepiness Scale (ESS). Excessive sleepiness correlates with an ESS score >10. Narcolepsy patients, who in general have a severe degree of sleepiness, have a mean ESS of 18.[7]

The International Classification of Sleep Disorders has recognized four categories of narcolepsy: narcolepsy with cataplexy, narcolepsy without cataplexy, narcolepsy due to a medical condition with or without cataplexy, and unspecified narcolepsy.[1] Narcolepsy due to a medical condition can be due to type C Niemann–Pick disease, Prader–Willi, sarcoidosis, multiple sclerosis, or a lesion in the hypothalamic region. Unspecified narcolepsy is a temporary classification until additional information is obtained for more precise classification.

Laboratory studies

More than 85% of narcoleptics with cataplexy share a specific HLA allele, DQB1*0602.[8] HLA DQBI*0602 is present in 20% of the general population which

makes having the HLA alleles of no diagnostic value. In certain clinical situations, it may be helpful to use the assay to exclude or lessen the likelihood of narcolepsy. However, HLA testing is not part of the usual diagnostic evaluation of a patient with possible narcolepsy. Cerebrospinal fluid (CSF) hypocretin levels below 110 pg/mL are strongly supportive of the diagnosis of narcolepsy.[9] In CSF, normal values are >200 pg/mL, with an average around 350 pg/mL.[10] However, it is primarily sensitive in patients in narcolepsy with cataplexy, so its utility is limited since cataplexy is pathognomonic for narcolepsy and the diagnosis can be confidently made from history and sleep laboratory testing. Neurodegenerative, neuromuscular, and immune-mediated diseases, as well as traumatic brain injury, have also been shown to have low CSF hypocretin levels.[10]

Imaging studies

Typically imaging studies are unrevealing and are not usually warranted unless there is a clinical suspicion of a CNS abnormality that may be contributing to the patient's symptoms. A few small studies have shown magnetic resonance imaging (MRI) changes of the pons within the reticular activating system and idiopathic narcolepsy may be due to structural abnormalities of the diencephalon and brainstem.[11]

Polysomnography

An overnight polysomnogram (PSG) followed by a next-day MSLT is the standard work-up in patients with suspected narcolepsy or hypersomnolence. Stimulants should be discontinued 2 weeks prior to the PSG and MSLT to avoid inaccurate results. The overnight polysomnogram will exclude sleep apnea and period limb movements of sleep as causes for disrupted nighttime sleep. The MSLT will provide information about the degree of hypersomnolence and the presence of sleep-onset REM periods (SOREM). The MSLT involves five opportunities to nap at 2-hours intervals during the daytime. Two or more SOREM and a mean sleep latency (MSL) of less than 8 min strongly suggest narcolepsy in the correct clinical context. In previous studies in patients with narcolepsy, the MSL was found to be <3 min.[7] These findings are not completely specific and also can be seen in patients with sleep deprivation and sleep apnea. Also, it is important to note that the use of stimulant or sedative medications (or their abrupt withdrawal) may affect the results. It is usually recommended that REM-suppressant medication (selective serotonin reuptake inhibitor [SSRI] antidepressants) and stimulant medication be discontinued before undergoing sleep lab evaluation with a MSLT.

Management

A multimodal approach with pharmacological therapy and behavioral therapy is required to treat narcolepsy. The patients should be instructed to:

- maintain a regular sleep schedule, getting adequate sleep at night with good sleep hygiene
- avoid heavy meals, high sugar snacks, and alcohol since these may contribute to "sleep attacks"
- schedule short naps (brief 10–20 min naps) which usually result in improved alertness. Narcolepsy patients should talk to their family, friends, and employers about their disease so they can understand that naps (which are usually restorative) can improve productivity and are not indicative of laziness or lack of interest
- not drive or operate heavy machinery when sleepy
- exercise daily, which can have stimulating effects.

Approach to pharmacotherapy

Effective pharmacotherapy can require multiple medications. Stimulant medications are used to treat excessive sleepiness and REM-suppressant medications are used to treat cataplexy. Sodium oxybate can treat both EDS and cataplexy. Modafinil and armodafinil are chosen as first-line stimulant medications due to their limited side-effect profile. Commonly used older stimulant medications include methylphenidate and dextroamphetamine. Newer REM-suppressant medications that are effective in cataplexy include the antidepressant venlafaxine.

Stimulant medications for excessive sleepiness (see Table 5.2)

- Modafinil (Provigil) is a wake-promoting agent that is thought to alter levels of dopamine, gamma-aminobutyric acid (GABA), or norepinephrine. It has few side-effects with the most

Table 5.2 Medications commonly used for excessive sleepiness

Medication	Action	Half-life (hours)	Dose (mg/day)	Side-effects
Modafinil	Promotes wakefulness	9–14	200–400	Nausea, HA, induces P450 and increases metabolism of oral contraceptives
Armodafinil	Promotes wakefulness	15	150–250	Nausea, HA, induces P450 and increases metabolism of oral contraceptives
Methylphenidate	CNS stimulant	2–7	10–60	Cardiovascular stimulation, drug tolerance, rebound hypersomnolence
Dextroamphetamine	CNS stimulant	10–12	5–60	Cardiovascular stimulation, drug tolerance, rebound hypersomnolence
Sodium oxybate	CNS depressant	0.5–1	4500–9000	Nausea, headache

CNS, central nervous system.

common being headache. Sympathomimetic activation is much lower compared to the traditional stimulants and as such, these agents are associated with much less hypertension and tachycardia. Modafinil's maximum concentration is reached in 2–4 hours. The dose can be taken in a single morning dose or split into a morning dose upon awakening and a noontime or midday dose. Usually the dosage range is 200–400 mg per day, but higher doses may provide additional benefit.

- Armodafinil (Nuvigil) is the r-enantiomer of modafinil and is primarily distinguished by its longer half-life which results in it being given once a day. Its side-effect profile is similar to modafinil. The dosage range is 150–250 mg daily.
- Methylphenidate (Ritalin) is one of the oldest and most frequently used stimulant medications. It is thought to act primarily through brainstem dopamine, nigrostriatal, and mesocorticolimbic pathways. It does not have major effects on monoamine storage and leads to milder side-effects than amphetamines. The side-effects include irritability, headache, nervousness, palpitations, insomnia, dyskinesias, anorexia, nausea, sweating, and psychosis. The dose is 10–60 mg a day divided in 2–3 doses during the daytime. Patients may need additional doses for certain occasions (such as before driving), along with their usual scheduled daily dosages. Sustained-release formulations are available for methylphenidate (as well as dextroamphetamine) and are often preferred as they avoid frequent doses of the medication and the "crash" that many patients experience as the stimulant medication wears off and the patient feels even more sleepy than before taking the medication.
- Amphetamines: the most commonly used is dextroamphetamine (Dexedrine) which works by releasing dopamine and noradrenaline. Amphetamines have a longer half-life than methylphenidate. The side-effect profile is similar to methylphenidate but the side-effects tend to be more more prominent. The usual dosage range is 5–60 mg daily.

Note: Mazindol is a weak releasing agent of dopamine and has been withdrawn from the market in several countries due to reports of cardiac valvular abnormalities resulting from its use. Selegiline, a monoamine oxidase B (MAO-B), is rarely used due to the need to maintain a low tyramine diet to avoid hypertensive crisis.

CAUTION

Modafinil and armodafinil induce the P450 system and increase the metabolism of oral contraceptives, amongst other medications. Women using birth control pills should be counseled regarding this issue.

Table 5.3 Medications commonly used for cataplexy

Medication	Mechanism	Half-life (hours)	Dose (mg/day)	Side-effects
Venlafaxine	Serotonin and norepinephrine reuptake inhibitor (SNRI)	5	37.5–300	Gastrointestinal upset
Clomipramine	SNRI	32	10–200	Nausea, anorexia, dry mouth, urinary retention, tachycardia
Sodium oxybate	Gamma-aminobutyric acid	0.5–1	4500–9000	Nausea, headache

Rapid eye movement-suppressant medications for cataplexy (see Table 5.3)

- Venlafaxine (Effexor) is a serotonin and noradrenaline reuptake inhibitor (SNRI). It is an antidepressant with some stimulating effects and should be taken in the morning to avoid nighttime sleep disruption. Its major side-effect is gastrointestinal upset. The dosage range is 37.5–300 mg daily.
- Tricyclic antidepressants (TCAs) have been used to treat cataplexy. The most commonly used medications in this class are clomipramine and protriptyline. Possible mechanisms include anticholinergic effects, adrenergic reuptake inhibition, or serotonergic reuptake inhibition. Clomipramine is typically used at a dose of 25–75 mg daily but lower doses of 10–20 mg are often effective. Protriptyline is used at a dose of 2.5–10 mg daily. The major adverse effects of these tricyclic antidepressants are the anitcholinergic side-effects. Contrary to the slow onset of TCA efficacy in treating depression, the cataplexy-suppressing effects are almost immediately seen upon initiating these drugs, but the effect is not sustained and multiple doses throughout the day are usually needed.
- Selective serotonin reuptake inhibitors (SSRIs) (such as fluoxetine) are sometimes used, but are less effective then the SNRI antidepressent medications.

Note: monoamine oxidase inhibitors (MAOI), while strong REM suppressants, are not commonly used due to numerous side-effects and drug interactions. Atomoxetine (Strattera) is a noradrenergic uptake inhibitor that has been used to decrease cataplexy but there has been rare but potential liver toxicity reported.

Sodium oxybate

Sodium oxybate (Xyrem) is the only treatment for cataplexy which is FDA approved.[12] It is a potent short-acting hypnotic that can be used to treat EDS in narcolepsy.[13] Sodium oxybate is an endogenous metabolite of GABA. It has been shown to decrease nocturnal awakening, increase slow-wave sleep, and consolidates REM sleep. The starting dose is 4.5 g divided in two doses taken at nighttime. The first dose is taken as the patient gets into bed. The nighttime doses are taken 3–4 hours apart and thus typically the patient has to set an alarm to wake them to take the second dose. The doses are increased every 1–2 weeks up to a maximum dosage of 9 g per day. Improvement is noticed within the first 3 months.

Sodium oxybate is usually used in patients with moderate-to-severe symptoms of narcolepsy. It is a CNS depressant medication and alcohol or other CNS depressants must be avoided during its use. Sodium oxybate improves daytime sleepiness, but concomitant use of modafinil or another stimulant medication is usually required. While clearly an effective agent for narcolepsy, some patients discontinue its use due to concerns regarding parasomnias (confusional arousals) or the effects of the heavy salt load present in the medication.

CAUTION

Gamma-hydroxybutyrate (GHB) has been used illegally as a "date rape" drug. Patients who take sodium oxybate, the sodium salt of GHB, should be counseled to take this medication in a safe environment. Due to concern about misuse of the drug, it is available only from a single mail order pharmacy and is sent by overnight delivery directly to the patient.

CAUTION

Due to insufficient clinical studies, stimulant and anticataplectic drugs are not typically recommended in pregnancy unless absolutely necessary. Most patients discontinue the medications prior to pregnancy. However, sodium oxybate is considered a class B medication for pregnant women.

Prognosis and complications

Patients tend to have a good response to treatment and have improved daytime performance. The excessive sleepiness decreases with stimulant medications. Episodes of cataplexy lessen with sodium oxybate or other REM suppressants. Co-morbid medical problems can develop, including sleep apnea, period limb movements of sleep, REM behavior disorder, depression, eating disorders, and diabetes.[14] Motor vehicle accidents are common and the patient should be counseled about not driving or operating heavy machinery when sleepy.

TIPS AND TRICKS

Most states do not have laws governing the operating of motor vehicles while sleepy, so there is no legal restriction of narcoleptic patients with respect to driving. However, individuals with narcolepsy are significantly more likely to be involved in motor vehicle accidents and should be advised to be aware of the potential dangers of driving and restrict driving if necessary.

Future treatments and therapies

The current treatments for narcolepsy are directed at the specific symptoms noted above. With developments in understanding the neurobiological basis of the disease, newer therapies are likely to emerge. Potential new therapies include medications that are histamine agonists to promote wakefulness and histamine antagonists for sedation. Thyrotropin-releasing hormone agonists have alerting properties and have been shown to increase wakefulness and decrease cataplexy in animals. Hypocretin deficiency is thought to be the cause of narcolepsy with cataplexy. Newer therapies are being explored with the aim of replacing this deficient neurotransmitter. These efforts include intranasal hypocretin administration, cell transplantation, and gene therapy. Narcolepsy is presumed to be an autoimmune disorder and therapy with intravenous immunoglobulin or plasmapheresis has been reported and offers a potential area of intervention to avoid or arrest the development of narcolepsy.

References

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*, 2nd edn. Westchester, IL: American Academy of Sleep Medicine, 2005.
2. Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep* 2007; **30**(1): 13–26.
3. Ohayon MM, Ferini-Strambi L, Plazzi G, et al. Frequency of narcolepsy symptoms and other sleep disorders in narcoleptic patients and their first-degree relatives. *J Sleep Res* 2005; **14**(4): 437–45.
4. Overeem S, Mignot E, van Dijk JG, et al. Narcolepsy: clinical features, new pathological insights, and future perspectives. *J Clin Neurophysiol* 2001; **18**: 78–105.
5. Dahlitz M, Parkes JD. Sleep paralysis. *Lancet* 1993; **341**: 406–7.
6. Black JL 3rd, Silber MH, Krahn LE, et al. Analysis of hypocretin (orexin) antibodies in patients with narcolepsy. *Sleep* 2005; **28**(4): 427–31.
7. Sangal RB, Mitler MM, Sangal JM. Subjective sleepiness ratings (Epworth sleepiness scale) do not reflect the same parameter of sleepiness as objective sleepiness (maintenance of wakefulness test) in patients with narcolepsy. *Clin Neurophysiol* 1999; **110**: 2131–5.
8. Mignot E. Genetic and familial aspects of narcolepsy. *Neurology* 1998; **50**(2 Suppl 1): S16–22.

9. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol* 2002; **59**(10): 1553–62.
10. Fronczek R, Baumann CR, Lammers GJ, Bassetti CL, Overeem S. Hypocretin/orexin disturbances in neurological disorders. *Sleep Med Rev* 2009; **13**(1): 9–22.
11. Bassetti C, Aldrich MS, Quint DJ. MRI findings in narcolepsy. *Sleep* 1997; **20**(8): 630–1.
12. US Xyrem1 Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 2003; **26**(1): 31–5.
13. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep* 2006; **29**(7): 939–46.
14. Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. *J Sleep Res* 2001; **10**(1): 75–81.