Recognition and Management of Excessive Sleepiness in the Primary Care Setting

Jonathan R. L. Schwartz, MD; Thomas Roth, PhD; Max Hirshkowitz, PhD; and Kenneth P. Wright, Jr, PhD

Background: Excessive sleepiness often goes unrecognized in the primary care setting despite its high prevalence and deleterious effects on both individual and public safety. Patients with neurologic and psychiatric illnesses, as well as those with acute and chronic medical conditions, plus those with sleep disorders, often have symptoms of excessive sleepiness, tiredness, and fatigue. Recognition and prompt treatment of these symptoms are important, even though their etiology may not be immediately understood. This review focuses on the underlying causes, consequences, identification, and treatment of excessive sleepiness.

Data Sources: A search of the literature to 2007 was performed using the PubMed search engine. English-language articles were identified using the following search terms: *excessive sleepiness, fatigue, circadian rhythm, obstructive sleep apnea, shift work disorder, narcolepsy, drowsy driving,* and *wakefulness.* Additional references were identified through bibliography reviews of relevant articles.

Data Synthesis: Current assessments of the prevalence, consequences, and etiologies of excessive sleepiness, with leading treatment strategies, were extracted, reviewed, and summarized to meet the objectives of this article.

Conclusions: Excessive sleepiness is associated with a wide range of medical, neurologic, and psychiatric disorders frequently seen in primary care practice. Excessive sleepiness is a serious, debilitating, potentially life-threatening condition, yet also treatable, and it is important to initiate appropriate intervention as early as possible. Physicians should place increasing emphasis on the substantial benefits that accompany improvements in wakefulness.

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Symptoms of excessive sleepiness, tiredness, and fatigue are frequent complaints of patients with acute and chronic medical conditions, sleep disorders, and neurologic and psychiatric illnesses. Despite its high prevalence and significant adverse effect on patients' functioning and quality of life, excessive sleepiness often goes unrecognized in the primary care setting.^{1,2} Given the deleterious consequences of excessive sleepiness on individual and public safety,^{3,4} improved recognition and therapy are urgently needed. Understanding the etiology of excessive sleepiness is necessary for proper and effective management, and prompt treatment is important. This review focuses on the underlying causes, consequences, identification, and treatment of excessive sleepiness.

A search of the literature to 2007 was performed using the PubMed search engine. English-language articles were identified using the following search terms: *excessive sleepiness, fatigue, circadian rhythm, obstructive sleep apnea, shift work disorder, narcolepsy, drowsy driving,* and *wakefulness.* Additional references were identified through bibliography reviews of relevant articles.

DEFINITION OF EXCESSIVE SLEEPINESS

Human physiology is organized in such a way that sleep is promoted during the night and wakefulness is promoted during the day. Sleep and wakefulness are regulated primarily by an interaction between sleep homeostatic and circadian processes.5,6 In general, the homeostatic drive for sleep increases with time awake and dissipates during sleep. The circadian process refers to the biologically determined near 24-hour rhythmic pattern of physiology and behavior governed by the master circadian pacemaker located in the hypothalamic suprachiasmatic nucleus. An alerting signal from the circadian pacemaker counteracts the increasing homeostatic drive for sleep and thus promotes wakefulness during the later part of the day. The circadian pacemaker also promotes sleep at night. Excessive sleepiness is characterized by difficulty maintaining wakefulness and/or an increased propensity to fall asleep when sleep is inappropriate or dangerous.⁷

Although the terms *excessive sleepiness* and *fatigue* are often used interchangeably, they represent 2 interrelated

Corresponding author: Jonathan R. L. Schwartz, MD, INTEGRIS Sleep Disorders Center, University of Oklahoma Health Sciences Center, 4200 South Douglas, Suite 313, Oklahoma City, OK 73109 (SchwJR@integris-health.com).

but distinct phenomena that frequently coexist in underlying medical, neurologic, and psychiatric conditions.⁸ Patients with excessive sleepiness have an increased propensity to fall asleep, especially when sedentary, whereas patients with fatigue may experience a general lack of energy or lethargy but with an ability to maintain wakefulness. However, patients with excessive sleepiness may also complain of fatigue, tiredness, a lack of energy, or difficulty concentrating. On the other hand, patients may deny these symptoms or fail to recognize their presence or severity.⁹

PREVALENCE OF EXCESSIVE SLEEPINESS

The reported prevalence of excessive sleepiness varies greatly (0.3%-35.8%), depending on its definition and the population studied.^{8,10} Epidemiologic studies have estimated that excessive sleepiness occurs in up to 13% of the population.¹¹ Among primary care patients, the prevalence of excessive sleepiness is reportedly 25% or higher.¹² Results from the National Sleep Foundation's 2002 "Sleep in America" poll indicate that daytime sleepiness frequently interferes with the daily activities of a sizable portion of adults, reportedly affecting 37% of respondents at least a few days per month, 16% at least a few days per week, and 7% every day.³ The pervasiveness of excessive sleepiness may also be promoting the growing popularity of energy drinks and the increasing dependence Americans have on caffeine, whose widespread use may have prompted a recent call for the inclusion of caffeine withdrawal in the Diagnostic and Statistical Manual of Mental Disorders.¹³

CAUSES OF EXCESSIVE SLEEPINESS

Excessive sleepiness can result from sleep deprivation; however, it has other major etiologies. The principal causes of excessive sleepiness in primary disorders of sleep-wake include (1) fragmented sleep (eg, obstructive sleep apnea), (2) pathological abnormalities of the central nervous system (CNS; eg, narcolepsy), and (3) circadian rhythm misalignment (eg, shift work disorder). Excessive sleepiness may also accompany a variety of medical, neurologic, and psychiatric conditions. Finally, factors that interfere with normal sleep-wake patterns and result in deficiencies in quality and quantity of sleep can also produce excessive sleepiness.^{4,7}

Insufficient Sleep and Chronic Sleep Restriction

The most common cause of daytime excessive sleepiness in the general population is insufficient sleep, which usually results from self-imposed sleep deprivation. In the 2002 "Sleep in America" poll,³ 68% of respondents reported sleeping fewer than 8 hours per night—the amount typically considered adequate for restorative function.^{14,15} Sustained sleep restriction results in the accumulation of "sleep debt," which increases an individual's propensity for sleep. Moreover, increasing "sleep debt" has been shown to be proportional to the severity of daytime excessive sleepiness.^{16,17}

Fragmented Sleep

Sleep fragmentation is characterized by repetitive brief awakenings or arousals. It is a common feature of many sleep disorders, including obstructive sleep apnea, periodic limb-movement disorder, and restless legs syndrome.^{4,7} In obstructive sleep apnea, the most common sleep-related breathing disorder, repetitive partial or complete airway occlusion produces sleep fragmentation as a result of the frequent arousals needed to initiate airway opening.

In the United States, approximately 4% of men and 2% of women have obstructive sleep apnea, while an estimated 24% of men and 9% of women have sleepdisordered breathing, as evidenced by an apnea-hypopnea index (episode-frequency per hour of sleep) ≥ 5 .¹⁸ These figures may underestimate obstructive sleep apnea, however, because the disorder is commonly underdiagnosed, at least in part because of variability in its presentation (eg, fatigue, lack of energy, snoring, or choking).^{9,18,19} Furthermore, the prevalence of obstructive sleep apnea is higher in overweight and obese adults and children.^{20,21} Thus, as the prevalence of obstructive sleep apnea.

Primary Disorders of Sleep and Wakefulness

Excessive sleepiness is also the hallmark symptom of some primary sleep disorders, including narcolepsy and idiopathic hypersomnia, both of which are mediated through the CNS.^{4,7} Excessive daytime sleepiness in primary disorders of sleep-wake dysregulation results from CNS dysfunction in 1 or more of the mechanisms that normally regulate sleep and wakefulness. Narcolepsy, for example, is associated with a deficiency of orexin/ hypocretin. Orexin/hypocretin cells are found in the anterior hypothalamus and are thought to facilitate wakefulness via projections to ascending subcortical arousal systems and the basal forebrain.²² A deficiency in orexin/ hypocretin protein is believed to result in narcolepsy. Loss of orexin/hypocretin cells are thought to contribute to narcoleptics having an increased drive for sleep during periods of normal wakefulness, along with exacerbated symptoms of excessive sleepiness associated with the disturbed sleep that is typical of this disorder.

Circadian Rhythm Sleep Disorders

In circadian rhythm disorders (eg, shift work disorder, delayed sleep phase syndrome, or advanced sleep phase syndrome), excessive sleepiness is caused by a mismatch between the timing of sleep and wakefulness and the timing of the internal circadian pacemaker.^{4,7} For example, in

shift work disorder, excessive sleepiness occurs during the time that the homeostatic sleep drive is high but the suprachiasmatic nuclei of the hypothalamus is not helping offset this drive by promoting wakefulness. By contrast, when the night shift worker then attempts to sleep in the morning, the circadian wake drive is increasing. The resulting misalignment between the work-rest/wakefulnesssleep schedule and the circadian pacemaker can cause the patient to experience clinically significant excessive sleepiness during the work shift, insomnia when trying to sleep the following day, or both.⁷

The majority of full-time night shift workers appear to be able to compensate for this temporal sleep-wake dysregulation. Nonetheless, it has been estimated that 32% of night shift workers and 26.1% of rotating workers experience levels of excessive sleepiness and daytime insomnia that meet the criteria for a diagnosis of shift work disorder.^{23,24} Because patients with shift work disorder are trying to sleep during the day, when the circadian pacemaker is promoting wakefulness, their sleep is often fragmented, short in duration, and nonrestorative. The result of this poor sleep quality and quantity is excessive sleepiness, especially during the night, as shift workers are attempting to function when the circadian pacemaker is promoting sleep.

Other Causes

Excessive sleepiness has also been associated with other sleep and circadian disorders such as multiple sclerosis, Parkinson's disease, lupus, cancer, chronic pain, gastrointestinal disorders, endocrine disorders, head injury, and other somatic disorders. It has also been associated with several psychiatric disorders (eg, depression, schizophrenia, seasonal affective disorders) and the use of some illicit or prescription drugs.^{4,7}

CONSEQUENCES OF EXCESSIVE SLEEPINESS

Regardless of etiology, excessive sleepiness can be a debilitating symptom and the cause of considerable morbidity. The consequences of excessive sleepiness include a range of social, familial, work, and cognitive impairments. For example, chronic excessive sleepiness is associated with decreased productivity, performance impairment, reduced psychological and social well-being, increased irritability, negatively affected interpersonal and marital relationships, and reduced quality of life.²⁴⁻²⁷

The neurobehavioral and cognitive effects of sleepiness include cognitive slowing; problems with memory, concentration, learning, and decision making; slowed reaction times; inability to sustain vigilant attention; and increased risk taking.²⁸ Not surprisingly, increased sleepiness and its associated wake-state instability contribute to an increased risk for serious functional consequences, including work-related errors and accidents,^{29,30} catastrophic accidents,³¹ and motor vehicle accidents.^{32,33} According to National Highway Traffic Safety Administration analyses, excessive sleepiness contributes to more than 100,000 motor vehicle accidents each year, 4% of which involve fatalities (> 1,500 deaths).³⁴

In addition to their serious impact on public safety, sleep problems and excessive sleepiness exact a significant economic burden on society. In 1990, direct costs related to sleep disorders in the United States were estimated to be \$15.9 billion per year, with another \$50 to \$100 billion annually attributed to indirect and related costs (eg, accidents and subsequent litigation, property destruction, hospitalization, and death).^{35,36}

IDENTIFICATION AND ASSESSMENT OF EXCESSIVE SLEEPINESS

For patients presenting with complaints of sleepiness, a sleep and medical history and physical examination are critical to determining the cause. Whether patient visits are related to acute conditions, chronic medical problems, or routine examinations, a medical history should include questions about the patient's sleep (eg, duration and quality, snoring, witnessed apneas, or other symptoms related to sleep disorders), sleep habits (eg, daily sleep patterns), and related safety concerns (eg, drowsy driving). A sleep history will help determine whether a patient's sleepiness is the result of a primary sleep disorder or is associated with a medical, neurologic, or psychiatric condition. Patients should also be asked about their current use of drugs (prescription or otherwise) and alcohol, as both may contribute to excessive sleepiness symptoms.

Because some patients may be unaware of their behaviors during sleep (eg, snoring, apneic events, and leg movements), soliciting information from their family members or bed partners can be especially valuable. Physicians should recognize that sleepiness poses an increased safety risk in specific patient groups, including, but not limited to, transportation workers and those with long commutes, medical staff, shift workers, 16-year-olds to 25-year-olds, and early risers.

Tools are available to help physicians screen for excessive sleepiness and determine its impact on daily functioning. Self-reported measures commonly used to index subjective sleepiness include the Epworth Sleepiness Scale (ESS),³⁷ the Stanford Sleepiness Scale (SSS),³⁸ and the Karolinska Sleepiness Scale (KSS).³⁹ These self-administered questionnaires provide a self-assessment of the level of sleepiness.

On the ESS, patients provide an assessment of their global symptoms of sleepiness by rating their likelihood of dozing during 8 common sedentary daily living situations. Item scores range from 0 (never) to 3 (high likelihood of dozing). A score ≥ 10 on the ESS is considered an indicator of excessive sleepiness.³⁷

By contrast, the SSS and KSS provide a subjective, momentary assessment of patients' sleepiness. On the SSS, patients provide an introspective measure of their current degree of sleepiness using a 7-point scale, with 1 being "feeling active, vital, alert, or wide awake" and 7 being "no longer fighting sleep, sleep onset soon, having dream-like thoughts."³⁹ Similarly, on the KSS, patients rate their current level of sleepiness on a 9-point scale (from 1 = "very alert" to 9 = "very sleepy, great effort to keep awake or fighting sleep").

Correspondingly, there are self-report instruments available to measure symptoms of fatigue. Examples of fatigue scales commonly used in both clinical screening and clinical trials include the Fatigue Severity Scale,⁴⁰ Fatigue Questionnaire,⁴¹ Fatigue Impact Scale,⁴² and Brief Fatigue Inventory.⁴³ In addition to providing an assessment of the patient's fatigue symptoms (eg, severity and impact on daily functioning), these tools may assist the physician in differentiating these symptoms from those related to frank excessive sleepiness.

Scales such as the ESS or the Brief Fatigue Inventory are simple, cost-effective tools that can be easily administered in the primary care setting to provide an initial assessment of a patient's excessive sleepiness. When a sleep disorder is suspected, the primary care physician may appropriately refer the patient to a sleep specialist for further consultation and diagnostic testing if needed.

Two objective (physiologic) measures of excessive sleepiness are the Multiple Sleep Latency Test (MSLT)⁴⁴ and the Maintenance of Wakefulness Test (MWT).⁴⁵ These laboratory-based assessments use polysomnography to monitor and record sleep and wakefulness, and the primary outcome measure is sleep latency.

The MSLT measures sleep tendency when an individual is placed in standardized, sleep-promoting conditions (ie, a dark, quiet room while the subject is lying on a bed) and is asked to relax and try to fall asleep. The MSLT is repeated 4 to 5 times at 2-hour intervals throughout the day, beginning 2 hours after initial morning awakening. The duration of the test is 20 minutes if sleep does not occur. If sleep onset occurs, the test is terminated 15 minutes later. During each session, polysomnographic measures are used to determine the amount of time that elapses until sleep onset (sleep latency). A mean MSLT sleep latency < 5 minutes reflects severe pathological sleepiness, > 10 minutes generally indicates normal alertness, and < 8 minutes is considered abnormal.⁴⁶

The MWT is conducted in a similar clinical setting and uses sleep evaluation methods similar to the MSLT. However, the MWT patient is instructed to try to remain awake for the duration of the test. Test sessions may last 20 to 60 minutes. Although normative data from the MWT are more limited, a mean sleep latency < 8 minutes on the 40-minute MWT generally indicates abnormal sleepiness.⁴⁶ Correlations between objective and subjective measures of sleepiness are generally weak, suggesting that these assessment tools may measure different components of sleepiness or that chronically sleepy individuals fail to perceive their degree of sleepiness accurately. When used in combination, however, these complementary measures generally provide a good overall assessment of the severity of sleepiness.⁴⁷

TREATMENT OF EXCESSIVE SLEEPINESS

Accurate identification of the underlying cause(s) of the patient's sleepiness is critical to direct therapeutic intervention. While the principal cause may dictate the initial approach to treatment, the overall goal remains the same: to improve wakefulness/alertness and functioning. As with any treatment strategy, setting realistic goals and expectations with the patient is essential before initiating treatment of excessive sleepiness, whether behavioral or pharmacologic or a combination of both. Additionally, regular and timely follow-up is crucial to assess effectiveness of and compliance with treatment.

Behavioral Measures to Improve Sleep

Improving duration of sleep and ensuring proper sleep hygiene (sleep-related behaviors) are essential first steps in helping to alleviate symptoms of excessive sleepiness in all patients. Patients should be encouraged to allow enough time in their schedules for an adequate amount of sleep to feel refreshed or well rested. Additionally, physicians should educate their patients on the practice of good sleep habits. These habits include maintaining a regular sleep-wake schedule (7 days a week); creating a quiet, cool, and comfortable bedroom environment that is conducive to sleep; limiting time spent in bed for activities other than sleep; and ensuring avoidance of caffeine, nicotine, alcohol, heavy meals, and strenuous exercise at least 3 hours before bedtime.

Treatments for Underlying Sleep-Wake Disorders: Obstructive Sleep Apnea and Shift Work Disorder

Treatment of obstructive sleep apnea includes a variety of strategies depending on the severity of the condition: positional therapy, positive pressure therapy, intraoral/ dental appliances (eg, mandibular advance devices), and, when craniofacial abnormalities are evident, surgery. The preferred treatment is nasal continuous positive airway pressure (nCPAP), a machine that generates an airflow administered to the patient, usually through a nasal mask. The administration of positive pressure maintains airway patency largely by creating a pneumatic splint.⁴⁸ Proper use of nCPAP therapy corrects sleep-disordered breathing, normalizes arterial blood oxygen saturation, and improves sleep quality and blood pressure, with consequent improvement in alertness, cognitive function, mood, and quality of life.^{49–51} Previous studies have shown that nCPAP use does not always return alertness to normal.

The 2003 meta-analysis by Patel et al⁵² of 12 nCPAP trials showed that nCPAP, the gold standard for treatment of patients with obstructive sleep apnea, only minimally improves subjective and objective sleepiness. Although nCPAP is effective in resolving recurrent upper airway obstruction in obstructive sleep apnea, those experiencing residual excessive sleepiness^{53,54} may benefit from adjunctive treatment with a wake-promoting agent.

More recent data indicate that significant proportions of patients continue to have excessive daytime sleepiness even with optimal nCPAP therapy. In a study of 149 patients with severe obstructive sleep apnea treated with nCPAP,⁵⁵ 34% of patients still had ongoing subjective sleepiness (ESS) and 65% had ongoing objective sleepiness (MSLT) after an average of 4.7 hours of nCPAP use per night for 3 months. Although these percentages decreased to 22% subjective sleepiness (ESS) and 52% objective sleepiness (MSLT) when nCPAP was used for 6 or more hours per night, they remained indicative of significant, unremitting subjective and objective daytime sleepiness despite optimal nCPAP use ⁵⁵

For the treatment of patients with circadian rhythm disorders (eg, shift work disorder), a variety of interventions have been proposed to appropriately shift their biologic circadian rhythms, maintain sleep continuity, and improve alertness. Proposed treatments include chronobiotic interventions (eg, bright light therapy, appropriately timed melatonin administration, hypnotic agents, and wake-promoting agents).⁵⁶ Because circadian rhythm disorders are influenced by both environmental and behavior factors, a multimodel treatment approach, including a structured sleep-wake schedule and proper sleep hygiene, is generally recommended.⁵⁷

Wake-Promoting Agents

Several medications are available to improve wakefulness and alertness in patients with symptoms of excessive sleepiness. It should be noted, however, that medications are not specific to underlying disorders, and pharmacologic management of excessive sleepiness does not replace the need for sleep.

Amphetamines. Since their development in the 1930s, amphetamines have historically been used to treat excessive sleepiness and narcolepsy. Dextroamphetamine and methamphetamine, 2 sympathomimetics approved by the US Food and Drug Administration (FDA) for use in narcolepsy, are fast acting and effective in ameliorating symptoms of excessive sleepiness. Methylphenidate, a psychomotor stimulant with pharmacologic mechanisms similar to amphetamine and commonly used in the treatment of attention-deficit/hyperactivity disorder, is also approved to treat narcolepsy. Few studies, however, have examined its effects on daytime excessive sleepiness.

Commonly reported side effects of these stimulants include anxiety, agitation, anorexia, tachycardia, and elevated blood pressure. At high doses, hallucinations and psychosis may occur. Additionally, patients treated with these stimulants may require increasingly greater doses to sustain improvements in alertness, and tolerance and tachyphylaxis may occur over time. On the basis of their higher potential for abuse, these US Drug Enforcement Administration schedule II medications require careful patient monitoring and should be used with caution.

Modafinil and armodafinil. Modafinil is a wakepromoting agent that is structurally and pharmacologically distinct from traditional CNS stimulants.^{58,59} It also has a lower abuse potential and lower risk for adverse cardiovascular events than sympathomimetic agents.^{60,61} Additionally, because of its negligible sympathomimetic activity, modafinil does not adversely affect nighttime sleep when used as directed.

Armodafinil is the *R*-enantiomer of modafinil and has been shown in double-blind studies to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea, shift work disorder, and narcolepsy.^{62–64} These studies have also shown that armodafinil improves wakefulness later during the day on an extended MWT and that it improves fatigue as shown by the Brief Fatigue Inventory.⁶⁵ Armodafinil was approved by the FDA in 2007.

Modafinil and armodafinil are both approved for use in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (as an adjunct to nCPAP), or shift work disorder. For patients with excessive sleepiness due to narcolepsy, modafinil is recommended as a "standard" treatment by the American Academy of Sleep Medicine.⁶⁶ For obstructive sleep apnea and shift work disorder, modafinil and armodafinil are the only FDAapproved agents for the excessive sleepiness associated with these disorders.

In several modafinil and armodafinil double-blind, placebo-controlled studies involving more than 2,200 patients with excessive sleepiness associated with these disorders,^{62-64,67-71} both agents consistently improved objective and subjective sleepiness, as demonstrated by improved MSLT or MWT sleep latencies and ESS or KSS assessments, respectively. The medications also improved the ability to sustain attention, overall clinical condition, and health-related quality of life in patients with excessive sleepiness associated with narcolepsy,^{62,71,72} obstructive sleep apnea,^{63,67,68,73} and shift work disorder.^{64,69,74} In addition to the improvements in alertness in shift work disorder patients following treatment with modafinil and armodafinil, proportionately fewer modafinil-treated and armodafinil-treated⁷⁵ patients reported having accidents or near accidents on the commute home.

Importantly, when used as an adjunct to nCPAP to treat residual excessive sleepiness associated with obstructive

sleep apnea, there was no reduction in nightly nCPAP use with either modafinil or armodafinil.^{63,67,68,76} Both modafinil and armodafinil are generally well tolerated; the most commonly observed adverse events occurring more frequently with modafinil and armodafinil ($\geq 5\%$) include headache, nausea, anxiety, and dizziness.^{77,78}

Sodium oxybate. Sodium oxybate (a sodium salt of γ hydroxybutyrate [GHB]) is a CNS depressant approved by the FDA for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. Sodium oxybate is a liquid agent that is administered immediately before bedtime, with a subsequent dose 2 to 4 hours later. The effect of sodium oxybate on daytime sleepiness was evaluated in a multicenter, double-blind, placebocontrolled study of 228 adults who had narcolepsy with cataplexy.⁷⁹ After 8 weeks, patients treated with sodium oxybate 6 g or 9 g demonstrated significant (P < .05) dose-related decreases in subjective excessive sleepiness symptoms, as assessed by the ESS, compared with placebo (P < .001 for each). Significant improvements in objective excessive sleepiness, assessed by the MWT, were seen in patients receiving 4.5-g or 9-g doses but were particularly robust in those receiving 9 g; these patients displayed an increase from baseline of more than 10 minutes-significant versus baseline as well as placebo $(P < .001 \text{ for each}).^{79}$

In clinical studies of sodium oxybate, most patients (approximately 80%) were treated concurrently with stimulants. Additionally, a recent study of patients with narcolepsy who were treated with sodium oxybate in combination with modafinil suggests that this combination may be more effective at reducing excessive sleepiness symptoms than monotherapy with either agent.⁸⁰

Commonly reported side effects of sodium oxybate ($\geq 5\%$ of patients in placebo-controlled studies) include nausea, dizziness, headache, vomiting, somnolence, and urinary incontinence.⁸¹ Because of this agent's abuse potential and association with significant CNS adverse events, sodium oxybate is a Schedule III medication when used for its approved indications of cataplexy and excessive sleepiness associated with narcolepsy.

CONCLUSION

Excessive sleepiness is a common symptom associated with a wide range of medical, neurologic, and psychiatric disorders and is frequently seen in primary care practice. Excessive sleepiness is a serious, debilitating, potentially life-threatening condition with enormous consequences not only for the individual, but also for public health and safety. Patients who are sleepy often present with vague complaints of tiredness or fatigue. A rapid assessment of these patients' general level of sleepiness can be made with a standardized screening tool, such as the widely used ESS, which is easily administered in the primary care setting. In patients with excessive sleepiness, it is imperative to identify its cause if possible and proceed with referral to a sleep disorder specialist if needed. Appropriate interventions can be thus initiated as quickly as possible.

Excessive sleepiness, when managed appropriately, improves the productivity and quality of life of patients with this increasingly common complaint. Excessive sleepiness is a very treatable condition, and increasing emphasis should be placed on the substantial benefits that accompany improvements in wakefulness.

Drug names: armodafinil (Nuvigil), dextroamphetamine (Dexedrine, Dextrostat, and others), methamphetamine (Desoxyn), methylphenidate (Daytrana, Ritalin, and others), modafinil (Provigil), sodium oxybate (Xyrem).

Author affiliations: INTEGRIS Sleep Disorders Centers, University of Oklahoma Health Science Center, Oklahoma City (Dr Schwartz); Henry Ford Sleep Disorder Center, Detroit, Michigan (Dr Roth); Michael E. DeBakey VA Medical Center, VAMC Sleep Center, and Baylor College of Medicine, Houston, Texas (Dr Hirshkowitz); and Department of Integrative Physiology, Sleep and Chronobiology Laboratory, University of Colorado at Boulder (Dr Wright). Financial disclosure: Dr Schwartz has served as a consultant to AstraZeneca, Boehringer Ingelheim, Cephalon, GlaxoSmithKline, Jazz, Pfizer, MEDPOINTE, Resmed, and Takeda and on the speakers' bureaus of AstraZeneca, Boehringer Ingelheim, Cephalon, GlaxoSmithKline, Pfizer, MEDPOINTE, and Takeda. Dr Roth has served as a consultant to Abbott, Acadia, Acoglix, Actelion, Alchemers, Alza, Ancil, Arena, AstraZeneca, Aventis, Bristol-Myers Squibb, BTG, Cephalon, Cypress, Dove, Elan, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Hypnion, Intec, Intra-Cellular, Jazz, Johnson & Johnson, King, Lundbeck, McNeil, MediciNova, Merck, Neurim, Neurocrine, Neurogen, Novartis, Orexo, Organon, Prestwick, Proctor & Gamble, Pfizer, Purdue, Resteva, Roche, Sanofi, Schering-Plough, Sepracor, Servier, Shire, Somaxon, Syrex, Takeda, TransOral, Vanda, Vivometrics, Wyeth, Yamanuchi, and Xenoport; has served on the speakers' bureaus of Cephalon, Sanofi, and Takeda; and has received grant/research support from Aventis, Cephalon, GlaxoSmithKline, Neurocrine, Pfizer, Sanofi, Schering-Plough, Sepracor, Somaxon, Syrex, Takeda, TransOral, Wyeth, and Xenoport. Dr Hirshkowitz has served on the speakers' bureaus of Cephalon, Takeda, and Sanofi-Aventis and has conducted contract research at Baylor College of Medicine with Merck, Evotec, Cephalon, Sanofi, Sepracor, Takeda, Organon, and Vanda. Dr Wright has served as a consultant to Cephalon, Zeo, and Takeda; has served on the advisory boards of Zeo, Novartis, and Axon; has served on the speakers' bureaus of Cephalon and Takeda; has received grant/research support from Takeda and honoraria from Associated Sleep Societies, Endocrine Society, Banner Health, and Arizona Psychological Association; and is a stock shareholder in Zeo. Funding/support: This article was supported by Cephalon, Frazer,

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REFERENCES

- Pigeon WR, Sateia MJ, Ferguson RJ. Distinguishing between excessive daytime sleepiness and fatigue: toward improved detection and treatment. J Psychosom Res. 2003;54(1):61–69.
- Zepf B. Problem sleepiness: an often unrecognized condition. Am Fam Physician. 1999;59(4):762, 770, 773.
- National Sleep Foundation. 2002 Adult Sleep Habits. 2002 "Sleep in America Poll." http://www.sleepfoundation.org/article/sleep-americapolls/2002-adult-sleep-habits.
- 4. Committee on Sleep Medicine and Research. Board on Health Sciences

Policy. Institute of Medicine of the National Academies. Colten HR, Altevogt BM, eds. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem.* Washington, DC: The National Academies Press; 2006

- Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci*. 1995;15:3526–3538.
- Borbely AA, Achermann P. Sleep homeostasis and models of sleep regulation. J Biol Rhythms. 1999;14(6):557–568.
- American Academy of Sleep Medicine. International Classification of Sleep Disorders, 2nd edition: Diagnostic and Coding Manual. Westchester, IL: American Academy of Sleep Medicine; 2005.
- Shen J, Barbara J, Shairo CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev.* 2006;10(1):63–76.
- Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *Chest.* 2000;118(2):372–379.
- Young TB. Epidemiology of daytime sleepiness: definitions, symptomatology, and prevalence. J Clin Psychiatry. 2004;65(suppl 16):12–16.
- D'Alessandro R, Rinaldi R, Cristina E, et al. Prevalence of excessive daytime sleepiness: an open epidemiological problem. *Sleep.* 1995; 18(5):389–391.
- Kushida CA, Nichols DA, Simon RD, et al. Symptom-based prevalence of sleep disorders in an adult primary care population. *Sleep Breath*. 2000;4(1):9–14.
- Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology (Berl)*. 2004;176(1):1–29.
- Wehr TA, Moul DE, Barbato G, et al. Conservation of photoperiodresponsive mechanisms in humans. *Am J Physiol.* 1993;265:R846–R857.
- Roehrs T, Timms V, Zwyghuizen-Doorenbos A, et al. Sleep extension in sleepy and alert normals. *Sleep*. 1989;12(5):449–457.
- Carskadon MA, Dement WC. Cumulative effects of sleep restriction on daytime sleepiness. *Psychophysiology*. 1981;18(2):107–113.
- Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep*. 1997;20(4):267–277.
- Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328(17): 1230–1235.
- Young T, Evans L, Finn L, et al. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep.* 1997;20(9):705–770.
- Gami AS, Caples SM, Somers VK. Obesity and obstructive sleep apnea. *Endocrinol Metab Clin North Am.* 2003;32(4):869–894.
- Tauman R, Gozal D. Obesity and obstructive sleep apnea in children. Paediatr Respir Rev. 2006;7(4):247–259.
- Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;27(3):469–474.
- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 2000.
- Drake CL, Roehrs T, Richardson G, et al. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. *Sleep.* 2004;27(8):1453–1462.
- Reimer MA, Flemons WW. Quality of life in sleep disorders. *Sleep Med Rev.* 2003;7(4):335–349.
- Thorpy MJ. Which clinical conditions are responsible for impaired alertness? Sleep Med. 2005;6(suppl 1):S13–S20.
- Baldwin CM, Griffith KA, Nieto FJ, et al. The association of sleepdisordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep.* 2001;24(1):96–105.
- Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Semin Neurol. 2005;25(1):117–129.
- Lockley SW, Cronin JW, Evans EE, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med.* 2004;351(18):1829–1837.
- Landrigan CP, Rothschild JM, Cronin JW, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med.* 2004;351(18):1838–1848.
- Dinges DF. An overview of sleepiness and accidents. J Sleep Res. 1995; 4(S2):4–14.
- Stutts JC, Wilkins JW, Scott-Osberg J, et al. Driver risk factors for sleeprelated crashes. Accid Anal Prev. 2003;35(3):321–331.

- Barger LK, Cade BE, Ayas NT, et al. Extended work shifts and the risk of motor vehicle crashes among interns. *N Engl J Med.* 2005;352(2): 125–134.
- Lyznicki JM, Doege TC, Davis RM, et al, for the Council on Scientific Affairs. Sleepiness, driving, and motor vehicle accidents. *JAMA*. 1998; 279(23):1908–1913.
- National Commission on Sleep Disorders Research. Report of the National Commission on Sleep Disorders Research. Washington, DC: Government Printing Office; 1992.
- Leger D. The cost of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. *Sleep.* 1994;17(1):84–93.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540–545.
- Hoddes E, Dement W, Zarcone V. The development and use of the Stanford Sleepiness Scale (SSS). *Psychophysiology*. 1972;9:150.
- Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci.* 1990;52(1–2):29–37.
- Krupp LB, LaRocca NG, Muir-Nash J, et al. The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol.* 1989;46(10):1121–1123.
- 41. Chalder T, Berelowitz G, Hirsch S, et al. Development of a fatigue scale. *J Psychosom Res.* 1993;37(2):147–153.
- Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the Fatigue Impact Scale. *Clin Infect Dis.* 1994;18(suppl 1):S79–S83.
- Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;85(5):1186–1196.
- Carskadon MA, Dement WC, Mitler MM, et al. Guidelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. *Sleep.* 1986;9(4):519–524.
- Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol.* 1982;53(6):658–661.
- American Academy of Sleep Medicine. Practice parameters for clinical use of the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. *Sleep.* 2005;28(1):113–121.
- Wise MS. Objective measures of sleepiness and wakefulness: application to the real world? J Clin Neurophysiol. 2006;23(1):39–49.
- Loube DI, Gay PC, Strohl KP, et al. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: a consensus statement. *Chest.* 1999;115(3):863–866.
- Faccenda JF, Mackay TW, Boon NA, et al. Randomized placebocontrolled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med.* 2001;163(2):344–348.
- Engleman HM, Martin SE, Deary IJ, et al. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/ hypopnoea syndrome. *Lancet.* 1994;343(8897):572–575.
- Jenkinson C, Davies RJ, Mullins R, et al. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet.* 1999; 353(9170):2100–2105.
- Patel SR, White DP, Malhotra A, et al. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea. *Arch Intern Med.* 2003;163(5):565–571.
- Sforza E, Krieger J. Daytime sleepiness after long-term continuous positive airway pressure (CPAP) treatment in obstructive sleep apnea syndrome. J Neurol Sci. 1992;110(1-2):21–26.
- Bedard M-A, Montplaisir J, Malo J, et al. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol. 1993;15(2):330–341.
- Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep.* 2007;30(6):711–719.
- 56. Schwartz JR, Roth T. Shift work sleep disorder: burden of illness and approaches to management. *Drugs.* 2006;66(18):2357–2370.
- 57. Lu BS, Zee PC. Circadian rhythm sleep disorders. *Chest.* 2006;130(6): 1915–1923.
- Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness,

evidenced by c-fos immunocytochemistry in the cat. *Proc Natl Acad Sci U S A*. 1996;93(24):14128–14133.

- Saper CB, Scammell TE. Modafinil: a drug in search of a mechanism. Sleep. 2004;27(1):11–12.
- Myrick H, Malcolm R, Taylor B, et al. Modafinil: preclinical, clinical, and post-marketing surveillance: a review of abuse liability issues. *Ann Clin Psychiatry*. 2004;16(2):101–109.
- Sackner-Bernstein J, Niebler G, Earl CQ. Cardiovascular profile of modafinil: effects on blood pressure and heart rate. *Chest.* 2004; 126:729S.
- Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin*. 2006;22(4):761–774.
- 63. Roth T, White D, Schmidt-Nowara W, et al. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther.* 2006;28(5):689–706.
- Drake C, Walsh J, Roth T. Armodafinil improves sleep latency in patients with shift work sleep disorder. *Sleep.* 2006;29(suppl):A64.
- Rosenberg R, Walsleben J. Armodafinil reduces daytime fatigue associated with excessive sleepiness in patients with obstructive sleep apnea or narcolepsy. *Sleep*. 2006;29(suppl):A228.
- Littner M, Johnson SF, McCall WV, et al. Practice parameters for the treatment of narcolepsy: an update for 2000. *Sleep.* 2001;24(4): 451–466.
- Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. *Sleep.* 2005;28(4):464–471.
- Pack AI, Black JE, Schwartz JR, et al. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2001;164(9):1675–1681.
- 69. Czeisler CA, Walsh JK, Roth T, et al. Modafinil for excessive sleepiness associated with shift work sleep disorder.

N Engl J Med. 2005;353(5):476-486.

- US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol.* 1998;43(1):88–97.
- Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. *Neurology*. 2000;54(5):1166–1175.
- Beusterien KM, Rogers AE, Walsleben JA. Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep.* 1999;22(6): 757–765.
- Dinges DF, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. *Sleep Med.* 2003;4(5):393–402.
- 74. Erman MK, Rosenberg R, for the US Modafinil Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with chronic shift work sleep disorder: effects on patient functioning and health-related quality of life. *Prim Care Companion J Clin Psychiatry*. 2007;9(3):188–194.
- Roth T, Czeisler CA, Walsh JK, et al. Randomized, double-blind, placebo-controlled study of armodafinil for the treatment of excessive sleepiness associated with chronic shift work sleep disorder. *Neuropsychopharmacol.* 2005;30(suppl 1s):S140.
- Hirshkowitz M, Black JE, Wesnes K, et al. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med.* 2007;101(3):616–627.
- 77. Provigil [package insert]. Frazer, PA: Cephalon, Inc; 2007.
- 78. Nuvigil. Frazer, PA: Cephalon, Inc; 2007. [FDA-approved label].
- Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med.* 2005;1(4): 391–397.
- Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;29(7):939–946.
- 81. Xyrem [package insert]. Palo Alto, CA: Jazz Pharmaceuticals.