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Selection from: Recognizing and Treating Excessive Sleepiness in Primary Care: Circadian Rhythm Sleep Disorders

A College Student With Excessive Sleepiness CME

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Disclosures

History of Present Illness

Jill is a 20-year-old, single, white college student who is referred for evaluation of excessive sleepiness. She complains of difficulty getting to sleep, with frequent awakenings once asleep. In addition, she finds herself feeling sleepy during the daytime. She denies restless legs, pain, neighborhood noises, or racing thoughts at bedtime or during the night. She also denies experiencing any irresistible urge to sleep, although she does take naps when feasible and has vivid dreams that occur sometimes at sleep onset. She reports having had trouble staying awake in school throughout childhood and into her teens, but so far has not had any problem when driving, including drifting out of her lane or accidents.

She reports that she drops objects she is holding in her hand when she laughs; this has happened with both hands, and sometimes she feels her knees buckling but she has never had a fall. She frequently wakes up feeling as if she is paralyzed and cannot move. She is not aware of any snoring or breathing pauses in sleep, and she does not wake up gasping or choking at night.

She denies sleep-talking and sleepwalking. She has no epilepsy or bruxism; she does not work rotating shifts. She reports that she has gained 100 pounds in the last 5 years. She denies smoking, consuming alcohol, and substance abuse. She reports normal mood at this time.

Past Medical History

Jill sees a psychiatrist because of depression and social anxiety disorder, and is stabilized on trazodone 50 mg daily and venlafaxine XR 75 mg 1 tablet daily. She also has hay fever, is obese with insulin intolerance, and is being treated for irregular menses with desogestrel/ethinyl estradiol. She has no history of heart, lung, thyroid, or neurologic disease. Family history is significant for sleep apnea in her father, but no one in her family has been diagnosed with narcolepsy.

Evaluation

Jill is obese with a body mass index of 41.9 kg/m². She has a Mallampati class 3 oropharyngeal airway, indicating a relatively narrowed oropharyngeal passage (the higher the Mallampati class, the greater the risk). Her Epworth sleepiness score is 19 (a score < 10 is considered normal; above that suggests hypersomnolence). Her affect is appropriate.

An overnight polysomnography (PSG; Figures 1 and 2 shows an apnea-hypopnea index (AHI) of 0.2 per hour (< 5.0 per hour is normal) and minimal snoring without hypoxia or significant arousals and thus is negative for obstructive sleep apnea syndrome, which otherwise was suspected because of her obesity, relatively narrowed oropharyngeal airway, and family history of sleep apnea. She experienced mild periodic limb movements in sleep (PLMS) with an index of 5.5 per hour (< 5.0 per hour is normal). She slept for roughly 7.5 hours with a normal sleep efficiency (the amount of time in bed actually sleeping), at 93.1% (< 90.0% is considered abnormal). The REM latency (the time for first REM sleep period to occur after sleep onset) was abnormally short at 2

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minutes, suggesting narcolepsy. The Multiple Sleep Latency Test (MSLT) that followed showed 2 sleep onset REM periods (SOREM), also characteristic of narcolepsy (Figures 3 and 4). The symptom of weakness on laughing is suggestive of cataplexy. Cataplexy is a phenomenon in which the patient experiences a tendency to lose muscle tone in response to emotional stimuli such as anger or laughter.

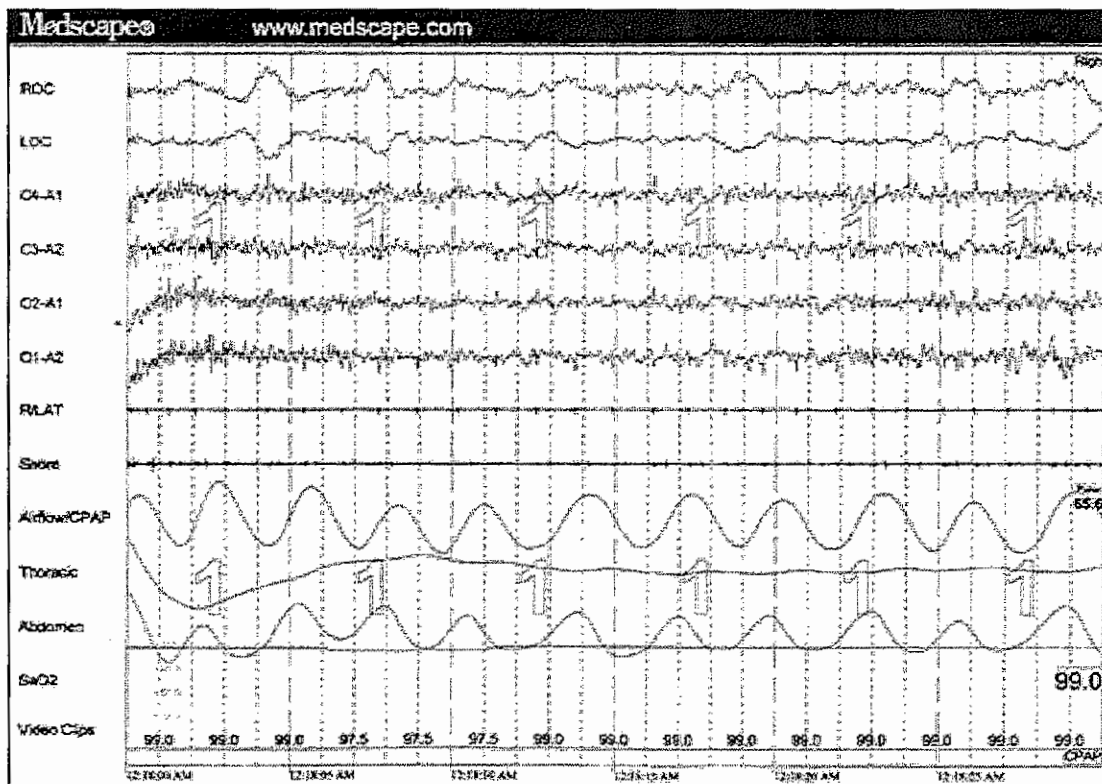


Figure 1. The 30-second epoch of PSG shows sleep onset at 12:18 AM with electroencephalogram (EEG) showing stage 1 sleep. The EEG shows loss of alpha waves in the first 5 seconds (O2-A1, O1-A2). The electro-oculogram (ROC, LOC) shows slow eye movements of drowsiness (note contour of the wave is smooth).

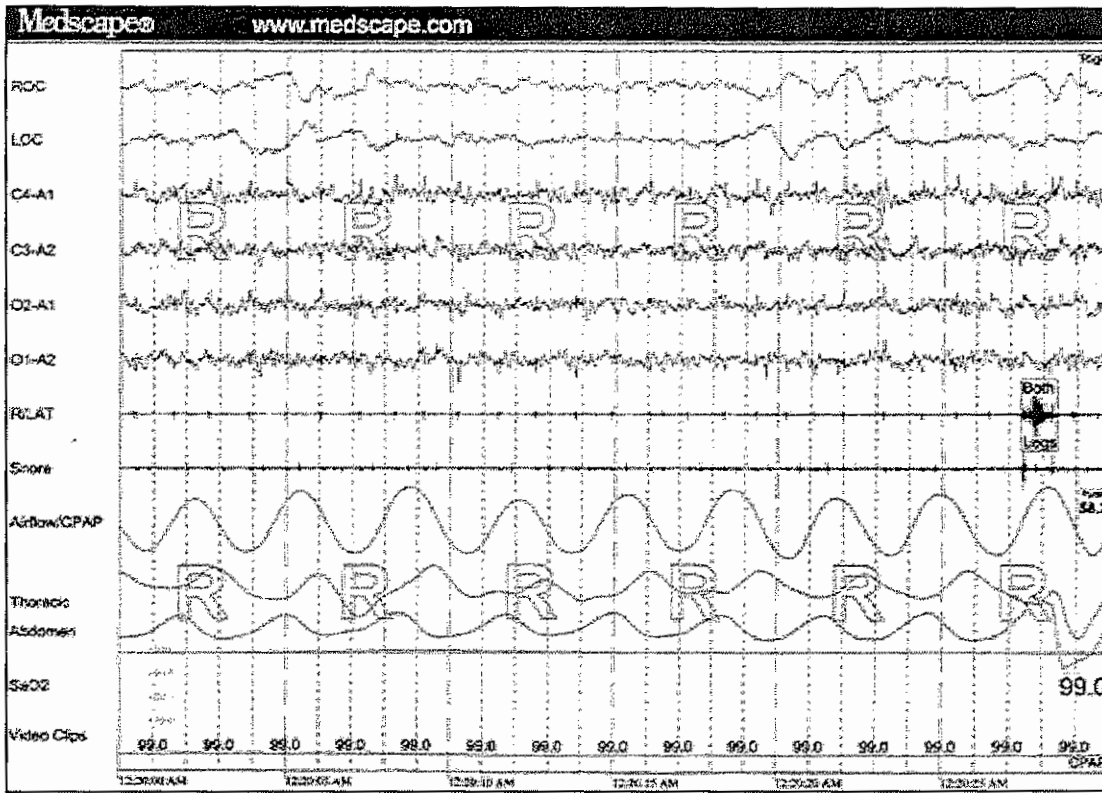


Figure 2. The 30-second epoch of PSG shows onset of REM sleep with EEG (C4-A1, C3-A2) showing saw tooth waves. The electro-oculogram (ROC, LOC) shows rapid eye movements (note the contour is sharp). Note that at the time 12:20 AM (bottom), 2 minutes after sleep onset as seen in Fig 1, REM sleep was observed.

Nap	Start	Stop	Latency to Sleep	Latency to REM
1.	0814	0835	5.5	9.5
The patient stated she did not know if she slept or dreamt.				
2.	1017	1040	9.0	N/A
The patient stated she did not know if she slept or dreamt.				
3.	1231	1254	7.5	N/A
The patient thinks she slept, but does not think she dreamt.				
4.	1429	1429	8.5	3.5
The patient does not think she slept or dreamt.				

Figure 3. The MSLT shows 2 out of 4 naps with REM sleep. The average sleep latency is 7.62 minutes. Thus, this MSLT satisfies the criteria for narcolepsy diagnosis, with 2 or more SOREM and mean sleep latency less than or equal to 8 minutes.

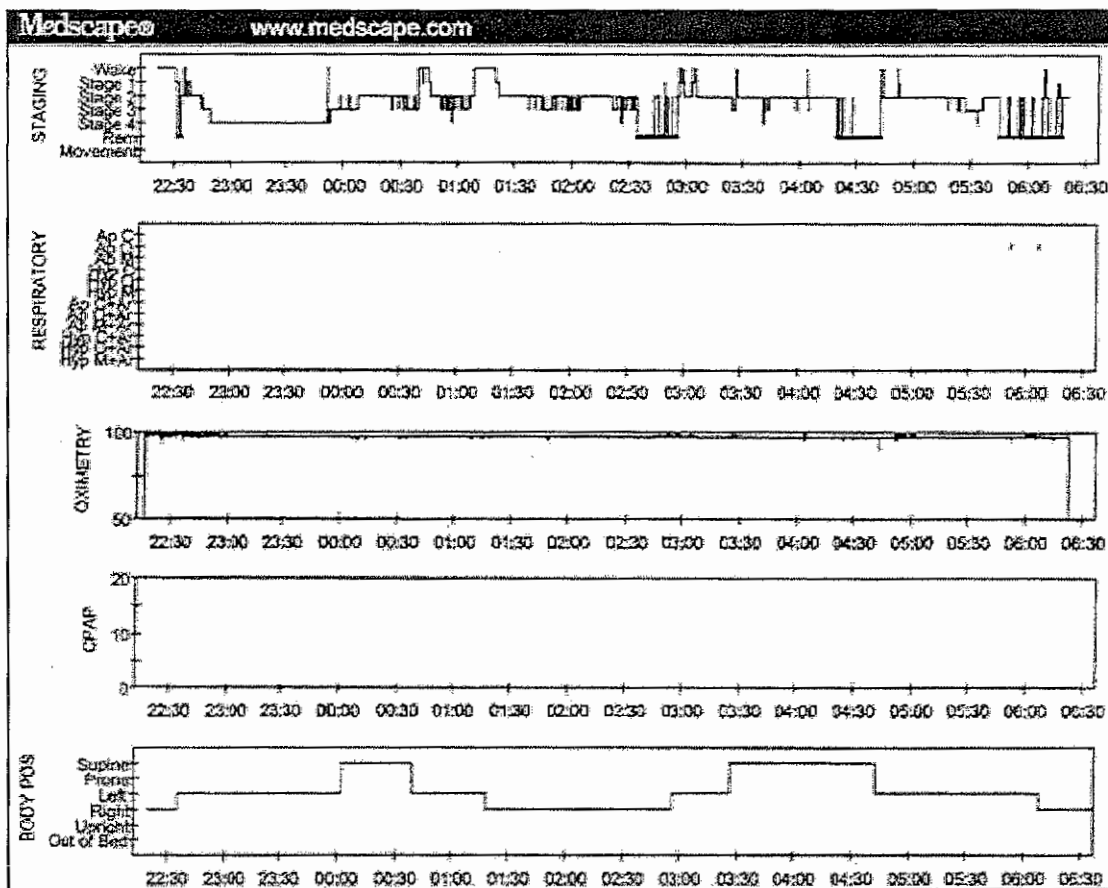


Figure 4. The histogram: Note the REM sleep early in the sleep cycle. Ordinarily, REM and NREM sleep cycles alternate about every 90 minutes. Note the paucity of respiratory events and no significant oxygen desaturations. Patient did not need continuous positive airway pressure therapy. Patient slept in all of the positions except prone.

Management and Clinical Course

Jill's symptoms, PSG, and MSLT all support the diagnosis of narcolepsy with cataplexy. She is prescribed modafinil 200 mg daily and imipramine 75 mg at bedtime to offset cataplexy; trazodone and venlafaxine are discontinued. Although venlafaxine is also used in the treatment of cataplexy, Jill clearly experienced symptoms while taking it. She prefers to use modafinil instead of the stimulant methylphenidate, which is a controlled substance drug, even though modafinil may increase the metabolism of desogestrel/ethinyl estradiol. She is also given instructions on sleep hygiene and is instructed to avoid sleep deprivation and to take short afternoon naps.

At subsequent visits, Jill initially reports improvement in daytime sleepiness but later reports the return of the symptom. However, her mood is stable, she is sleeping better at night, and she no longer experiences cataplexy. Her modafinil dose is titrated to 400 mg daily.

She continues to complain of daytime sleepiness in the late afternoon; splitting the modafinil dose does not improve this symptom. She reports sleepiness typically between 2 PM and 4 PM, a time when she cannot nap because of her class schedule. She denies snoring or witnessed apneas.

One possible reason for her sleepiness is the natural dip in the sleep-wake circadian rhythm at this time favoring sleepiness, superimposed on her inherent narcolepsy-related hypersomnolence. The other possibility is sleep disruption from PLMS, which may be worsened by her evening dose of imipramine. She decides to try drinking a caffeinated beverage to promote wakefulness rather than taking one of the dopamine agonists for PLMS. She later reports that drinking iced tea helps the

afternoon sleepiness, which is now resolved.

Discussion

Narcolepsy is classically characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. The term "narcolepsy" is derived from the Greek language and is literally translated as "seized by somnolence." This was coined by Gelineau, who was the first to delineate the syndrome in 1880.

Narcolepsy is frequently underrecognized, and approximately 50% of adults with the disorder retrospectively report that symptoms began in their teenage years. The average delay in the diagnosis of narcolepsy is typically more than 10 years, primarily because only one third of patients will experience all 4 classic symptoms: excessive sleepiness (ES), cataplexy, hypnagogic hallucinations, and sleep paralysis. Moreover, patients with narcolepsy have a higher than expected incidence of other sleep disorders such as obstructive sleep apnea (most narcoleptics gain weight), restless legs syndrome, periodic limb movement disorders, and REM behavior disorder (RBD), which further camouflage the picture. Lack of awareness also plays a major role. A high index of suspicion is required by the primary care physician for referral to a sleep specialist.

Narcolepsy has more serious implications than originally recognized, and the impact on the quality of life is equal to that of other chronic neurologic disorders such as Parkinson's disease.^[1]

Pathophysiology

Narcolepsy now seems to be more complex than a simple sleep disorder.^[2] The precise etiology of narcolepsy is not clear, but may include a combination of genetic predisposition, abnormal neurotransmitter functioning and sensitivity, and abnormal immune modulation. Current research implicates certain human leukocyte antigen (HLA) subtypes and abnormalities in monoamine synaptic transmission.^[3] Studies have found strong associations with human leukocyte antigen (HLA)-DR2 and DQB1*0602 antigens,^[3] especially in cataplectic patients.

Recent research has also revealed possible involvement of proteins called hypocretins, which appear to be deficient in the cerebrospinal fluid of narcoleptic patients.^[4-6] Hypocretins are involved in various hypothalamic functions, including feeding, energy homeostasis, and neuroendocrine regulation.^[7,8]

Epidemiology

The incidence of narcolepsy is 0.02% to 0.18%. First-degree relatives of narcoleptics have a 10 to 40 times greater risk than the general population. Men and women are equally affected. The age-of-onset distribution is biphasic; the highest peak occurs at 15 years, with a less pronounced peak at 36 years.

Clinical Presentation

Narcoleptic patients do not sleep more than normal controls during a 24-hour period; the instability of the sleep/wake state control is what leads to the intrusion of REM sleep into wakefulness and vice versa. The classic symptom tetrad is present in only 50% of patients. Only cataplexy is pathognomonic to narcolepsy (Table).^[9,10]

Table. Narcolepsy Classifications

- | |
|--|
| <ul style="list-style-type: none"> • Narcolepsy with cataplexy • Narcolepsy without cataplexy • Secondary/ Symptomatic narcolepsy |
|--|

Excessive daytime sleepiness is the primary symptom of narcolepsy; it is characterized by persistent sleepiness resulting from fragmented nocturnal sleep, and sleep attacks resulting from REM intrusion into wakefulness. These attacks occur on a background of essentially continuous drowsiness and differ from ES seen in patients with obstructive sleep apnea because these narcoleptic naps are refreshing. They can occur under active conditions such as while eating and

talking, which results in severe disability.

Cataplexy is an abrupt attack of muscle weakness that typically lasts for a few minutes but occasionally continues longer.^[9] Patients are usually alert and oriented despite their inability to respond. The most characteristic form is triggered by emotions; positive emotions such as laughter are more likely to produce a cataplectic attack than negative emotions such as anger. Cataplexy is seen in about 70% of patients with narcolepsy, and its presence strongly suggests the diagnosis of narcolepsy. Partial cataplectic symptoms, such as head drop, jaw drop, slurred speech, and bilateral ptosis, also are seen and should raise the index of suspicion.

Sleep paralysis is the inability to move upon falling asleep or at awakening, with intact consciousness. Roughly 33% of patients experience this phenomenon. These episodes are understandably alarming, particularly the first time, and if they occur with the feeling of an inability to breathe or are accompanied by hallucinations. Diaphragmatic activity and air exchange usually remain adequate.

Sleep-related hallucinations may occur at sleep onset (hypnagogic) or awakening (hypnopompic) and are usually visual (most common), auditory, tactile, or multisensory in nature. These hallucinations can present a confusing picture to the clinician and may provide the impetus to wrongly prescribe antipsychotic agents.

Automatisms are indicative of severe sleepiness and result in automatic behavior, a symptom that allows semiconscious continuation of an activity in the midst of sleep attacks with no memory of the event.

Fragmented nocturnal sleep with sleep maintenance insomnia is often a very disabling symptom that may exacerbate all other symptoms.

The classic picture of narcolepsy may be different in young children. Other symptoms experienced by these patients may include fatigue, depression, eating binges, and difficulty concentrating.

Diagnostic Workup

History and physical. Narcolepsy with cataplexy is a clinical diagnosis based on detailed history with special emphasis on sleep pattern. Additional testing and referral to a sleep medicine specialist can be requested in order to confirm the diagnosis, discern the severity of the disorder, or exclude other sleep disorders.

Primary narcoleptic patients do not have any specific general physical and neurologic findings on examination. A detailed physical examination should be performed if findings are equivocal on history and to exclude secondary causes of narcolepsy.

PSG and MSLT. An overnight PSG followed by MSLT is essential in the workup. Nighttime PSG will usually document fragmented sleep with a normal amount of REM sleep but with a pattern of sleep-onset REM. PSG is also helpful for excluding other sleep disorders, namely obstructive sleep apnea. MSLT is performed the day after nocturnal PSG recording. The patient is monitored during 4-5 naps taken at 2-hour intervals. A supportive test includes mean sleep latency of 5 minutes or less and at least 2 sleep-onset REM periods. This criterion achieves the highest specificity (99.2%) and positive predictive value (87%) for MSLT,^[11] although 20% to 30% of the general population and patients with untreated obstructive sleep apnea also have SOREM on MSLT. The second revision of the International Classification of Sleep Disorders (ICSD) uses a mean sleep latency of less than 8 minutes during MSLT.^[12]

Laboratory studies. The clinical utility of HLA typing including DQB1*0602 and DQA1*0602 is very restricted because 12%-38% of population will be positive, depending upon the ethnicity of the patient. HLA typing is never used for the diagnosis of narcolepsy without cataplexy.

Low CSF hypocretin-1 has been found consistently in patients with narcolepsy with cataplexy, with 90% sensitivity. Low CSF hypocretin-1 levels (< 110 pg/mL) were also included in the 2nd revision of the ICSD. Its full clinical utility remains to be determined for evaluating patients with narcolepsy without cataplexy (10%) and those with idiopathic hypersomnia.

Imaging studies. The clinical utility of brain magnetic resonance imaging (MRI) for diagnosing primary narcolepsy is limited but has a definite role if the symptoms are atypical and there are focal findings on the neurologic examinations. MRI will easily reveal structural lesions of the brainstem and diencephalon (hypothalamic hamartoma) causing symptomatic narcolepsy.^[13]

Management

Patients with narcolepsy need support and understanding from their families and education about the disorder and career counseling from healthcare providers. They should be advised to keep to a strict sleep schedule, with 7-8 hours of sleep at night. Strategically scheduled daytime naps are restorative, as is regular exercise to maintain proper physical fitness and improve energy levels.

Pharmacologic Treatment

For ES, central nervous system (CNS) stimulants such as methylphenidate, dextroamphetamine sulfate, methamphetamine, or amphetamine can be used. Undesirable side effects include headache, irritability, nervousness, and gastrointestinal complaints. Nocturnal sleep may be impaired by CNS stimulants, thus reducing sleep time. Clinicians who are concerned about long-term use may instruct patients to abstain from medication 1 day each week (typically on a weekend), to avoid developing tolerance and escalating dosage regimens.

Modafinil, a novel wake-promoting agent, has also been used for several years. It does not appear to alter levels of dopamine or norepinephrine. It has provided both subjective and objective improvements in sleepiness in a multicenter trial.^[14] Unlike traditional medications, modafinil does not appear to affect total sleep time or suppress REM sleep. One review suggests that modafinil improves but does not normalize measures of sleepiness and, for some narcoleptic patients, other stimulants may be more effective.^[15] It is approved by the US Food and Drug Administration (FDA) to improve wakefulness in individuals with ES associated with narcolepsy, obstructive sleep apnea-hypopnea syndrome, or shift-work sleep disorder.

Tricyclic antidepressants (imipramine, clomipramine, protryptiline) or selective serotonin reuptake inhibitors (SSRIs; fluoxetine) and selective serotonin-norepinephrine-reuptake inhibitors (SNRIs; venlafaxine) are prescribed to treat cataplexy, hypnagogic hallucinations, and sleep paralysis.^[16]

Sodium oxybate (gamma-hydroxybutyrate) has been recently approved by the FDA for treating cataplexy. In addition to having anticataplectic properties, sodium oxybate reduces ES by preventing nocturnal fragmentation, and is not associated with anticholinergic side effects.^[17,18] Because of sodium oxybate's history of abuse as a recreational drug (date rape), the FDA approved it as a Schedule III controlled substance.

For consolidating nocturnal sleep in refractory patients, nighttime use of short-acting benzodiazepine hypnotic may be effective.

Complications

Narcolepsy is a lifelong disease that can be effectively managed with medication and support from teachers, employers, and families. Possible complications include the following:

- Status cataplecticus: typically triggered by strong emotions and by withdrawal of anticataplectic medications;
- Injuries from cataplectic attacks;
- Side effects from unnecessary medications (eg, antipsychotics for hypnagogic hallucinations); and
- Social embarrassment or ostracism.

In addition, patients with narcolepsy experience a higher incidence of other sleep disorders, including obstructive sleep apnea from weight gain, RBD from medication side effects/REM state instability, or both; medical problems such as type 2 diabetes; and psychiatric disorders such as

depression.

Future Directions

The presence of low CSF hypocretin-1 levels is very specific for narcolepsy when compared with other sleep disorders. Measuring CSF hypocretin-1 is rapidly becoming a new diagnostic tool for this condition. Because most narcolepsy-cataplexy subjects are hypocretin ligand deficient, hypocretin agonists may be promising in the treatment of narcolepsy.

Resources

The American Academy of Sleep Medicine and The American Academy of Family Physicians have produced guidelines^[19,20] that will assist primary care physicians in making the diagnosis.

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References

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