

When sleep is the enemy

Excessive daytime sleepiness can create a rapid decline in daily functioning and the potential for hazardous situations. By understanding sleep physiology and offering a range of interventions, the primary care physician can turn an unhealthy situation around.

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Article at a glance

- Up to 30% of patients in primary care have occasional difficulty sleeping, and 10% of those may have a chronic sleep disorder.
- Causes of excessive daytime sleepiness (EDS) include poor sleep hygiene, sleep apnea, and narcolepsy.
- Long-term EDS is associated with lower quality of life, psychological disturbances, and increased cardiovascular disease.
- Structured behavioral and cognitive interventions can correct many cases of EDS.
- Pharmacotherapy includes the short-term use of hypnotics or stimulants for EDS and modafinil for narcolepsy.
- An investigational hypocretin analog for narcolepsy shows potential for greater efficacy.

Sleep has been a source of interest and speculation for centuries. As recently as 100 years ago, most medical practitioners regarded sleep as something akin to death, a period in which brain activity more or less ceased. We now know that sleep may include some of the most active periods of brain function in the 24-hour cycle. The growing field of sleep medicine is based on neurophysiologic research initially conducted in the 1920s and 1930s. The active period of rapid eye movement (REM) sleep was only discovered in the 1950s.

CAUSES OF HYPERSOMNIA

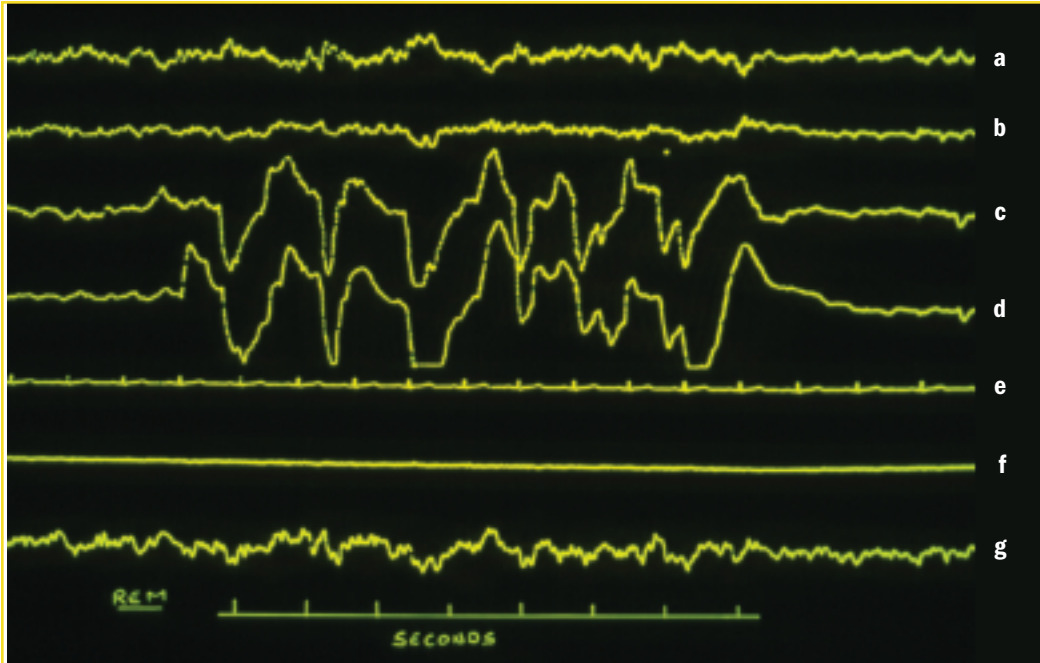
Hypersomnia is characterized by excessive daytime sleepiness (EDS) or prolonged nighttime sleep. Prevalence of EDS has been variously estimated at between 7% and 20%.¹⁻⁴ In primary care practice, as many as 30% of patients may have an occasional difficulty falling asleep, and 10% of those may report a chronic sleep problem.⁵

EDS can be associated with a number of causes. The most common is simply a lack of adequate, the consequence of poor sleep behavior, an endemic feature of contemporary life. Work pressures, family obligations, and the creeping shift toward a 24-hour lifestyle have placed heavy demands on waking hours and can intrude upon the ability to sleep at night.

Among the pathologies related to EDS, obstructive sleep apnea is the most frequent contributor, and this condition can have a severely detrimental effect on both sleep quality and quantity. Individuals suffering from sleep apnea may wake up hundreds, or even thousands, of times during the night. Their sleep is fragmented so they miss out on the deeper and more restorative stages of the sleep cycle. Sleep apnea also reduces oxygen saturation in the blood, contributing to lower levels of energy that may increase the likelihood of daytime sleepiness.

Narcolepsy is another important cause of EDS. Approximately 200,000 people in the United States suffer from narcolepsy (although only 50,000 have received a diagnosis), making it one half to one third as common as multiple sclerosis and Parkinson's disease.⁶

EDS may also result from a number of pathologies that are not strictly sleep-related. Depression, substance abuse, seasonal affective disorder (SAD), restless leg syndrome (RLS), fibromyalgia, and chronic fatigue syndrome, are all commonly associated with hypersomnia, while hypoglycemia and hy-



This series of false-color traces was made during stage 5 rapid eye movement (REM) sleep. The lines represent EEGs (a and b); electrooculograms of right- and left-eye movements, respectively (c and d); the ECG (e); and electromyelograms showing muscle activity in the larynx (f) and neck (g).

pothyroidism may also lead to daytime sleepiness. Normal use of some medications, such as antihistamines, can lead to EDS (see Table 1, page 32). In rare cases, lesions in certain parts of the brain (particularly damage to the posterior hypothalamus), may manifest as hypersomnia.

Individuals who are typically considered night owls, and clinically described as experiencing delayed sleep phase syndrome, are often subject to hypersomnia since the natural pattern of their circadian rhythm may not conform to the demands of normal daily life. Finally, *idiopathic hypersomnia* describes those cases of EDS in which no clear cause has been identified.

WHAT IS THE RIGHT AMOUNT OF SLEEP?

Hypersomnia is a broad term for a disorder that encompasses a range of experience from the very mild, such as falling asleep at work or while watching TV, to more severe and hazardous manifestations, such as falling asleep behind the wheel while driving. Even a moderate course of EDS, if not properly dealt with, may cause a substantial lowering of quality of life (QOL) over time.⁷ A detrimental effect on cognition can occur, leading to poorer academic, professional, and social functioning. Sexual issues, poor self-image, and decreased economic achievement are also features of hypersomnia, while in extreme cases, psychological disturbances, such as paranoia and hallucinations, may result.

EDS is also associated with increased risk of cardiovascular disease (CVD) and higher rates of mortality.⁸ The Cardiovascular Health Study examined 5888 patients and found that daytime sleepiness was the only sleep factor associated with CVD morbidity and mortality, MI, and congestive heart failure.

IMAGE: JAMES HOLMES/PHOTO RESEARCHERS

TABLE 1
Agents that may cause insomnia

Antiparkinsonian agent
Appetite suppressant
Beta-agonist
Caffeine
Corticosteroid
Decongestant
Diuretic near bedtime
Nicotine patch, cigarette smoking
Selective serotonin reuptake inhibitor antidepressant
Stimulant laxative near bedtime
Theophylline

Daytime sleepiness identifies older adults at increased risk for CVD, and is an independent risk factor in women. It is also worth noting that people who sleep 1 or 2 hours *more* than the optimal daily amount, which is generally considered to be 7 hours for most adults, appear to be more likely to have reduced life spans than those who sleep 1 or 2 hours *less* than the optimum.⁹⁻¹¹

Unfortunately, there is no standard of what constitutes the correct amount of sleep for the entire population. This fact is confirmed in sleep laboratories, where EEG data is highly individualized for each patient. Further, hypersomnia is self-reported, and the physician must identify what, for the patient, constitutes an “adequate” amount of sleep. A patient who lives with an insomniac, for example, may believe that he or she is a hypersomniac in comparison. Some patients who report insomnia do not substantially differ in their sleep patterns from age-matched people who do not report insomnia.

Physicians, therefore, must be aware of the gap between perception and reality, since patients may not only misjudge what is an adequate amount of sleep, but may misperceive how much sleep they are actually getting. In sleep laboratories, patients commonly report only 1 hour of sleep, but the EEG readings indicate 6 hours. This discrepancy is not always easily resolved, and may simply be a result of patient misperception or caused by other factors such as sleep disruption.

To firmly establish whether an abnormal sleep pattern may be described as a disorder, the clinician must determine whether a patient’s daily function-

ing is impeded. If a patient reports he is only getting 5 hours of sleep each night, but his daytime performance and QOL are satisfactory and other potential health issues have been ruled out, then the physician may decline to make a diagnosis of hypersomnia. The same premise is true for the patient who sleeps 10 hours a day without symptoms of dysfunction or reduced QOL.

Sleep-wake cycles

A sleep cycle consists of 5 stages and lasts about 90 to 100 minutes. The first 2 stages are considered light sleep, and involve a slowing of heart and breathing rates and a decrease in body temperature. Stages 3 and 4, when deep sleep takes place, are the most restful and restorative sleep stages. Stage 5, the period of REM sleep, is a neurologically active period during which dreams are generally most vivid.

Sleep regulation is a function of a 2-part process, processes S and C.¹² Process S refers to a sleep-wake homeostasis in which the urge to sleep increases with the duration of wakefulness. Process C refers to the circadian rhythm, which is governed by the suprachiasmatic nucleus in the hypothalamus. The 24-hour circadian rhythm is itself set by exposure to light.

The neurologic underpinnings of the process S homeostasis has been supported by research suggesting that adenosine, a substance related to energy metabolism, may accumulate in the basal forebrain when a person is awake.¹³ Accumulated adenosine has the effect of suppressing those areas of the brain associated with wakefulness. According to this theory, the increased metabolic rate of a wakeful state induces a high rate of adenosine production, and a subsequent inclination to sleep. Once the threshold of sleep desire or need overcomes wakefulness—that is, once the brain enters the sleep cycle—adenosine levels diminish until wakefulness returns.

Neurologic research has also demonstrated interesting properties in the relationship between sleeping and wakefulness and the function of the hypothalamus. For example, stimulation of the posterior hypothalamus produces arousal, while

stimulation of the anterior hypothalamus produces sleep. Lesion in the posterior hypothalamus causes sleep, while lesion of the anterior hypothalamus causes insomnia. Damage or irritation to the brain, which may occur in the case of a tumor, but is more commonly the result of ingested brain-active chemicals, could have either one of these effects. Indeed, there are a large number of potentially sleep-inducing medications including anticholinergics, norepinephrine receptor blockers, and antihistamines.

Changing cycles

Numerous factors may disrupt, fragment, or shift the normal sleep cycle. Age is a central factor, although the commonly held notion that older people need less sleep is not necessarily the case. Older people often do experience a deterioration of quantity and quality of sleep, but in many cases, this is a consequence of declining health.^{14,15} Poor health can have a significantly detrimental effect on the sleep cycle. In extreme cases, such as in patients with pre-Alzheimer's dementia, sleep may be very severely affected. Mood disorders and depression tend to cause a shift in the sleep cycle, with REM sleep occurring earlier in the cycle. Early REM sleep is also a defining feature of narcolepsy. In patients with narcolepsy the REM stage may occur almost immediately but in normal patients, it may take 45 minutes or an hour before REM sleep is reached.

Age-related sleep changes also affect the young. Adolescents commonly experience delayed sleep phase syndrome, which involves a shift in the circadian rhythm entailing a natural propensity to go to sleep and wake up later than normal.¹⁶ The classic experience of the teenager struggling to wake up in the morning is not a symptom of an innate laziness or rebelliousness, but rather it is a feature of that particular period in their youthful development when their circadian rhythm is programmed to a different schedule. In fact, a movement advocating later school start times to accommodate the circadian rhythms of teenagers has arisen in recent years, although its successes have so far been sporadic.

Drugs mentioned in this article

Clonazepam (Klonopin)	Oxazepam
Dextroamphetamine (Dexedrine, DestroStat)	Phenytoin (Dilantin, Dilantin Infatab, Dilantin Kapseals)
Diazepam (Valium)	Propranolol (Inderal, Inderal LA, InnoPran XL)
Flurazepam (Dalmane)	Quazepam (Doral)
Gabapentin (Neurontin)	Ramelteon*
Gamma-hydroxybutyric acid	Temazepam (Restoril)
Hypocretin (Orexin)*	Theophylline
Lorazepam, injection (Ativan)	Triazolam (Halcion)
Melatonin	Zaleplon (Sonata)
Methylphenidate	Zolpidem (Ambien)
Modafinil (Provigil)	*Investigational drug.

Delayed sleep phase syndrome is also present in subset of the adult population, and it may have a genetic basis. It is not considered a disorder as long as the individual's lifestyle accommodates a preference for late hours. Late-shift work often attracts people with delayed sleep phase who regard the late night hours as an ideal working schedule. A problem only arises when a person with delayed sleep phase syndrome is forced to conform to a more typical daily schedule against his natural propensity, and thus lives with an ongoing struggle to be awake and to sleep at what is, for him, unnatural times. In these cases, life becomes like a constant state of jet lag, where the pursuit of adequate sleep is in perpetual conflict with the demands of an undesirable lifestyle.

DIAGNOSIS

EDS may be divided into 3 causative categories; insufficient *quantity* of sleep, insufficient *quality* of sleep, and excessive sleep drive disorder. The first category, insufficient quantity of sleep, may result from lifestyle issues, and can in a sense be described as "voluntary" to distinguish this problem from a genuine sleep disorder. The degree to which the lack of sleep is truly voluntary may be debatable, but the treatment of EDS in patients in this category involves a change in the patient's behavior and priorities rather than a clinically therapeutic approach. Other causes of insufficient quantity of sleep include shift work sleep

disorder and delayed sleep phase syndrome.

Poor sleep quality is most commonly a result of sleep apnea, and can also be caused by conditions such as RLS and periodic limb movement disorder (PLMD). Excessive sleep drive disorder as a category largely consists of narcolepsy, although certain varieties of idiopathic hypersomnia may be so described.

The first step to making a diagnosis is to distinguish between patients who do not set aside sufficient time for a proper amount of sleep from those with a true disorder. An initial interview addressing sleep schedule and habits should be able to accomplish this, during which the physician can outline the key features of EDS. One way of identifying those whose lack of sleep is "voluntary" is to establish the precise nature of their sleep behavior. For example, the patient who sleeps only 3 or 4 hours, but describes falling asleep promptly upon going to bed and feels more refreshed upon waking, is not necessarily suffering from a sleep pathology.

Interviewing the people familiar with the patient's sleep behavior (such as a spouse, child, or roommate) can help corroborate the patient's self-report. Their accounts may also provide additional information about traits that the patient is either unaware of, such as snoring, or reluctant to admit to, such as falling asleep while driving. An interview can also determine whether the sleep disorder involves a seasonal variation. If the patient only experiences problems in the winter, then SAD may be the cause.

A number of questionnaires and instruments are available to measure the extent and specific features of EDS. Visual analogue scales are available in versions for adults and children, as well as verbal analog scales such as the Stanford Sleepiness Scale. The most commonly used instrument for determining EDS is the Epworth Sleepiness Scale, which offers the patient a variety of situations in which they rate themselves for likelihood of falling asleep (see Figure 1, page 35). The patient is given 8 situations to score from 0 (no chance of dozing) to 3 (high chance of dozing). With a potential total score ranging

from 0 to 24, clinical diagnosis of EDS is determined by a score of 10 or more.

By establishing the nature of a given sleep disorder, the clinician can determine whether a patient can be treated in the primary care setting or should be referred for further care. Generally, patients requiring improved sleep hygiene, certain shift workers, those suffering from a non-sleep-related primary medical condition in which EDS is a symptom, and those taking sleep disrupting medications can be well-served by primary care practitioners. The clinician can also determine whether the sleep disturbance may have a primarily psychological etiology, as with depression or SAD, and whether referral for psychological evaluation and treatment is indicated.

If the patient does not fall into any of these categories, the next step would be referral to a sleep study center to determine if the patient is suffering from sleep apnea, narcolepsy, RLS, PLMD, or idiopathic hypersomnia. One of the key diagnostic tools available to sleep specialists is the Multiple Sleep Latency Test (MSLT). The MSLT involves having the patient try to nap 4 or 5 times in a darkened room on a schedule in which naps are attempted every 1½ hours, while an EEG measures sleep latency (the propensity to fall asleep). The MSLT determines the extent to which a patient is experiencing EDS. At bedtime, a normal adult has a sleep latency of about 7 minutes. A patient with narcolepsy would have an extremely short sleep latency period, and may fall asleep almost immediately. Short latency to REM sleep is symptomatic of narcolepsy, but it is also common with depression.

One of the challenges faced by the clinician dealing with a patient who complains of EDS is the amount of time required to arrive at a proper diagnosis. Detailed interviews and application of instruments, such as the Epworth Sleepiness Scale, may be too time-consuming for a primary care setting, and referral to a sleep center is appropriate.

FIGURE 1

Name _____

Today's date _____ Your age _____

Your sex (M/F) _____

How likely are you to doze off or fall asleep in the following situations in contrast to just feeling tired? This refers to your usual way of life in the recent past. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

- 0 Would never doze
- 1 Slight chance of dozing
- 2 Moderate chance of dozing
- 3 High chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (such as a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car while stopped for a few minutes in traffic	_____
TOTAL	_____

The Epworth Sleepiness Scale is used to measure the severity of sleepiness during normal daily activities. Excessive daytime sleepiness is defined by many sleep experts as a total score of 10 or higher, although different definitions are sometimes used.

Adapted with permission from Johns MW: A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540-545.

TREATMENT

Treatment of sleep disorders can consist of simple interventions that address lifestyle modifications, nonpharmacologic therapies that alter behavior, and pharmacologic regimens. The choices will depend on the etiology and severity of the problem.

Continued on page 36

ON THE HORIZON

Novel medications for insomnia

One of the most promising areas of research in the treatment of narcolepsy involves the use of hypocretin or hypocretin analog medications. Loss of hypocretin is the cause of most human narcolepsy.¹ Effective administration of hypocretin would constitute a miracle drug of sorts for people with narcolepsy, having much the same role as insulin for diabetics in addressing the cause of the disease and not simply treating its symptoms.

Unlike modafinil, hypocretin is a natural (not synthetic) substance, and also unlike modafinil, its neurologic action is fairly well understood.² Animal studies employing peripheral administration of hypocretin has shown efficacy in producing arousal; however, the effect is very short-lived.³ Further work may be required to produce a drug suitable for humans, possibly in a patch or long-acting oral form, that would provide potent arousal over the long-term, and potentially far greater efficacy than currently available medications.

The National Center for Sleep Disorders Research (NCSDR) of the National Institutes of Health released a plan for treatment and makes recommendations for research. The NCSDR proposes that efforts should be made to validate potential new diagnostic procedures, such as measuring hypocretin levels in the blood or performing imaging studies of the hypothalamus to diagnose narcolepsy. In addition, it suggests that further studies are needed to identify the cause of hypocretin destruction in human narcolepsy, to define a possible immune connection, and to

explore the existence of a genetic component.⁴

In late 2004, ramelteon, an investigational drug for transient and chronic insomnia, was submitted to the FDA for a new drug approval. Ramelteon is a compound in a new class of drugs known as selective ML-1 receptor agonists, and represents a new investigative approach to the treatment of insomnia. Ramelteon specifically targets the brain's ML-1 receptors located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Known as the body's master clock, the SCN regulates circadian cycles, playing an important role in the sleep cycle. Results from preclinical trials for ramelteon, presented at the 2004 annual meeting of the American Neurological Association, showed the drug to have significantly higher affinity, selectivity, and potency for the ML-1 receptors than melatonin.⁵

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Nonpharmacologic options

For patients who are not suffering from a primary sleep disorder such as sleep apnea or narcolepsy, a number of nonpharmacologic options may be helpful in normalizing sleep patterns. Sleep hygiene may be recommended to individuals with voluntary sleep issues. This approach is a primary treatment option for patients with shift work disorder, in which desynchronization occurs between the circadian rhythm and available opportunities to sleep within a patient's daily schedule. This disorder is primarily seen in night-

shift workers, although it also affects individuals who work irregular shifts. Good sleep hygiene requires a structuring highly disciplined approach to sleeping and waking times. It calls for creating an environment that is conducive to sleep; darkening a room with window shades and using eye masks helps. So does muffling loud noises and using ear plugs. Good sleep hygiene also requires exposure to light as much as possible during waking hours, and avoidance of excess light leading up to the allotted period of sleep.

Other lifestyle habits for optimizing sleep

include going to sleep at the same time every night and avoiding daytime naps. Excessive alcohol use and drinking alcohol before going to bed should be avoided, because alcohol has a destructive impact on sleep. Tobacco smoking should also be avoided, particularly before sleep, as should any medications that may stimulate wakefulness. Exercise is recommended to promote better sleep, but it should be avoided near bedtime. Trying to achieve an ideal body weight is also advised, particularly since there is a strong correlation between obesity and sleep apnea.

The 2 main nonpharmacologic treatments available for patients experiencing delayed sleep phase syndrome are chronotherapy and light therapy. Especially useful in treatment of patients with delayed sleep phase disorder, chronotherapy involves moving the bedtime forward by several hours each day until the desired sleep time is reached. At that point, the bedtime is locked in through a disciplined approach that may involve multiple alarm clocks, wake-up calls, and cohabitants who can assist in enforcing a consistent sleep regimen. This discipline must also be extended to any potential exceptions to the regimen, such as social activities and weekends, in which the risk of disrupting the new sleep schedule is particularly high.

Light therapy, a somewhat less radical approach, involves exposure to bright light during waking hours, particularly during the period right after waking. Apart from having an alerting effect, bright light has a corrective effect on the circadian rhythm, shifting the internal clock to correspond with the normal light and dark rhythms of day and night.

Pharmacologic options

Drug therapy for sleep disorders can be considered after a trial of nonpharmacologic interventions has proven unsuccessful. A review of all the

TABLE 2

Comparison of short- and long-acting hypnotics

Agent	Onset of action (min)	Half-life (h)	Adult bedtime dosage (mg) *
Short-acting			
Lorazepam [†]	30-60	10-20	1-2
Oxazepam [†]	15-30	5-20	15-30
Temazepam	45-60	10-40	15-30
Triazolam	30	2.5	0.25
Zaleplon	30	1.5	5-10
Zolpidem	30	2.5	5-10
Long-acting			
Clonazepam [†]	20-60	18-50	0.5-2
Diazepam [†]	30	20-100	5
Flurazepam	45-60	40-114	15-30
Quazepam	20-45	25-115	15

*Generally, patients older than 65 should receive only one half the adult dosage.
[†] Unlabeled use for sleep disorders

patient's medications will help determine whether they are contributing to the patient's sleep disorder. Treatment choices include hypnotics, stimulants, antidepressants, melatonin, and modafinil, a drug indicated specifically for the treatment of narcolepsy.

Hypnotics Hypnotics are used for short-term therapy to facilitate a regularized sleep schedule. Benzodiazepine receptor agonists are employed most frequently for this indication, having a positive effect on both daytime and nighttime symptoms. Short-acting benzodiazepines may be chosen for patients who need to be alert during the day, while longer-acting medications will help patients who experience daytime anxiety.⁵ Long-term use of hypnotics is not recommended, in part, because of their potentially detrimental health effects, and also because hypnotic use will treat symptoms but will not address the underlying cause of a sleep disorder, and may in fact mask the disorder (see Table 2).

Stimulants CNS stimulants can be used to bring intermittent symptom relief. Dextroamphetamine and methylphenidate are FDA-approved for the treatment of narcolepsy. Dextroamphetamine can be given as necessary in divided doses of 5 to 60 mg/d. Methylphenidate has also been used for the

treatment of hypersomnia when lack of alertness would be hazardous. The dosage of methylphenidate is up to 60 mg/d in divided doses, bid or tid. Patients should be screened and monitored for potential abuse of these controlled medications.

Antidepressants The use of sedative antidepressants in patients suffering from depression has been shown to relieve concomitant insomnia. There is little evidence to support their use in nondepressed patients. If an antidepressant is used, the specific choice should be tailored toward the individual patient's needs.

Melatonin This hormone is produced in the pineal gland, and has an opposite effect on the circadian rhythm to that of bright light. Because of this influence, melatonin may be used in treating delayed sleep phase syndrome. While it facilitates going to sleep, it does not function particularly well in maintaining sleep.

A variety of OTC melatonin formulations are available. A 3-mg initial dosage can be increased up to 10 mg, and patients trying to promote an earlier bedtime can take it in the evening. When melatonin is used to treat shift work sleep disorder, the right time to take the medication depends on the desired sleep schedule for a given individual.

Melatonin is well-tolerated, making it an attractive choice for older patients with cognitive impairment. Note that melatonin's effect on humans is not fully understood, so it should be prescribed and used cautiously. Furthermore, a standard dose of melatonin contains about 10 times the normal amount secreted by humans. It is unclear how much melatonin is absorbed when the drug is taken orally, but even an absorption rate of 20% would still represent twice the normal levels for human beings.

Modafinil This drug was first introduced to the US market in 1998 as a treatment for narcolepsy although it had been available in Europe for several years before that. In 2004, the FDA extended modafinil's indication to include adjunctive treatment for sleep apnea and for treatment of shift-work sleep disorder. The dosage for this indication is 100 mg/d to 200 mg/d given in the morning as an initial dosage. Some clinicians

increase this to 400 mg/d in the morning, predicated on patient response, but the data to support higher dosages are questionable. The duration of therapy depends on the clinical situation. Ongoing therapy will probably be required in a chronic situation. If the hypersomnia is transient, modafinil can be given as necessary.

Modafinil's mechanism of action is uncertain, but clearly it operates quite differently from earlier stimulants and based on its limited use to date, possesses a side-effect profile considerably more benign than other prescription stimulants.¹⁷ Headache is the most common side effect, occurring in about one third of patients, and nausea is seen in 11% of patients. Anecdotal reports suggest that most cases of headache and nausea are mild.

Some practitioners choose to make a distinction between modafinil and other stimulants and refer to it as a wakefulness-promoting agent.¹¹ Modafinil has not been associated with addictive behavior and does not appear to pose the kind of cardiovascular or hypertensive risks associated with standard stimulants.¹⁷ To date, there have been no reports of serious effects with modafinil overdose. Because it does have some interaction with birth control pills, women of childbearing age should be cautioned about its use. Modafinil is an inhibitor of CYP2C19 (cytochrome P-450, family 2, subfamily C, polypeptide 19), and can increase the circulating levels of certain drugs, including diazepam, phenytoin, and propranolol. Other potential drug-drug interactions have yet to be determined.

Experience with modafinil in the treatment of pathologies and conditions other than narcolepsy is much more limited. It does appear to be very helpful for patients with sleep apnea who are compliant with their primary treatment, and it has also been used off-label treatment to a bridge to the initiation of continuous positive airway pressure therapy, as well as to treat idiopathic hypersomnia and residual hypersomnia after treatment for sleep apnea.

As a prescription medication, modafinil compares favorably with other prescription stimulants in efficacy, tolerability, and safety. When

compared as a stimulant to the most widely used stimulant such as caffeine, its advantages are somewhat less absolute. Caffeine, usually in the form of coffee, is easily available, and far less expensive than modafinil, but there is some speculation that modafinil and caffeine may produce different effects.

A 2001 sleep deprivation study conducted at the Walter Reed Army Institute of Research, Silver Spring, MD, compared the effects of caffeine versus modafinil for alertness and performance in 50 healthy young adults.¹⁸ This initial study found no significant difference between the 2 drugs for either alertness or performance. Side effects for both drugs were few. Further research at Walter Reed, published in 2004, found that both drugs had a comparable effect on attenuating fatigue, but that modafinil was somewhat superior in reversing fatigue.¹⁹ The potential for abuse of modafinil as a stimulant is a cause of concern, as its off-label use is becoming widespread.

Other drugs for sleep disorders

RLS has been found to respond to dopamine agonists, opiates, and gabapentin.* REM sleep disorder

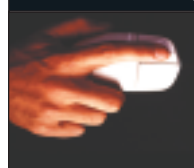
may respond to clonazepam,* while amphetamine-like stimulants and gamma-hydroxybutyric acid* are used to treat narcolepsy.²⁰ Valerian has been used for centuries to induce sleep. The recommended dosage is 2 to 3 g of dried root as an herbal tea tid or at bedtime. As with most herbal preparations, some time may be required before effects are seen. No side effects have been reported, but headache and daytime sleepiness may occur. □

* Unlabeled use.

This consensus article was written by James Borwick in consultation with Drs Siegel, Badr, and Krieger.

Drs Siegel, Badr, and Krieger disclose that they have no financial relationship with any manufacturers doing business in this therapeutic area.

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