NOTES

EXCESSIVE SLEEPINESS
Evaluation and Management

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U.S. Pharmacist Continuing Education

Goal: To review the causes and evaluation of excessive sleepiness (ES), with particular emphasis on newer pharmacological approaches and on the pharmacist's role in the recognition and management of narcolepsy, obstructive sleep apnea, and shift work sleep disorder

Objectives After reading this article, the pharmacist should be able to:

- **Identify** factors contributing to excessive sleepiness (ES).
- **Describe** subjective and objective tools used in measuring ES.
- **Recommend** several non-pharmacological interventions with respect to sleep hygiene.
- **Assess** the role of newer pharmacological agents in the treatment of narcolepsy, obstructive sleep apnea, and shift work sleep disorder.
- **Assist** patients in recognizing the significance of ES and the need for referral, when appropriate, as well as contribute to the education and monitoring of patients being treated with wake-promoting agents.

Excessive sleepiness (ES) is a very common complaint that can significantly impair a person's ability to function. Common etiologies include obstructive sleep apnea, narcolepsy, and sleep deprivation. This syndrome has been shown to significantly impair judgment, memory, and concentration. Excessive sleepiness must be evaluated promptly and thoroughly, because it may represent a significant underlying medical disorder and because the symptom itself can have catastrophic consequences.

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CASE PRESENTATION

M.G. is a 20-year-old male patient with a history of allergic rhinitis who presents with complaints of progressive daytime sleepiness for the past three years. He states that the symptoms began in high school when he first noticed frequent fatigue and sleepiness in class. More recently he has been falling asleep in other situations, such as at baseball games, at the movies, and while driving. He recalls one instance where he even fell asleep while painting his house. His grades in college have been affected by his inability to stay awake in class. He finds that no matter where he sits in the classroom, he is likely to doze off. M.G. has tried drinking coffee prior to class attendance, but it does not seem to help.

He reports getting an average of eight hours of sleep per night. There is no history of frequent awakenings during the night, and he generally awakens in the morning feeling refreshed. However, as the day progresses, his sleepiness increases. He frequently takes unintentional naps throughout the day. If he is given the opportunity, he can nap during the day for three to four hours at a time. M.G. also adds that he has noticed developing occasional, transient weakness in his jaw, neck, and limbs, especially in response to laughing at a joke. These episodes started about one year ago. The weakness sometimes prevents him from being able to talk, although he is able to hear others. He has no history of falls, but he has had one or two near-falls as a result of these episodes. He denies experiencing any loss of consciousness. M.G. also denies having a history of snoring, witnessed apneas, nightmares, or sleepwalking. His Epworth Sleepiness Scale (a subjective questionnaire used to assess daytime sleepiness) score is 21 out of 24, indicating he is prone to severe sleepiness.

Excessive sleepiness (ES) is a very common complaint that can significantly impair a person's ability to function. ES has a wide spectrum of presentation, ranging from mild sleepiness to unrecognized episodes of "microsleeps" and uncontrollable sleep attacks. Excessive sleepiness can occur due to a variety of reasons (Table 1). Common etiologies include obstructive sleep apnea, narcolepsy, and sleep deprivation. Other causes include circadian rhythm disorders (eg, nightshift work), underlying medical disorders, and drug effects. Young adults often complain of ES, but it is usually a result of poor sleep hygiene and sleep deprivation. The advent of highly technological societies has placed an impetus on productivity and efficiency. This thrust has brought about longer workdays and 24-hour work shifts. The individuals in modern society are chronically sleep-deprived, resulting in excessive sleepiness that is transparently manifest in passive situations. At present, human error causes the majority of industrial and transportation accidents.[1] The increased prevalence of motor vehicle and work-related accidents are in large part due to the effects of ES. This syndrome has been shown to significantly impair judgment, memory, and concentration. Excessive sleepiness must be evaluated promptly and thoroughly, because it may represent a significant underlying medical disorder and because the symptom itself can have catastrophic consequences. Because of the numerous potential causes of excessive sleepiness, early referral to a board-certified sleep specialist should be considered for anyone presenting with this problem.

CAUSES

Narcolepsy

This is a medical disorder defined as irresistible sleepiness, usually occurring in association with a specific subset of symptoms, such as cataplexy, sleep paralysis, automatic behavior, and hypnagogic hallucinations. The prevalence of narcolepsy is estimated to be 0.03% to 0.05% in the general population.[2] The peak onset of symptoms occurs in adolescence, with a second peak near 40 years of age. Narcolepsy is not a progressive disorder, but it does usually persist for life. Approximately 1-2% of the first-degree relatives of narcoleptic patients develop the illness. It can become evident as pathologic daytime sleepiness when the individual develops a tendency to fall asleep in unusual circumstances, such as during physical exertion or a stimulating activity.[2]

The most dangerous aspect of narcolepsy is the potential for sudden sleep onset, which can result in accidents occurring while driving or working. Typically, patients with narcolepsy take a variable amount of naps during the day. These naps can range from very brief microsleeps to hours of extended sleep. Patients often find these naps refreshing, at least for a while. Even with treatment, narcolepsy can have a negative impact on health, social function, and performance at school or work.

The classic tetrad of symptoms associated with narcolepsy includes ES, cataplexy, sleep paralysis, and hypnagogic hallucinations. These latter three symptoms may not always be pre-

sent. In fact, it is estimated that only 10% to 15% of patients demonstrate all four of these symptoms.[3] However, most patients with narcolepsy have cataplexy, which is described as a sudden weakness in the muscles of the face, neck, or limbs in response to a strong emotional stimulus. The emotional stimulus usually triggering a cataplectic attack is laughter or anger. Occasionally, cataplexy can be generalized, causing complete loss of skeletal muscle tone and reversible paralysis. Usually these episodes last only a few seconds. During an episode of cataplexy, the patient remains aware of his or her surroundings but may be unable to respond to verbal stimuli. Also, the individual with cataplexy usually does not suffer any bodily harm, even if falling to the ground, because the weakness is gradual, allowing one to brace for the descent. Cataplectic attacks can vary in frequency from once every few years to 15 to 20 episodes per day. Approximately 70% of all narcoleptic patients have occasional cataplexy.[4]

Sleep paralysis occurs in about 25% of individuals with narcolepsy.[4] The typical episode is described as feeling paralyzed for a few seconds at sleep onset or upon awakening from sleep. There is no loss of consciousness.

Hypnagogic hallucinations are vivid auditory, visual, or somesthetic hallucinations that usually occur at sleep onset, and they occur in about 30% of narcoleptic individuals.[4] These experiences usually last for a few minutes and may be associated with sleep paralysis.

The pathogenesis of narcolepsy remains unknown. Specific HLA (human leukocyte antigen) alleles have been found in nearly all narcoleptic patients.[4] Further, the increased prevalence in first-degree relatives also indicates a genetic basis. However, the small incidence of familial cases and the low concordance rate (25% to 30%) of narcolepsy between identical twins suggest there are other factors involved. It seems likely that environmental factors play a role in the development of this disorder in genetically susceptible individuals. There are also numerous case reports of "secondary" narcolepsy, including some with cataplexy. Such cases have been associated with head trauma, stroke, multiple sclerosis, brain tumor, neurodegenerative disorders, and central nervous system (CNS) infections. Recent studies have shown abnormalities of the hypocretin system in the CNS of narcoleptic individuals.[5,6] Hypocretins, also known as orexins, are neuropeptides found in hypothalamic neurons. These hypocretin-containing neurons project throughout the CNS, including areas of the brain known to effect regulation of the sleep-wake cycle. Hypocretin deficiency in the cerebrospinal fluid has been demonstrated in large studies of narcoleptic patients. These findings suggest that hypocretins may play a central role in the pathophysiology of narcolepsy.[6]

The patient history is of crucial importance in the diagnosis of narcolepsy. The most helpful symptom in diagnosing narcolepsy is clear-cut cataplexy. Once a reliable history is established, a subjective instrument for ES may be used (eg, the Epworth Sleepiness Scale). To confirm the diagnosis, polysomnographic evaluation is essential. A multiple sleep latency test (MSLT) can be used to detect the mean latency to sleep onset and to determine if there are any sleep-onset REM periods. Two or more of these sleep-onset REM periods (SOREMs) during an MSLT are confirmatory of the clinical diagnosis. Also, one would expect to find a very short latency period to sleep onset (ie, less than five minutes) in a narcoleptic patient.

Obstructive Sleep Apnea Syndrome (OSAS)

A more prevalent cause of ES in our society is OSAS. OSAS with ES has been estimated to occur in 2% to 4% of the population. One study estimated that sleep apnea itself is present in 24% of men and 9% of women in the general population.[7] Risk factors for OSAS include obesity, increasing age, male gender, and a positive family history. However, sleep apnea can occur at all ages and in both sexes.

OSAS is a syndrome characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation. This upper airway collapse can be partial or complete, resulting in airflow limitation or apnea, respectively. Apnea is defined as a complete absence of airflow at the nose and mouth for a period of at least 10 seconds in an adult. Any obstruction to respiratory airflow can cause a decrease in the body's ability to uptake oxygen. The increasing respiratory effort required to breathe with obstruction can result in arousals from sleep. These arousals function to signal the body to adjust its position in order to restore patency to the airway. This process is often witnessed as a sudden gasping or choking for air during sleep. These frequent arousals from sleep produce sleep fragmentation, leaving the patient feeling unrefreshed upon awakening and very tired and sleepy during the day. ES may be subtle to very severe. Frequently, patients with mild OSAS will deny any daytime sleepi-

ness or fatigue. However, any degree of OSAS can have catastrophic consequences, such as falling asleep while driving.

In addition to daytime symptoms of excessive sleepiness and fatigue, nocturnal symptoms often found in association with OSAS include snoring, witnessed apneas, gasping or choking, restless sleep, nocturia, and morning headaches. Patients with OSAS will commonly report awakening with a dry mouth, likely a result of breathing through the mouth during sleep. Occasionally, depression, impaired memory and concentration, and personality changes are noted. Impotence can be a problem associated with OSAS in men. Children with OSAS may present with nocturnal bedwetting (enuresis). OSAS in children frequently causes mood changes, increased irritability, and a decline in school performance. All of these problems are usually reversible with treatment.

OSAS is causing a significant impact on modern society. ES caused by OSAS has been demonstrated to decrease productivity through impaired memory, concentration, and learning. Furthermore, research studies have shown that the driving skills of subjects with OSAS were almost identical to those of a comparative group without OSAS who had an average alcohol level of 0.10 (above the legal limit of most states).[8] So obviously the ES related to OSAS largely increases the risk of motor vehicle accidents and work-related accidents. Moreover, the dangers of OSAS are not limited to the cognitive impairment caused by ES. The NIH-sponsored Sleep Heart Health Study has demonstrated that OSAS independently increases a person's risk for cardiovascular events, including hypertension, heart disease, and stroke.[9]

As previously stated, OSAS occurs due to repetitive obstructions in the upper airway during sleep. There are a number of reasons for this recurrent collapse in the upper airway. First of all, there is a natural decrease in the muscle tone in the oropharynx during sleep. However, this muscle relaxation alone is not enough to cause upper airway obstruction. Current evidence suggests that most patients with sleep apnea have a small oropharyngeal airway, due to hereditary and environmental factors. Further, tonsillar enlargement, nasal turbinate hypertrophy, and nasal congestion can all contribute to upper airway obstruction.

Guilleminault has demonstrated that the airway collapse in OSAS is likely a result of relaxation in the upper airway musculature in the presence of a primary narrow airway.[10] Repetitive apneic events result in frequent drops in oxygen saturation and a resultant release of catecholamines with adrenergic effects. This increase in sympathetic tone can cause elevations in blood pressure. At the same time, during apnea there is a large increase in intrathoracic pressure due to the increase in respiratory effort. This elevated intrathoracic pressure results in increased venous return to the heart and decreased cardiac output. The effects over time can be very serious. Congestive heart failure, hypertension, and stroke are secondary effects of chronic, untreated OSAS. Also, pulmonary hypertension caused by OSAS has been well documented. Clinical studies have confirmed that OSAS exacerbates chronic pulmonary diseases, such as asthma and chronic obstructive pulmonary disease (COPD).[11,12]

To confirm the diagnosis of OSAS, nocturnal polysomnography conducted by an accredited sleep laboratory is indicated. The diagnosis is made based on clinical history and physical examination, along with nocturnal polysomnographic monitoring. To meet the criteria for diagnosis, the sleep study must demonstrate five or more respiratory events per hour. These respiratory events must be longer than 10 seconds in duration and be associated with an arousal from sleep. With apneic episodes, arterial oxygen desaturation is often seen. Overnight pulse-oximetry monitoring alone is inadequate to diagnose OSAS, because of the high rate of false- negative results. According to *The International Classification of Sleep Disorders*, an overnight polysomnogram is required to diagnose OSAS.[13] The American Academy of Sleep Medicine has outlined the standard indications of nocturnal polysomnography.

Insomnia

This is another cause of ES, but it should be clear that insomnia itself is a symptom, not a diagnosis. Insomnia has been defined as difficulty initiating or maintaining sleep, or a complaint of not feeling rested despite a sufficient opportunity for sleep. There are an array of causes of insomnia, which include medical, psychiatric, neurological, environmental, and behavioral disorders. Proper diagnosis requires a complete and thorough history and evaluation of underlying conditions. People with insomnia often complain of experiencing racing thoughts while lying in bed and they frequently develop poor sleep habits over time. These poor sleep habits become difficult to change. Insomniacs often lose the association of sleep with the bedroom. In other words, the bedroom becomes a mentally charged environment. Also, insomniacs have difficulty sleeping during the

day, even if they are experiencing ES or fatigue. However, this inability to sleep results in sleep deprivation, thereby impairing memory, concentration, and judgment.

Other Causes of ES

These include sleep deprivation and circadian rhythm disturbances. Sleep deprivation can be self-induced or secondary to another medical disorder. Sleep deprivation generally refers to inadequate quantities of sleep due to poor sleep hygiene or social constraints. The spectrum for sleep deprivation ranges from subtle to very severe, leading to potentially catastrophic ES. A prime example of human error and poor judgment related to sleep deprivation is the Space Shuttle Challenger accident in 1986. A Presidential Commission found that specific key figures in the event had less than two hours of sleep the night before and had been on duty for excessive hours.[14] Numerous other examples of accidents related to sleep deprivation exist such as those associated with the Exxon Valdez, the Chernobyl nuclear plant, and the Three Mile Island nuclear plant.

Shift work sleep disorder affects up to five million people in the United States. It is defined as a complaint of insomnia or excessive sleepiness that occurs as a transient phenomenon in relation to work schedules. It increases the incidence of sleep disruption, excessive sleepiness, chronic fatigue, and gastrointestinal complaints.[15] A sudden work shift change of eight hours may cause the sleep-wake schedule to be out of synchronization with other circadian biorhythms. When the circadian physiology is desynchronized, sleep can be disrupted. This sleep disruption adds to numerous accidents on the job and while driving. Shift workers are also reported to have a higher incidence of chronic depression, emotional problems, substance abuse, gastric ulcers, and heart disease than the general population. Shift work problems can be understood by taking into consideration the various dynamics involved. The interaction of circadian rhythms, sleep demands, and social factors all play a role in determining shift work coping ability.

Another circadian rhythm disturbance that occurs more commonly in adolescents and young adults is delayed sleep phase syndrome. With this syndrome, individuals often develop a phase shift delay in their sleep circadian cycle, with a tendency to sleep later and wake up later than the rest of society. The sleep onset and wake times are delayed from three to six hours relative to conventional sleep-wake times. This delayed sleep phase can create problems with ES, especially if the person has an obligation to wake up early in the day. These individuals have great difficulty both in initiating sleep at night and in waking up early in the morning. To accommodate for this circadian phase delay in students at Stanford University, William Dement recommended rescheduling classes or working later in the day. Results were positive, as demonstrated by improvement in test scores, and it is now evident that these individuals generally do well if their work requirements do not place a burden to wake up earlier than preferred. In cases where this is not possible, adjustment of the sleep-wake cycle may be attempted under the supervision of a skilled sleep disorders physician.

Table 1

Frequent Causes of Excessive Sleepiness

Sleep apnea and other sleep-related breathing disorders
Narcolepsy
Idiopathic hypersomnia
Psychiatric disorders
Periodic limb movement disorder
Chronic use of drugs or alcohol
Other medical disorders
Insufficient sleep
Sleep-wake cycle disorder

ASSESSMENT

The degree of excessive sleepiness can easily be estimated with rating scales, such as the Stanford Sleepiness Scale and the Epworth Sleepiness Scale. But to objectively measure excessive sleepiness, two tests have been developed in clinical practice. The multiple sleep latency test (MSLT) is more commonly used; it measures the ability of an individual to fall asleep. The Maintenance of Wakefulness Test (MWT) is administered under similar conditions, but it tests the ability of the individual to stay awake. These tests can be performed at any accredited sleep center.

The MSLT consists of a series of five nap opportunities at two-hour intervals during which the subject tries to fall asleep. Each trial is terminated after either 20 minutes of wakefulness

or 15 minutes of sleep. Time to sleep onset is measured and averaged over all naps to determine the mean sleep latency. A mean sleep latency of less than 10 minutes is considered significant. The MSLT can be used to quantify the severity of ES and to assess response to therapy.

The MWT consists of a series of four to five trials at two-hour intervals during which the participant tries to stay awake under conditions of minimal stimulation. Each trial is terminated at the onset of sleep or if sleep onset is not achieved by 20 minutes. Again, the sleep latency is measured. The MWT is useful in assessing the ability of an individual to stay awake.

TREATMENT

Sleep disturbance resulting from an insomnia disorder or poor sleep habits should prompt a trial of sleep extension, along with education about sleep hygiene and insomnia. These non-pharmacological interventions are a helpful first step. Some sleep hygiene measures are presented in Table 2.

In addition to the measures noted in Table 2, stimulus control is an important behavioral intervention for poor sleep habits. The patient should understand that the bedroom is to be used only for sleep and sexual activity. Activities such as eating, drinking, watching TV, working on the computer, and paying bills should be done elsewhere, because they can interfere with sleep onset. Also, emphasis should be placed on avoidance of spending time in bed worrying. If patients find themselves unable to sleep after about 30 minutes at any time during the night, they should get out of bed and try reading or performing a relaxing activity. They should then return to the bedroom only when they feel sleepy again. This habit will prevent the development of a conditioned arousal to the sleep environment.

Pharmacological interventions for ES are commonly used. Caffeine has long been used as a stimulant in many societies throughout history. Caffeine competes for adenosine receptors, and it produces increases in awakenings and decreases in total sleep time during nocturnal sleep. Sensitivity to the effects of caffeine can last up to 14 hours.[16] The average cup of coffee contains 100 mg of caffeine. A strongly brewed cup of coffee contains about 200 mg of caffeine, whereas tea and cola drinks contain up to 100 mg. The amount of caffeine intake should be determined for any patient presenting with ES.

At the present time, the treatment of narcolepsy consists of medications, education, support, and behavioral changes. The most important goal should be to help in preventing the patient from falling asleep while driving or working in a dangerous situation. Behavioral interventions are an essential component of a multifaceted approach. The first step is to optimize sleep hygiene to maximize the quality and quantity of nocturnal sleep. The next step should be to have the patient schedule regular daytime naps. Naps of 20 to 30 minutes' duration at regular intervals a few times per day can be very refreshing for the narcoleptic patient. Finally, another key to success is to educate the patient and the patient's family, teachers, and employers regarding the treatment and the natural history of this illness.

Pharmacological treatments for narcolepsy have classically consisted of stimulants and anti-cataplectic compounds. A newer agent, modafinil (Provigil), has recently been approved for the treatment of excessive sleepiness associated with narcolepsy and will be discussed in detail in the following section. The most commonly prescribed stimulants consisted of amphetamine-like drugs such as dextroamphetamine, methamphetamine, methylphenidate, and pemoline. Similar to tricyclic antidepressant medications (TCAs), these drugs are very nonspecific pharmacologically. Their main effect is to globally increase monoaminergic transmission by stimulating monoamine release and blocking monoamine reuptake. Studies have demonstrated that the wake-promoting effects of these compounds are secondary to dopamine-release stimulation and reuptake inhibition.[17] Interestingly, drugs selective for dopaminergic transmission have no effect on cataplexy, whereas amphetamine-like compounds with combined dopaminergic and adrenergic effects have some anti-cataplectic properties at high doses.[18] Reports of the increased risk of liver damage with pemoline, an oxazolidine derivative, have reduced its use in the treatment of children. Use of pemoline is no longer recommended. Dextroamphetamine and methamphetamine produce the greatest improvement in daytime alertness. However, side effects of anorexia, tachycardia, and elevations in blood pressure are common. Further, high doses of these compounds can produce hallucinations and psychosis.

Methylphenidate is recommended for the treatment of ES in narcolepsy because it tends to be better tolerated compared to other agents.[19] Methylphenidate has a short half-life and is available in a slow-release form. The recommended dose is based on weight, with a maximum of 30 mg per day. The drug is administered in the morning (15 mg) and at lunchtime (15

mg maximum). In adults, methylphenidate and amphetamines at dosages of more than 60 mg per day do not significantly improve ES without side effects.[20] This combination therapy is usually given in three divided doses: in the morning, at lunchtime, and in the early afternoon (no later than 3 p.m.).

REM-associated muscle atonia occurs at inappropriate times during wakefulness in narcoleptic patients and is responsible for cataplexy. Thus, treatment of cataplexy typically involves the use of REM-suppressing drugs. Agents that block the reuptake of norepinephrine, such as the TCAs, have been effective. However, the use of TCAs for cataplexy is limited by their side effect profile, particularly their anticholinergic effects that may lead to impotence in males.

Serotonin reuptake inhibitors such as fluoxetine are also helpful, but relatively high doses may be necessary.[21] The most common dosages are 40 to 60 mg per day of fluoxetine or 100 mg per day of clomipramine. Recently, venlafaxine has been used successfully to treat cataplexy at dosages of 150 to 300 mg per day. Patients should be withdrawn from these medications slowly. Abrupt withdrawal of these drugs will induce a significant rebound of cataplexy, sleep paralysis, and hypnagogic hallucinations. The recommended withdrawal schedule is one dose every four days. Even with such a schedule, cataplexy rebound will occur. There is an increased risk of bodily injury from falls during this period, depending on the severity of the rebound of cataplexy. Patients must be warned about this side effect and should abstain from driving during the withdrawal period.

To date, there are no pharmacological agents that have been shown to be effective in curing obstructive sleep apnea. Only one drug, modafinil, has been approved to treat residual ES in patients who are already under standard treatment for OSAS. Traditionally, treatment for OSAS consists of nasal CPAP (continuous positive airway pressure), surgery, or dental appliance use.

Nasal CPAP is a very valuable device in treating OSAS patients. It works by providing an optimal amount of air pressure to the upper airway, thus preventing collapse of the tissues. This "stenting" of the upper airway allows the patient to breathe without any airflow limitation, obstruction, or snoring. Nasal CPAP generally requires a period of about four weeks for patient adjustment and comfort. However, once past this initial adjustment period, most patients with OSAS can feel the difference. Nasal CPAP has been proven to reduce the frequent nocturnal arousals from sleep due to sleep-disordered breathing, thus preventing apneic events and respiratory oxygen desaturations. With regular use of nasal CPAP, all of the adverse effects of OSAS may be reversed.[22]

Table 2

Sleep Hygiene Measures

Restrict sleep to amount needed to feel rested
Avoid forcing sleep
Keep a regular sleep-wake schedule, even on weekends
Avoid caffeine after lunch
Avoid alcohol near bedtime
Adjust bedroom environment for comfort
Exercise regularly, but at least three hours prior to bedtime
Do not go to bed hungry
Create a wind-down time at least 30 minutes prior to bedtime

An option to nasal CPAP is surgery. Various surgical interventions to the upper airway can be helpful in reducing the effects of sleep-disordered breathing. The type of surgery indicated depends on the specific anatomy of each patient with OSAS. Frequently, adenotonsillectomy, uvulopalatopharyngoplasty, and nasal turbinate reduction are effective.[23]

Finally, dental appliances must be mentioned as a treatment option for patients with mild to moderate OSAS. Occasionally, use of an oral appliance to keep the mandible or tongue protracted during nocturnal sleep has been shown to be helpful.[24]

More conservative measures to reduce the effects of OSAS have been described. Patients are advised to avoid alcohol or sedative hypnotic medications, which can exacerbate OSAS. In addition, weight gain can worsen symptoms; therefore, patients are encouraged to exercise regularly and monitor their food intake. Most people with sleep apnea tend to have more events when sleeping supine as compared to sleeping on their side. Avoidance of supine sleep can be helpful. Classically, patients have been directed to wear a shirt with a pocket in the back to hold a tennis ball in order to prevent supine sleep. Sleep deprivation will apparently compound the excessive sleepiness associated with OSAS, and patients should be instructed to extend their sleep time if possible. Pharmacists should caution

all patients with ES not only to avoid CNS depressants, but also to avoid operating motor vehicles or dangerous equipment until daytime alertness improves.

Treatment of circadian rhythm disorders is best achieved through specific adjustments in the sleep-wake cycle through chronotherapy. Chronotherapy is the adjustment of circadian sleep-wake rhythm through means of light therapy. Bright light exposure at specific times of the day can help to shift the circadian rhythm to suit the individual's needs. Chronotherapy has been used successfully in the treatment of delayed sleep phase syndrome. However, it should be pointed out that chronotherapy requires a significant amount of patient motivation.

The treatment of shift work sleep disorders depends on whether the subject is having problems with insomnia or with excessive sleepiness. Shift workers having difficulty with initiating or maintaining sleep when off-duty may benefit from hypnotic medications, such as zolpidem (Ambien) or zaleplon (Sonata). However, hypnotics should be considered for those with only occasional shift work. Hypnotic use on a chronic basis by long-term shift workers should not be encouraged. Melatonin has been given a considerable amount of attention as a possible hypnotic agent. But melatonin has a half-life of only 20 to 30 minutes, so it most likely has an impact only on sleep onset.[25] Studies have shown that melatonin may be beneficial in the treatment of various sleep disorders, including shift work sleep disorder. Nevertheless, the safety and efficacy of melatonin remain largely unknown, and it is not recommended for long-term use at this time.

Conversely, workers who suffer from ES related to shift work sleep disorder often use caffeine or tobacco to cope. Caffeine used in reasonable amounts can be helpful, but caffeine misuse can have a negative impact on sleep onset later in the cycle. A newer agent has been approved for treatment of this disorder, and it will be discussed further in the following section.

RECENT ADVANCES

Over the last few years, newer agents have emerged for the treatment of ES. One of these recent developments is modafinil, which is indicated to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea syndrome, and shift work sleep disorder, the latter two indications being added only a short time ago. Modafinil has just recently been approved by the FDA for use as an adjunctive therapeutic agent for ES secondary to obstructive sleep apnea. It is indicated as an add-on to standard treatment for the underlying obstruction, increasing the average time to sleep onset during MWT by 1.5 minutes in patients given 200 or 400 mg daily, as compared with a 1.1-minute decrease in those given placebo. If CPAP is the treatment of choice for a patient with OSAS, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating modafinil.

Prior to this new indication, modafinil has been used in the treatment of narcolepsy and shift work sleep disorder. For patients experiencing sleepiness during nightshift work, modafinil can be very helpful in maintaining wakefulness to prevent serious accidents on the job. It can also be beneficial in patients either adjusting to shift work or having occupations requiring rotating shift work. In a 12-week controlled clinical trial, only patients who were symptomatic for at least three months were enrolled, and modafinil showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by a nighttime MSLT.[26]

Modafinil is a good choice as the initial treatment in newly diagnosed cases of narcolepsy. In adults who have already been treated with amphetamine-like agents, it has been found to be less efficacious. Also, modafinil does not control cataplexy, and it may need to be given with anti-cataplectic medications if this symptom is an important clinical problem. Long-term use of modafinil has not been well studied, and periodic re-evaluation of long-term utility is necessary in these cases.

The precise mechanism of action of modafinil remains unknown.[27] Modafinil has wake-promoting properties similar to amphetamine-like compounds, although its pharmacologic profile is different. At therapeutic concentrations, it does not bind to most potentially relative receptors for sleep-wake regulation. Modafinil is not a direct or indirect agonist of dopamine receptors. Further, it has been shown to have no effect on dopaminergic activity in research studies.[28] There is no evidence for any direct or indirect α_1-adrenergic effects. Modafinil is a racemic compound whose enantiomers have different pharmacokinetics. Steady states are reached after two to four days of dosing. Absorption is rapid, with peak plasma concentrations occurring at two to four hours. The major route of elimination is metabolism, primarily by the liver, with the metabolites being subsequently renally excreted. The effective elimination half-life of modafinil is 15 hours.

Two nine-week, double-blinded, placebo controlled multi-

center trials demonstrated improvement in subjective and objective measures of ES for both the 200-mg and 400-mg doses compared to placebo.[29,30] The objective tests used to measure ES in these clinical trials were the MWT and MSLT. Nocturnal sleep measured by polysomnography was not affected by modafinil. Treatment protocols with modafinil that extend beyond nine weeks may require periodic re-evaluation by both the pharmacist and the physician.

Modafinil is generally well tolerated. Controlled clinical trials found that adverse effects were mild to moderate. The most commonly observed adverse events are headache, infection, nausea, nervousness, anxiety, and insomnia. The most frequent reasons for discontinuation include headache (1%), nausea (1%), depression (1%), and nervousness (1%). As an inducer of cytochrome P-450 3A4 (CYP 3A4), modafinil has the potential to increase the metabolism and to decrease the efficacy of such drugs as cyclosporine and oral contraceptives. In a controlled study in patients with narcolepsy, chronic dosing of modafinil at 400 mg once daily resulted in about a 20% mean decrease in plasma trough concentrations by week nine, compared to levels at week three, suggesting that chronic use of modafinil may cause induction of its metabolism.[30] Coadministration of potent inducers or inhibitors of the cytochrome P-450 enzyme complex may alter the levels of modafinil. Studies evaluating the coadministration of modafinil with either methylphenidate or clomipramine showed there were no significant effects on the pharmacokinetics of either drug.

The dose of modafinil is 200 mg/day, given as a single dose in the morning. Doses of up to 400 mg/day, given in divided doses in the morning and at lunchtime, may be effective for patients not responding to lower doses. There is no evidence that doses greater than 400 mg /day confer any additional benefit.

Another novel agent receiving notice for the treatment of ES related to narcolepsy is sodium oxybate (Xyrem). Sodium oxybate has been used for years in Europe and Canada for the treatment of cataplexy in narcolepsy, but only recently has it been approved for such use in the US, representing the first drug with FDA approval for this indication. Sodium oxybate is a CNS depressant with anti-cataplectic activity in patients with narcolepsy. Results of clinical studies in other countries have indicated a slow but progressive improvement in daytime alertness, which narcoleptic patients regard as the most important benefit of the drug.[31] This effect may not occur until the

Table 3

The Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. 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 nymber for each situation:

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

- Sitting and reading? _____
- Watching TV? _____
- Sitting inactive in a public place (eg, 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 lunch without alcohol? _____
- In a car, while stopped for a few minutes in traffic? _____

The Epworth Sleepiness Scale Key

- 1-6, congratulations you are geting enough sleep
- 7-8, your score is average
- 9 and up, seek the advice of a sleep specialist without delay

agent has been used for several weeks, suggesting that there is a slow reorganization of sleep-wake control over time. There is ample evidence that non-REM sleep is drastically affected in patients with narcolepsy, and restoration of a normal balance of nocturnal non-REM and REM sleep may be one of the benefits of sodium oxybate.

This chemical compound also goes by the name of gamma-hydroxybutyrate (GHB), a drug often associated with abuse. This abuse potential has been shown to effect significant CNS adverse events, including death. However, when used responsibly and under strict regulation (currently, through a single centralized dispensing pharmacy), sodium oxybate is a very effective tool in patients suffering from narcolepsy.

CASE ANALYSIS

M.G.'s history is typical of a patient with ES secondary to narcolepsy. He describes an irresistible sleepiness that is interfering with his daily activities. Even in stimulating social situations, he finds it difficult to stay awake. His ES is becoming socially debilitating, affecting his school and work performance, in addition to the embarrassment he feels in social settings. M.G. also describes symptoms of cataplexy. M.G. reported having 10 to15 episodes per day and, as it turned out, he was anxious to get this symptom under control.

M.G. was scheduled for a nocturnal polysomnogram with a subsequent MSLT. In the meantime, he was advised to avoid driving while sleepy. He was also encouraged to avoid water sports and to avoid operating heavy machinery until his EDS improved with treatment. Within two weeks, the sleep studies were performed. The nocturnal polysomnogram showed sleep fragmentation with no evidence of any significant sleep-disordered breathing. His MSLT revealed a mean sleep latency of 3.5 minutes with three sleep-onset REM periods, thus confirming the diagnosis of narcolepsy.

Treatment was initiated with modafinil 200 mg per day and venlafaxine 75 mg per day. After careful titration of the dosages of these medications, M.G. had appreciated significant overall improvement in his sleep quality and daytime alertness. He also experienced considerably fewer episodes of cataplexy. Sodium oxybate would have been an alternative treatment. The patient was given instruction on proper sleep hygiene to improve the quality and quantity of his nocturnal sleep and on the need for scheduled naps during the day to reduce his daytime sleepiness. Although narcolepsy will be a life-long illness for M.G., he is better prepared to cope with it through the implementation of these pharmacological and behavioral interventions.

The precise mechanism by which sodium oxybate produces an effect on cataplexy is unknown. Sodium oxybate is rapidly but incompletely absorbed after oral administration. It has an absolute bioavailability of about 25%. Following oral administration, the plasma levels of sodium oxybate increase more than proportionally with increasing doses. Absorption is delayed and decreased by a high fat meal. Metabolism is the major elimination pathway for sodium oxybate. On average, less than 5% of unchanged drug appears in the urine within six to eight hours after administration.

The effectiveness of sodium oxybate as an anti-cataplectic agent was established in two randomized, double-blind, placebo-controlled clinical trials in patients with narcolepsy. [31,32] Over 80% of these patients were also being treated with CNS stimulants. The high frequency of concomitant stimulant use has made it virtually impossible to assess the safety and efficacy of sodium oxybate independent of stimulants. The combined use of alcohol with sodium oxybate may cause potentiation of the CNS-depressant effects of these drugs. Therefore, patients should be warned strongly against the use of any alcohol in conjunction with sodium oxybate. In addition, sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants.

The most commonly reported adverse events associated with sodium oxybate were dizziness, headache, nausea, pain, sleep disorder, confusion, infection, vomiting, and urinary incontinence. Sleepwalking was reported in 7% of 448 patients treated in clinical trials with sodium oxybate.[33] Therefore, patients should be warned about this possibility, and precautions should be considered. Also, the risk of falls resulting in injury is increased after sodium oxybate administration. Patients should be instructed to lie down and sleep after each dose of sodium oxybate and not to take this drug at any time other than at night. It is required to be taken at bedtime while in bed and again 2.5 to 4 hours later.

The recommended starting dose for sodium oxybate is 4.5 grams per day divided in two equal doses. Sodium oxybate is

effective at doses of 6 to 9 grams per day. Given the increased risk of adverse effects, doses greater than 9 grams per day are not routinely administered. Because food significantly reduces the bioavailability of sodium oxybate, patients should try to eat well ahead of their anticipated sleep time.[33]

CONCLUSION

Pharmacists are of vital importance in the education of patients with respect to medications used to treat individuals with ES. The Epworth Sleepiness Scale can be used to screen patients for ED (Table 3). One should be aware of the various causes of ES. Patients should be cautioned about the risks associated with ES, including work-related injury and accidents while driving. Those presenting with ES should be encouraged to learn more about sleep and to inform their physicians of their symptoms. Resources for sleep and its disorders can be obtained through the American Academy of Sleep Medicine (www.aasmnet.org) and the National Sleep Foundation (www.sleepfoundation.org). Patients should be advised that with behavioral therapy, symptoms will improve over time. However, some patients who present with primary complaints of ES may need pharmacotherapy. In addition to knowing the best pharmaceutical agents for the treatment of ES, pharmacists can take the iniative to assure the best possible continuity of treatment and quality of care for their patients. During patient counseling sessions, pharmacists should emphasize the side effect profiles of these medications. *

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EXAMINATION

Select the one correct answer to each of the following questions and record your response on the examination answer sheet. The answer sheet should be removed from this supplement and mailed to *U.S. Pharmacist*, address shown on the exam sheet. (Photocopies are acceptable.)

2 CE Credits

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EXCESSIVE SLEEPINESS: EVALUATION AND MANAGEMENT

1. Which of the following has been associated with excessive sleepiness (ES)?
A. Obstructive sleep apnea
B. Narcolepsy
C. Shift work
D. All of the above*

2. The most common cause of ES is:
A. Narcolepsy
B. Insufficient sleep*
C. Cataplexy
D. Sleep paralysis

3. Obstructive sleep apnea is characterized by:
A. Episodes of absence of airflow lasting at least 10 seconds*
B. Hypnagogic hallucinations during delta sleep
C. Muscle weakness in the face and neck
D. A deficiency in CSF hypocretin

4. Narcolepsy is characterized by all of the following except:
A. Hypnagogic hallucinations
B. Cataplexy
C. Above average CSF hypocretin levels*
D. Sleep paralysis

5. Disasters such as the Space Shuttle Challenger and Three Mile Island accidents have been attributed, in large part, to:
A. Narcolepsy
B. Sleep deprivation*
C. Obstructive sleep apnea
D. Chronic, poor sleep hygiene

6. Subjective measures of ES include:
A. Stanford Sleepiness Scale and the MSLT
B. Epworth Sleepiness Scale and the MWT
C. The MSLT and the MWT
D. Stanford Sleepiness Scale and Epworth Sleepiness Scale*

7. The MSLT consists of:
A. Three nap opportunities three hours apart
B. Five nap opportunities two hours apart*
C. Three attempts to stay awake three hours apart
D. Five attempts to stay awake two hours apart

8. Which of the following would not be included in recommendations for good sleep hygiene?
A. Having a regular time to go to bed
B. Having a regular time to wake up
C. Vigorous exercise just before going to bed*
D. Avoiding caffeine and alcohol late in the evening

9. Which of the following is approved by the FDA for treatment of residual ES associated with obstructive sleep apnea already treated with traditional approaches?
A. Sodium oxybate
B. Modafinil*
C. Fluoxetine
D. Pemoline

10. Which of the following is approved by the FDA for the treatment of ES associated with shift work sleep disorder?
A. Sodium oxybate
B. Modafinil*
C. Fluoxetine
D. Pemoline

11. Modafinil differs from traditional central nervous system stimulants (e.g., amphetamine, methylphenidate) in all of the following ways except:
A. Mechanism of action
B. Common occurrence of tachycardia
C. Ability to increase daytime vigilance*
D. Both A and B

12. For which of the following drugs could there be a decrease in efficacy after initiating modafinil?
A. Penicillin
B. Cyclosporine
C. Oral contraceptives
D. Both B and C*

13. Modafinil is generally effective at doses of:
A. 30 to 60 mg per day
B. 15 to 30 mg per day
C. 200 to 400 mg per day*
D. 6 to 9 grams per day

14. Common adverse effects of modafinil include all of the following except:
A. Rash*
B. Headache
C. Nausea
D. Anxiety

15. Sodium oxybate shares which one of the following characteristics with clomipramine?
A. Adverse effect of constipation
B. Ability to decrease the cataplexy associated with narcolepsy*
C. FDA-approved indication for cataplexy
D. Both B and C

16. With respect to drug interactions involving sodium oxybate, which of following is the most significant concern?
A. Its ability to inhibit cytochrome P450 isoenzymes 1A2, 2D6, and 3A4
B. Its pharmacokinetic interaction with protriptyline
C. Its pharmacokinetic interaction with modafinil
D. Its potentiation of the CNS depressant effects of ethanol*

17. Initial studies indicate that, in addition to its approved indication, sodium oxybate may:
A. Produce a slow but progressive improvement in daytime alertness*
B. Interact in a potentially lethal manner with methylphenidate
C. Increase the incidence of hypnagogic hallucinations
D. Be metabolized hepatically to acetaldehyde

18. Sodium oxybate is generally effective at doses of:
A. 30 to 60 mg per day
B. 15 to 30 mg per day
C. 200 to 400 mg per day
D. 6 to 9 grams per day*

19. Common adverse effects of sodium oxybate include all of the following except
A. Dizziness
B. Headache
C. Urinary retention*
D. Sleepwalking

20. Which of the following should be included in the pharmacist's counseling of a patient presenting with a complaint of ES that has lasted for several months despite an average of eight hours of sleep each night?
A. Caution regarding associated risks of injury and accidents
B. Resources available from the AASM and NSF
C. Importance of seeing a physician for further evaluation
D. All of the above*

ANSWER SHEET T/K

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