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Advances in the Management of Shift-Work Disorder

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CONTINUING EDUCATION INFORMATION

Target Audience: Pharmacists

Type of Activity: Knowledge

Program Description: Approximately 22 million Americans regularly work between 7 PM and 7 AM and are classified as "shift workers." These individuals are at risk for shift-work disorder (SWD), a circadian rhythm sleep/wake disorder characterized by symptoms of insomnia and/or excessive sleepiness that have been present for at least 1 month and are associated with a work schedule that overlaps with usual sleep time. Shift workers who meet the criteria for SWD are at increased risk for impairments to health, safety, and quality of life. Although effective nonpharmacologic and pharmacologic strategies are available to treat patients with SWD, most individuals with this condition remain undiagnosed and untreated. As the scope of pharmacy practice continues to evolve to more patient-centered care, the community pharmacist is well positioned to contribute to closing many of these gaps in patient care through screening individuals at risk for this sleep/wake disorder, as well as interacting with the broader healthcare team to provide counseling, medication management, and follow-up to those undergoing treatment for SWD.

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U.S. PHARMACIST CONTINUING EDUCATION

Goals: To educate participants on strategies to identify individuals at risk for SWD and to describe opportunities for community pharmacists to collaborate with the healthcare team to facilitate effective management of patients with SWD through patient education and treatment monitoring.

Learning Objectives: After completing this activity, participants should be better able to:
- **Identify** patients at risk for SWD utilizing assessment tools available in the pharmacy setting
- **Collaborate** with patients, prescribers, and other healthcare providers to facilitate a team approach to the diagnosis and treatment of patients with SWD
- **Describe** available approaches to the management of patients with SWD
- **Provide** patient education on strategies to improve sleep health and the safe and effective administration of pharmacotherapy to treat patients with SWD

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Advances in the Management of Shift-Work Disorder

Part I: Pathophysiology and Health-Related Consequences

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Introduction

Restorative sleep contributes to individuals' overall health in many ways, yet its importance traditionally has not been emphasized by clinicians or patients. However, over the past decade the importance of sleep health has received increasing attention from national organizations and public health initiatives.[1-3] Prominent among these is a 2006 report from the Institute of Medicine that called sleep/wake disorders "an unrecognized and unmet public health problem."[3] Calls from the Centers for Disease Control and Prevention for increased recognition and assessment of sleep disorders in primary care to ensure appropriate intervention or referral underscore the increased recognition of sleep issues as crucial to public health.[2]

For the first time, sleep health has been added as a topic in the US Department of Health and Human Services' Healthy People initiative.[1,4] The initiative describes the public health burden of sleep disorders as substantial and awareness as lacking.[4] It includes several objectives related to sleep health, including increasing treatment of sleep disorders, increasing the proportion of citizens getting sufficient sleep, and reducing the rate of vehicular accidents.[1] The stated goal of the Healthy People sleep initiative is to "increase public knowledge of how adequate sleep and treatment of sleep disorders can improve health, productivity, wellness, quality of life, and safety on roads and in the workplace."[4] Partially in recognition of the role that excessive sleepiness plays in accidents, in November 2010 New Jersey became the first state to implement a "drowsy driving" law, making sleepy drivers criminally negligent in accidents.[5]

This public health emphasis on sleep occurred during a decade in which adequate, good quality sleep eluded many Americans. The 2009 Behavioral Risk Factor Surveillance System survey of almost 75,000 Americans in 12 states found that within the 30 days prior to taking the survey 37.9% of respondents reported falling asleep unintentionally, 4.7% of respondents reported nodding off or falling asleep while driving, and 35.3% of respondents reported getting less than 7 hours of sleep.[6] The Sleep in America poll conducted in 2008 by the

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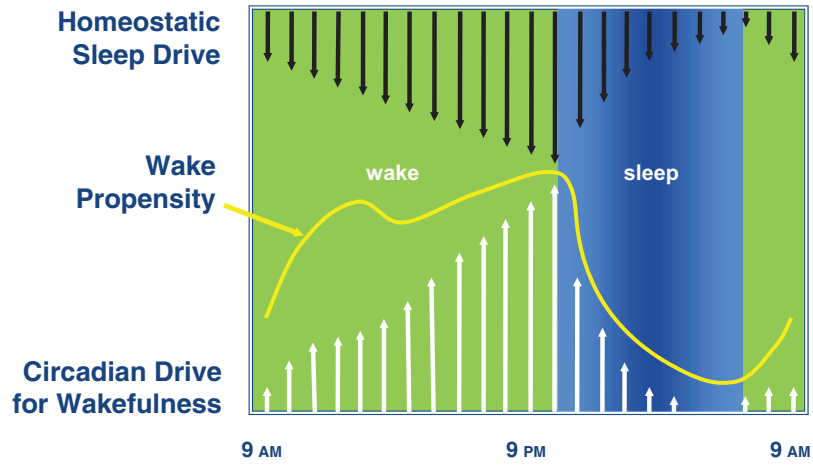
National Sleep Foundation, found that 29% of respondents reported falling asleep or becoming very sleepy while at work.[7]

There are many reasons why sleep/wake disorders go unrecognized. These include an underestimation of the clinical impact of sleep/wake disorders on the part of healthcare providers[8]; the tendency of clinicians to seek a "single diagnosis, even though sleep disorders are multifaceted[9]; the relatively recent emergence of sleep medicine as a specialty (2004); and lack of adequate training in sleep medicine among healthcare providers.[3,6,9,10]

Community pharmacists have been identified as important members of the sleep health multidisciplinary team, with roles in screening and patient education, as well as monitoring for potential drug interactions and adverse reactions to therapy.[11-13] Their roles in community health initiatives and patient interaction make community pharmacists well positioned for recognizing sleep disorders in individuals who may not understand the important ramifications of their own sleepiness or who may otherwise not seek or receive necessary clinical care. Several studies that will be addressed in detail in this supplement provide evidence for the feasibility of pharmacist-driven screening in identifying sleep disorders and referring individuals for appropriate care.[14-16] To put sleep health in proper perspective, this article reviews key concepts in normal sleep physiology and circadian rhythms, with a focus on the health and safety consequences of shift-work disorder (SWD), a condition associated with a misalignment of circadian rhythm and chronic partial sleep loss.

Figure 1. Physiologic Determinants of Sleepiness



In the normal diurnal cycle, a circadian drive for wakefulness builds throughout the day into early evening, balancing against the sleep drive. Overnight, the wakefulness drive declines, allowing sleep pressure to dominate. As sleep relieves that pressure, the body builds again toward a waking state. Source: Adapted from Reference 18.

POP QUIZ

For the majority of people, the circadian drive for wakefulness is highest at:

A. 9 AM
B. 12 PM
C. 3 PM
D. 9 PM

Normal Sleep Processes

A working knowledge of basic sleep physiology can improve understanding, diagnosis, and treatment of SWD and circadian rhythm disorders.[17] In humans the states of sleep and wakefulness are believed to result from a balance between 2 opposing processes, the circadian drive toward wakefulness and the homeostatic sleep drive (FIGURE 1).[18,19] Both the duration of time since waking after an adequate sleep and endogenous circadian rhythms influence this balance and the propensity to remain awake during the day and the propensity to initiate sleep and maintain consolidated sleep during the course of the night.

The human endogenous sleep/wake cycle is thought to be under the primary control of 2 suprachiasmatic nuclei (SCN), located in the hypothalamus.[17,19,20] The endogenous sleep/wake period of oscillation is 24.1 to 24.3 hours long. However, this sleep/wake cycle is synchronized to the ambient light/dark cycle, a process referred to as entrainment, through the effects of zietgebers, the most important of which is environmental light. The SCN are thought to play a direct role in promoting wakefulness at specific times of day. The wake-promoting role of the SCN works in opposition to the homeostatic sleep drive, and the strength of the drive depends on the extent of prior wakefulness. Therefore, as the day proceeds, the homeostatic sleep drive increases in strength; however, this propensity to fall asleep during the day is opposed by the circadian drive for wakefulness, which is mediated by the SCN. As the wakefulness drive of the SCN recedes at night, a time

Table 1. Melatonin Receptors of SCN and Peripheral Tissues

Body System	Melatonin Receptors
SCN	MT_1, MT_2
Adrenal gland	MT_1
Arteries and heart	MT_1, MT_2
Kidney	MT_1
Liver	MT_1, MT_2
Lung	MT_1, MT_2
Lymphocytes (T and B)	MT_1
Small intestine	MT_2
Skin	MT_1, MT_2

SCN: suprachiasmatic nuclei.
Source: Reference 23.

when the homeostatic drive is at its maximum, the sleep drive predominates, and sleep is initiated.[18] Other key components of the circadian process are the pineal gland, which releases melatonin—partly in response to SCN signaling, and partially in response to the onset of darkness—to promote sleep during the individual's normal period of darkness.[19]

During normal sleep, the brain cycles 4 to 6 times a night between 90-minute periods of rapid-eye movement (REM) and non-REM sleep. REM sleep resembles active waking on an electroencephalogram, yet is distinguished from wakefulness by the presence of rapid eye movements and atonia of skeletal muscles. Non-REM sleep is divided into 3 stages, N1, N2, and N3.[21] Stage N3, characterized by low-frequency, high-amplitude wave forms, is also known as slow wave (or delta wave) sleep (SWS). In healthy young adults, about 20% of the night is spent in SWS, and in older adults 5% to 10% of the night is spent in SWS with the rest divided between REM (25%) and other non-REM stages.[22]

Melatonin: Melatonin is a time-keeping hormone actively involved in regulation of the circadian clock in vertebrates. Its release is dependent on exogenous light/darkness levels: brighter light suppresses melatonin secretion, while darkness increases it.[23] In humans, retinal receptors sensitive to light send a signal through the retinohypothalamic track to the SCN that then suppresses melatonin release from the pineal gland.[23] Exposure to light at night has been shown to lower melatonin levels to different degrees depending on the type, wavelength, and brightness of the light. Red-wavelength light has the least effect and blue-wavelength light the greatest effect on melatonin suppression.[23]

In general, melatonin levels are higher at night, tapering off toward morning and waking hours.[23] In most individuals, peak melatonin secretion is related closely to the nightly nadir in core body temperature, maximum sleepiness and fatigue, and reduced alertness and performance.[23] Each individual secretes melatonin in a uniquely consistent pattern from day to day over time, but substantial differences exist among individuals in the onset of rise in melatonin secretion.[23]

Melatonin secretion is affected by several factors: it generally decreases with older age; physical disease (eg, cirrhosis or end stage renal disease) can dysregulate its release; and psychiatric illness (eg, depression) is associated with lower levels. Low melatonin levels have been associated with cardiovascular disease and diabetic neuropathy.[23] The clinical significance of these associations is unclear.

Two types of melatonin receptors have been identified: ML_1 and MT_3 (the latter formerly called ML_2). Within ML_1, 3 subtypes of receptors have been identified: MT_1, MT_2, and Mel_{1c}. It appears that physiologic response to melatonin primarily is associated with MT_1, which is more prevalent than MT_2. In the brain, MT_1 is found in the hypothalamus, including the SCN. MT_2 is found in the retina, hippocampus, SCN, and cerebellum.[23]

These receptors are also found in various peripheral tissues (TABLE 1). Results from animal studies have shown that specific physiologic functions are mediated depending on whether the MT_1, MT_2, or MT_3 melatonin receptor is activated.[24] For example, some of the actions resulting from activation of MT_1 are induction of vasoconstriction, inhibition of prolactin secretion, and inhibition of neuronal transmission in the SCN. Actions of the activated MT_2 receptor include induction of vasodilation and phase shifting of SCN-generated circadian rhythms, whereas reduction of intraocular pressure is one of the actions of the activated MT_3 melatonin receptor.[24] Available pharmacologic agents (see *Part II. General Approach to Screening, Diagnosis, and Management of Shift-Work Disorder*) are active at the MT_1 and MT_2 receptor sites.[23]

Role of Genetic Factors in Sleep/Wake Rhythms: As in other facets of life, genetic factors underlie an individual's specific circadian tendency and allow some to adjust more readily to "odd" hours than others. Researchers have identified specific proteins and genes that influence circadian rhythms in mammals. These include proteins encoded by the *Per1, Per2,* and *Per3* genes (PERIOD1, PERIOD2, and PERIOD3), as well as the protein prod-

ucts of the *Cry1* and *Cry2* genes.[20] In a roughly 24-hour cycle, promoters of the *Per* and *Cry* genes are activated by CLOCK and BMAL1 proteins, which initiates a process whereby the PERIOD and CRY proteins encoded by the *Per* and *Cry* genes are produced and build up in the cytoplasm over the course of the day. By evening, these proteins combine into complexes with each other and a third protein, casein kinase I. These complexes enter the SCN at night and inhibit CLOCK and BMAL1, which, in turn, inhibits production of the PERIOD and CRY proteins. The inhibiting complexes are short-lived, and by morning their effect wears off, allowing the cycle to start again.[20]

In animal studies, single knockouts of a *Per* or *Cry* gene alter the circadian period. Functional double knockouts of *Per1* and *Per2* eliminate circadian cycling entirely, while altering expression of *Per3* shortens the circadian cycle.[20] Differences in the sequence of these genes that occur among individuals (called "polymorphisms") influence "morningness" versus "eveningness" (ie, diurnal preference[25]) as well as the degree to which changes in schedule affect individuals. Specifically, a *Per1* polymorphism has been identified that predisposes individuals to extreme morningness, while polymorphisms in *Per2* have been associated with familial advanced sleep phase syndrome.[26] *Per3* contains a 54-nucleotide coding sequence that normally repeats 4 ($Per3^{4/4}$) or 5 ($Per3^{5/5}$) times in humans. About 10% of the population is homozygous for the $Per3^{5/5}$ allele and 50% are homozygous for the $Per3^{4/4}$ allele.[27] Individuals homozygous for $Per3^{5/5}$ are prone to morningness and are more susceptible to the effects of sleep deprivation, having a greater proclivity for cognitive decline following sleep deprivation, whereas those homozygous for $Per3^{4/4}$ are prone to extreme eveningness and even delayed sleep phase syndrome.[20,27]

Although these findings provide further insight into normal sleep patterns, many factors other than genetic polymorphisms contribute to an individuals' susceptibility to the effects of sleep deprivation and forced alterations in sleep/wake times (FIGURE 2).[27]

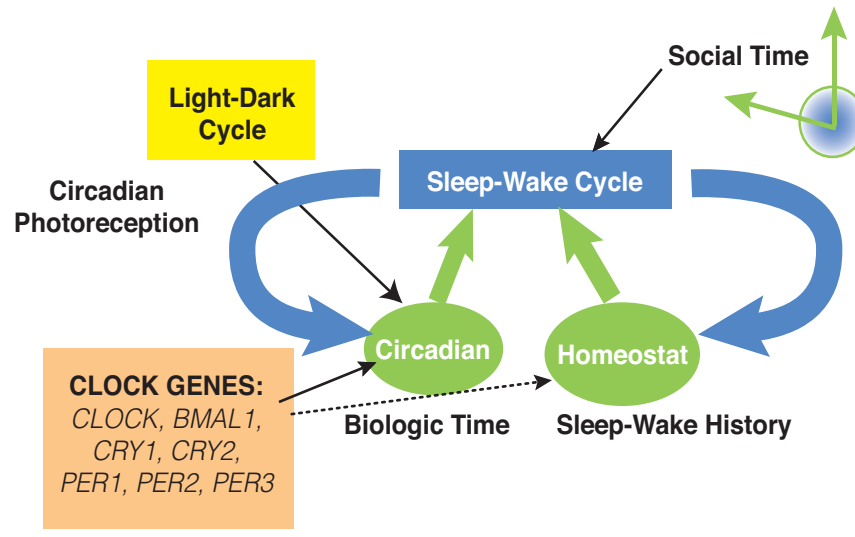
Physiologic Correlates of Normal Sleep and Sleep Loss

In SWD, complaints of insomnia and daytime somnolence can result not only from a disruption in circadian alignment, but also from a disruption in the amount or quality of sleep. The process of sleep has a modulatory effect on neuroendocrine function and glucose regulation.[22] In addition, a number of important metabolic functions are affected by SWS: overnight reductions in heart rate, blood pressure, and other markers of sympathetic nervous system activity. Also noted are release of growth hormone and prolactin and inhibition of the hypothalamo-pituitary-adrenal (HPA) axis activity.[28]

Although cortisol secretion, a marker of HPA axis activity, is primarily under circadian influence, sleep processes also appear to modulate this.[29] Sleep onset at any time of the cortisol cycle has the effect of lowering cortisol release for a few hours, while arousal from sleep has the effect of elevating cortisol levels. In one study of daytime sleepers, highest levels of cortisol were still observed in the morning, but the amplitude of the response tended to be lower than those of nighttime sleepers.[29,30]

Despite evidence of an association between adequate sleep and metabolic health, chronic partial sleep loss in the form of too-short sleep periods or interrupted sleep is highly prevalent in the United States.[22] There is evidence that chronic sleep deprivation results in an increase in the levels of glucocorticoids.[29] Moreover, epi-

Figure 2. Elements of Sleep-Wake Regulation



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demiologic studies demonstrate an association between chronic, partial sleep deprivation and obesity/weight gain. In nondiabetic individuals, the body's response to exogenous glucose administration is higher in the evening, and glucose tolerance is lowest in the middle of the night, thereby allowing the maintenance of glucose levels during the overnight fast. This response is believed to be due to reduced insulin sensitivity and reduced insulin secretion in response to an increase in blood glucose levels during the evening, although it also appears to also be sleep-dependent[31] as glucose metabolism is altered following sleep disruption (FIGURE 3).[31,32] The effects of fragmented sleep on glucose regulation and insulin resistance are likely to be intensified in individuals who have diabetes.[33] Recent studies have also shown associations between sleep curtailment and levels of ghrelin, leptin, appetite for carbohydrates, and insulin resistance, suggesting that sleep deprivation may not only promote excessive calorie consumption, but may result in diminished ability to metabolize glucose once absorbed, possibly contributing to obesity and increased risk of type 2 diabetes.[32,34,35] Additional studies are needed to confirm these associations.

Cross-sectional studies indicate that individuals with poor quality sleep or short sleep durations are also more likely to have hypertension. Evidence from the large, ongoing CARDIA study of middle-aged adults demonstrated that higher levels of systolic and diastolic blood pressure were predicted by short sleep duration or lower quality sleep. Over 5 years, individuals who reported these sleep disturbances also had greater increases in systolic blood pressure and smaller decreases in diastolic blood pressure than those with normal sleep patterns.[36]

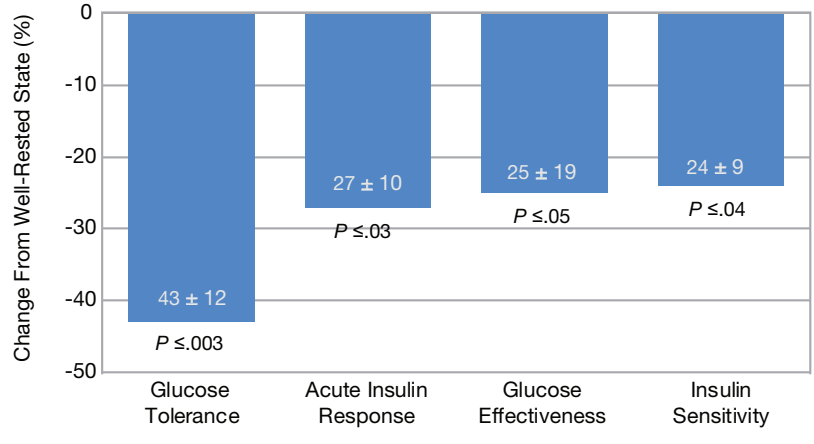
Circadian Effects on Physiologic Processes

Circadian rhythms are central to regulation of sleep and wakefulness. Synchronous activity between the body's master clock and environmental cues of light and darkness impact an individual's daily variation in cognition, vigilance, sleep propensity, mood, and many physiologic parameters.[17] Physiologic processes that follow a circadian pattern include hormones such as cortisol, growth hormone, leptin, and ghrelin; glucose levels; and other metabolic processes.[29,32] Cortisol follows a 24-hour pattern, with highest levels of activity in the early morning, a slow decline during the day, a quiet period overnight (with lowest levels around midnight), and subsequent rebuilding to morning highs.[29] Interestingly, bright light exposure in normal humans increases cortisol levels in the early morning, but not in the afternoon, suggesting that the effects of light on the corticotropic axis are dependent on time of day.[37]

Circadian rhythms also are evident in regulation of blood pressure. In humans, blood pressure tends to be lowest at night and rises in the morning in a roughly 24-hour cycle. The opposite rhythm occurs in nocturnal animals.[38] Within the circadian control system, animal studies indicate the presence of central "brain" and peripheral clocks that coordinate external cues (eg, light/dark) with metabolic outputs (eg, fasting/feeding). While the brain clock controls behavioral rhythms of sleep, feeding, and wakefulness, the peripheral clocks are involved in metabolic rhythms, such as glucose homeostasis, lipogenesis, and sterol and oxidative metabolism.[39]

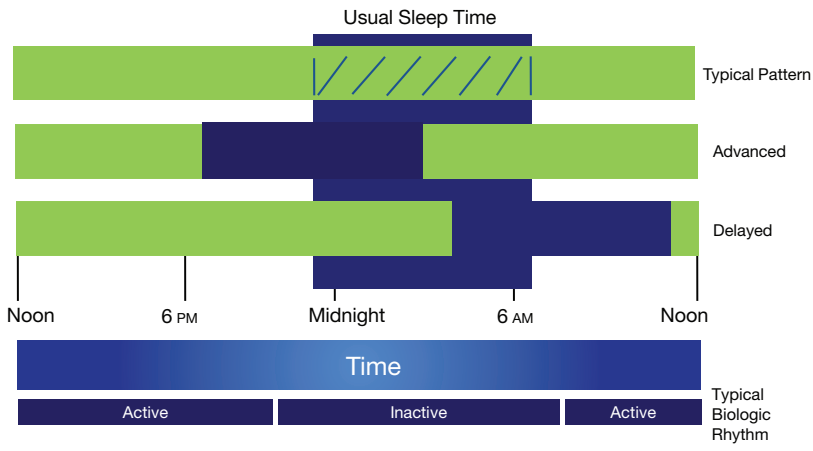
The effects of certain medications also seem to follow a circadian pattern. The effects of certain antihypertensive agents on blood pressure are greater when administered at certain times of the day; for example, the administration of an alpha-adrenergic antagonist in primary hypertension results in more pronounced effects on blood pressure control when administered before sleep.[38,40] Timing of administration also may be relevant for other medications, including verapamil hydrochloride, H_2 antagonists, statins, theophylline for nocturnal asthma, some chemotherapy agents, and, of course, hypnotic

Figure 3. Effects of Sleep Deprivation on Metabolism: Change in Metabolic Parameters in Healthy Adults After 5 Nights With Only 4 Hours' Sleep



Source: Reference 32.

Figure 4. Circadian Misalignment



This example illustrates individuals with advanced-phase or delayed-phase sleep disorder. Those with advanced-phase disorder tend to fall asleep and awake much earlier than the norm, while those with delayed-phase disorder have the opposite issue and fall asleep later. Problems arise when these patterns interfere with normal activities of daily living, including work.

agents.[41] The relationship between time-of-day administration of medications and physiologic effects is complex and may depend on a variety of factors, such as:

1. Circadian variation in physiologic processes and disease states
2. Influence of circadian rhythms on pharmacokinetics of medications due to circadian variation in absorption, distribution, metabolism, and elimination
3. Influence of circadian rhythms on pharmacodynamics of certain medications

Circadian Rhythm Misalignment and Potential Physiologic Consequences: Under certain circumstances, the endogenous master clock can become misaligned with respect to the environmental light/darkness cycle, with a range of consequences.[17] This misalignment, thought to be the basis of circadian rhythm sleep/wake disorders, can occur when alterations in the endogenous circadian timing system occur that are incompatible with the required sleep-wake schedule or when exogenous factors that affect timing and/or duration of sleep are not compatible with the endogenous circadian rhythm.[42] Examples of the former type of misalignment include advanced and delayed-phase sleep disorders (FIGURE 4); SWD and jet lag are examples of the latter type of circadian rhythm sleep/wake disorder.[19,43,44] People with circadian rhythm disorders typically are too sleepy during the hours they need to maintain wakefulness and have difficulty falling or staying asleep during their normal sleep hours.[43-45] It is important to recognize that not all individuals exposed to exogenous factors affecting timing and/or duration of sleep develop a sleep/wake disorder, but rather that these factors act as triggers in individuals who are genetically or otherwise susceptible.[19]

If individuals are unable to cope when these clocks are out of sync because of factors such as shift work and jet lag, various physiologic functions may be impacted negatively. Preliminary studies in humans subjected to experimental misalignment of circadian rhythms have shown evidence of significantly altered metabolic measures including higher glucose and insulin levels, suggesting a decrease in insulin sensitivity or increased insulin resistance, possibly indicating circadian misalignment may contribute in select patient populations to the development of a prediabetic or diabetic state, although such relationships await confirmation by larger studies.[46]

In studies investigating the effects of delays or advances in the rest/activity cycle on healthy individuals, an 8-hour delay in the sleep phase caused an initial dysregulation of cortisol with adaptation to the new schedule after about 5 days. However, adaptation of certain aspects of cortisol metabolism were not observed following an abrupt 8-hour advance in the rest/activity cycle in normal humans; whereas a rapid partial adaptation of certain temporal profile markers of cortisol was seen, a marked disruption of the cortisol quiescent period also was noted.[29,47,48] The failure of complete adaptation in markers of HPA activity to extreme forced advances in rest/activity cycles suggests that forced manipulations of normal sleep/wake times may negatively impact a number of physiologic functions.[47]

POP QUIZ

Insomnia or excessive sleepiness is experienced by:

A. Almost all shift workers
B. <5% of shift workers
C. Up to ≈1/3 of shift workers
D. Up to ≈1/2 of shift workers

Prevalence and Characteristics of Shift Workers

Millions of Americans work nontraditional "shift" hours. It is typical to think of "shift" work as "night"

work, but shift work can adopt many patterns, including rising early after minimal sleep at night for occupational reasons, rotating work schedules, and night work. Individuals who work during the night often sleep during the day on workdays, yet reverse their sleep/wake pattern on weekends or days off to conform to societal needs. Surveys suggest that 14% to 17.7% of American workers—approximately 22 million individuals—are shift workers by this definition.[49-51]About 3.5% of workers work night shifts, 4.6% work evening shifts (2 PM-midnight), and 2.9% work rotating shifts.[50] Percentages are higher among specific professions, including 55% of protective service workers (police and fire), 30% of healthcare workers, 30% of transportation workers, and 26% of machine operators.[50]

Many shifts require workers to be "awake" during the times normal circadian pressures would promote sleep and to sleep during times when circadian alerting signals are at their highest, putting these workers at a disadvantage in staying awake and acquiring sufficient quality and quantity of sleep during their off hours. Individuals doing shift work tend to have shorter duration and less satisfactory sleep. In a survey of workers, 40% of all workers (regardless of shift) reported getting less than 6.5 hours of sleep daily; night workers and those with rotating shifts were almost twice as likely as others to report getting less than 6 hours of sleep.[52] In a survey of shift workers, those working rotating shifts reported having more trouble falling asleep after work.[53] Individuals working rotating shifts or fixed night shifts had shorter sleep duration than those on fixed daytime schedules.[53] It is notable that even individuals rotating between morning and afternoon shifts with no night work were affected in terms of sleep duration and sleep latency.[53]

Table 2. International Classification of Sleep Disorders Diagnostic Criteria for SWD

A	Complaint of insomnia or excessive sleepiness temporally associated with a work schedule that overlaps the usual time for sleep
B	Symptoms are associated with the shift-work schedule over the course of ≥1 month
C	Sleep log or actigraphy monitoring for ≥7 days demonstrates disturbed circadian and sleep-time misalignment
D	Sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder

SWD: shift-work disorder.
Source: Reference 42. American Academy of Sleep Medicine. *The International Classification of Sleep Disorders Diagnostic and Coding Manual, 2nd edition*. Westchester, Illinois: American Academy of Sleep Medicine, 2005.

Shift work is associated with higher rates of insomnia during sleep time and excessive sleepiness during wake hours. Approximately 32% of night workers and 26% of rotating shift workers report having insomnia or excessive sleepiness compared with 18% of day workers.[54] For all shifts, including daytime shifts, sleepiness without insomnia occurs more often than insomnia alone or combined sleepiness and insomnia; rates are highest for night and rotating workers versus day workers.[54] Among night workers, 15.2% report sleep attacks, ie, episodes of falling asleep without warning, and 26.6% report excessive sleepiness when at work.[52]

Excessive sleepiness puts these individuals at high risk for accidents on the job or on their way home from work. Among shift workers, 19% to 29% (depending on the shift) report excessive sleepiness at times they are required to be awake, typically at night.[53] In general, those working shifts have higher rates of accidents than those working fixed daytime schedules,[53] and certain types of shift workers are at higher risk for accidents, including transportation workers, healthcare workers, and people with long commutes to and from work.[44] Night- or rotating-shift workers are 2 to 4 times as likely as daytime workers to fall asleep while driving,[52] reflecting cumulative effects of a number of factors such as impairment in concentration, reaction times, and alertness, resulting from potential underlying causes including excessive sleepiness, sleep deprivation, and changes in circadian rhythm.[55]

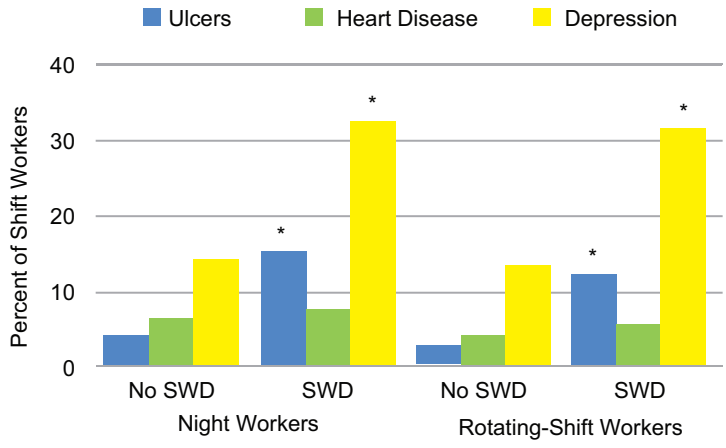
POP QUIZ

Sleep/wake symptoms of SWD include:
A. Insomnia only
B. Excessive sleepiness only
C. Insomnia and/or excessive sleepiness

Shift-Work Disorder

Not all shift workers develop SWD. However, any of these individuals is at risk for developing SWD, a sleep/wake disorder associated with increased risks of accidents and health problems, impaired performance at work and home, and a decreased quality of life. Individual factors that may increase a shift worker's likelihood of developing SWD include predisposition to insomnia, genetic vulnerability that reduces the ability to adapt to sleep loss, and an individual's innate circadian variation (morning-type people are more susceptible to SWD).[19] The true prevalence of SWD is unknown, but estimates from a land-

Figure 5. Health Effects of SWD: SWD Versus Shift Workers Without SWD



Workers with SWD have higher rates of various illnesses, including ulcers and depression.
*P <.05 vs workers without SWD. SWD: shift-worker disorder.
Source: Reference 54.

mark survey of 2570 individuals found that 14.1% of night-shift workers and 8.1% of rotating-shift workers met criteria for SWD.[54] A study of oil-rig shift workers in Norway found that 23.3% met SWD criteria.[56]

SWD: Criteria: Diagnostic criteria for SWD according to *The International Classification of Sleep Disorders* from the American Academy of Sleep Medicine (AASM) are listed in TABLE 2.[42] According to the AASM, SWD is associated with curtailed sleep periods, unsatisfactory sleep, and impaired performance at work, which usually resolve when shift work is stopped.[42]

SWD: Impact on Health, Safety, and Quality of Life: Individuals with SWD suffer a number of detriments compared with shift workers without SWD. Shift workers who meet criteria for SWD have significantly higher rates of ulcers and depression, and higher rates of heart disease than shift workers without SWD (FIGURE 5). They also have higher rates of these conditions than daytime workers who have symptoms of insomnia and/or excessive sleepiness.[54] In one study of Norwegian oil-rig workers, those meeting criteria for SWD had significantly higher rates of musculoskeletal pain and gastrointestinal complaints than similar workers without SWD.[56] Workers with SWD report more sleep disturbances and daytime dysfunction than shift workers without SWD.[56] Night-shift and rotating-shift workers meeting SWD criteria have higher rates of sleepiness-related accidents than similar workers without SWD.[54]

Other complications associated with SWD include exacerbation of gastrointestinal and cardiovascular disorders; increased risk of cancer, mood, and anxiety disorders; reduced fertility; and an increased risk of substance dependence.[42,57] It is important to recognize that while these types of complications have been associated with SWD as well as shift work itself, it still is not clear that a cause and effect relationship exists.[57] Similarly, it is accepted that sleep deprivation has negative effects on cognitive tasks of memory consolidation, learning, alertness, and task performance.[57] Night-shift workers with SWD tend to have even less sleep than other workers on the same shift,[54] presumably putting them at high risk for these cognitive detriments.

SWD also is associated with psychosocial upheaval. Workers with SWD miss significantly more family and social activities, and daytime sleeping requirements often disrupt social and family life.[42,54] Workers with SWD show reduced efficiency at work and miss more days of work than workers on the same shifts without SWD.[53,54]

Summary

Adequate sleep length and quality of sleep appear to be an important aspect of normal human functioning. Nevertheless, the demands of society leave many individuals with too little or fragmented sleep and the need to work outside the typical daytime hours. These individuals may be at increased risk for a variety of physical and mental detriments, including obesity, diabetes, cardiovascular disease, and depression. Shift work is practiced by multiple professions, including police and fire services, healthcare workers, truck drivers, pilots, and people involved in manufacturing or other 24-hour industries. In total, approximately 22 million Americans are "shift workers."

Although night-shift and rotating-shift workers are at higher risk for SWD, not all of these workers develop SWD. Some are better equipped to cope with the challenges imposed on their central and peripheral clocks, possibly owing to genetic variations. However, those who cannot cope may develop circadian rhythm misalignment–SWD. These individuals are at higher risk for a variety of illnesses and accidents than similar workers without SWD. An important aspect to successful intervention for these individuals is identifying those at risk and referring those who require it to receive appropriate intervention.[17]

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Advances in the Management of Shift-Work Disorder

Part II: General Approach to Screening, Diagnosis, and Management of Shift-Work Disorder

SCREENING FOR SLEEP/WAKE DISORDERS

Sleep/wake disorders can be associated with difficulty in falling or staying asleep, sleepiness during wake time, or some combination of these factors. These disturbances can be associated with social and occupational impairment and may suggest the existence of underlying serious medical and psychiatric conditions. It is important to screen all patients for sleep/wake disorders as part of routine health maintenance evaluation. Some important screening questions include, "Do you have problems sleeping during sleep time?" "Do you have problems staying awake during wake time, such as during working hours?" A few simple questions regarding occupation and work hours should also be asked of all patients. These questions can help identify those individuals who may have a circadian rhythm sleep/wake disorder, such as shift-work disorder (SWD).

Some algorithms which facilitate screening for sleep/wake disorders have been published (FIGURE 1). Nevertheless, it is important to realize that more than 1 diagnosis may contribute to reported symptoms, and that sleep/wake disorders are not mutually exclusive.[1-3] A finding of a putative misalignment of circadian rhythm does not rule out the possibility of other factors contributing to the sleep/wake disturbance. Other potential sources (eg, medical conditions, pharmacologic agents) of the sleep/wake disorder must be assessed. Conversely, diagnosis of an underlying medical condition associated with a sleep/wake disorder does not preclude the possibility of a comorbid disturbance in circadian rhythm, such as SWD.

Questioning the patient regarding a proclivity to fall asleep during inopportune times or to feel sleepy during the portion of day when they are typically awake is an essential part of evaluating sleep/wake health. It can also be problematic, as some sleepy patients are unaware of the extent of their impairment during wake time and may underestimate the functional impact of a sleep/wake disorder, in part because they may have learned coping mechanisms or because sleep disturbances may interfere with cognitive ability, motivation, and judgment.[4,5] Instead, patients may report feeling "tired" or "fatigued."

DIAGNOSIS OF SWD

Because SWD is only one of a myriad of disorders that can be responsible for sleep/wake complaints,[6] a systematic and comprehensive approach is needed to uncover the underlying cause(s) of the problem. This typically involves taking a detailed history of the nature of the complaint, sleep/wake patterns, medical and psychiatric conditions, medication and drug use, and family and social history. In addition, potential comorbid conditions that may be causing insomnia and excessive sleepiness (ES), the hallmark symptoms of SWD, must be ruled out.[1,7,8] As part of the sleep/wake history, behaviors that can disrupt sleep, as summarized in TABLE 1, also should be assessed.[3]

Table 1. Sleep-Related Habits and Behaviors That Can Disrupt Sleep

- Caffeine and alcohol prior to bedtime
- Nicotine (smoking and cessation)
- Large meals or excessive fluid intake within 3 hours of bedtime
- Exercising within 3 hours of bedtime
- Using the bed for nonsleep activities (work, telephone, Internet)
- Staying in bed while awake for extended periods of time
- Activating behaviors up to the point of bedtime
- Excessive worrying at bedtime
- Clock-watching prior to sleep onset or during nocturnal awakenings
- Exposure to bright light prior to bedtime or during awakenings
- Bedroom temperature too hot or too cold
- Noise
- Behaviors of a bed partner (eg, snoring, leg movements)

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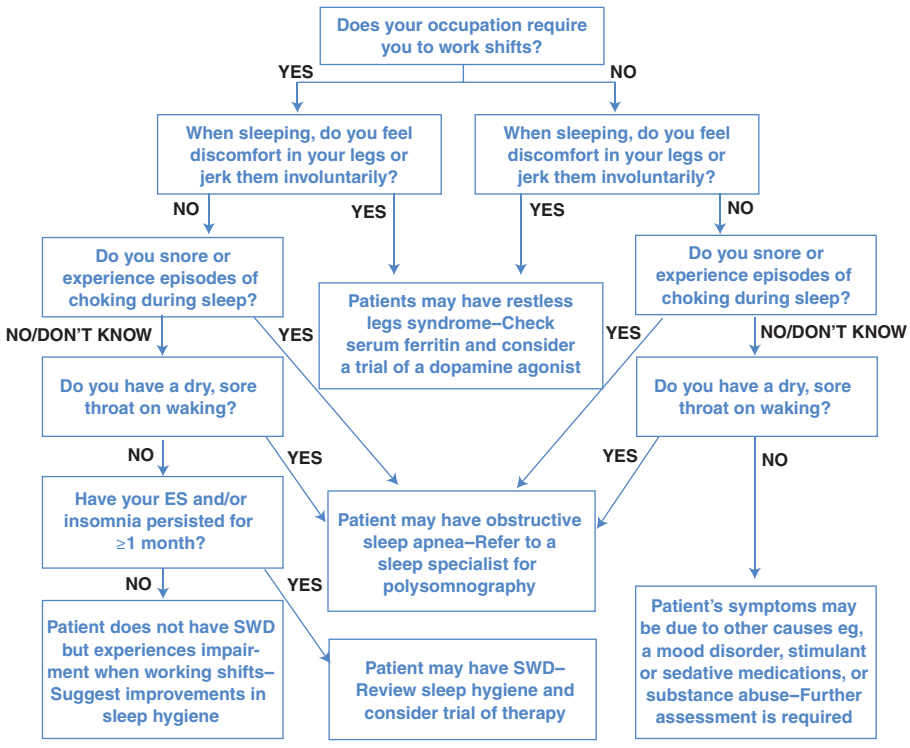
Figure 1. Differentiating SWD



ES: excessive sleepiness; SWD: shift-work disorder.
Source: Reference 17. Reproduced with permission from Schwartz JRL. *J Fam Pract.* 2010;59:S18-S23. Copyright 2010 Quadrant HealthCom Inc.

The 5 domains of clinical sleep medicine can be iterated using a "5-finger" mnemonic (TABLE 2) that takes into account circadian misalignment, pharmacologic, medical, psychiatric and psychosocial factors, and primary sleep diagnoses.[1] Each area represents a potential source of disturbance to a patient's sleep/wake quality and a potential contributor to insomnia and/or excessive sleepiness.

A fundamental part of the sleep/wake history that is critical to uncovering a circadian rhythm sleep/wake disorder is an assessment of times of sleep and wakefulness. TABLE 3 lists some of the key parameters in this regard.[3] For example, delayed sleep phase syndrome is characterized by an inability to fall asleep and awaken at the desired times, whereas advanced sleep phase syndrome is characterized by an inability to stay awake until the desired bedtime and remain asleep until the desired awakening time.[3,9] Diagnostic criteria for circadian rhythm sleep disorder, shift-work type (SWD) include a complaint of ES and/or insomnia occurring for at least 1 month that is associated with a recurring work schedule (see *Part I. Shift-Work Disorder: Pathophysiology and Health-Related Consequences*).[10]

Pharmacologic agents, including prescription and nonprescription drugs, should be noted, especially those known to be associated with sleep disruption and ES, such as caffeine and alcohol (see *Part III. Role of the Pharmacist in Identification, Treatment, and Follow-up of Patients With Shift-Work Disorder*).[1,3] Medical disorders that can affect sleep, such as gastroesophageal reflux, prostatic hypertrophy, chronic obstructive pulmonary disease, musculoskeletal pain syndromes, and chronic pain are relevant. Psychiatric and psychosocial factors represent a vast scope of diagnoses and behavior patterns that may affect sleep quality. Primary sleep diagnoses focus on those expected to occur within the domain of clinical sleep medicine, such as

Table 2. The 5 Domains of Clinical Sleep Medicine

- Circadian misalignment
  – Cornerstone importance
- Pharmacologic factors
- Medical factors
- Psychological and psychosocial factors
- Primary sleep diagnoses

Source: Reference 1.

Table 3. Key Sleep Parameters in the Sleep/Wake History

- Bedtime
- Sleep latency (time to fall asleep after lights out)
- Nocturnal awakenings; number and duration
- Time of final morning awakening
- Rising time (ie, time out of bed)
- Number, time, duration of daytime naps
- Daytime symptoms including levels of sleepiness and fatigue over the course of the day

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Table 4. Symptoms of Some Common Sleep/Wake Disorders

Disorder	Symptoms
Psychophysiological (primary) insomnia	"Trying" to fall asleep Difficulty falling asleep at desired bedtime Frequent nocturnal awakenings Anxiety regarding sleeplessness
Restless legs syndrome	Irresistible urge to move the extremities Limb paresthesiae Onset of symptoms during periods of rest and in the evening or at bedtime Relief of symptoms with movement
Periodic limb movement disorder	Repetitive involuntary movements of the extremities during sleep or just prior to falling asleep
Narcolepsy	Excessive daytime sleepiness Cataplexy Sleep paralysis Hypnopompic hallucinations
Obstructive sleep apnea syndrome	Snoring Breathing pauses during sleep Choking Gasping Morning dry mouth
Chronic obstructive pulmonary disease	Dyspnea
Gastroesophageal reflux	Epigastric pain or burning Laryngospasm Acid taste in mouth Sudden nocturnal awakenings
Prostatic hypertrophy	Frequent nocturia
Nocturnal seizures	Thrashing in bed Loss of bladder or bowel control
Nocturnal panic attacks	Sudden surges of anxiety Tachycardia Diaphoresis Choking Laryngospasm
Post-traumatic stress disorder	Recurring, vivid dreams and nightmares Anxiety and hypervigilance in sleep environment
Delayed sleep phase syndrome	Inability to fall asleep at desired time Inability to awaken at desired time
Advanced sleep phase syndrome	Inability to stay awake until the desired bedtime Inability to remain asleep until the desired awakening time

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obstructive sleep apnea (OSA), narcolepsy, sometimes associated with an abrupt attack of muscular weakness and hypotonia (ie, cataplexy), restless legs syndrome, and primary insomnia; these factors are considered last to emphasize that other diagnoses potentially contributing to a patient's symptoms should not be overlooked.[1] Hallmark symptoms of some of these conditions are listed in TABLE 4.

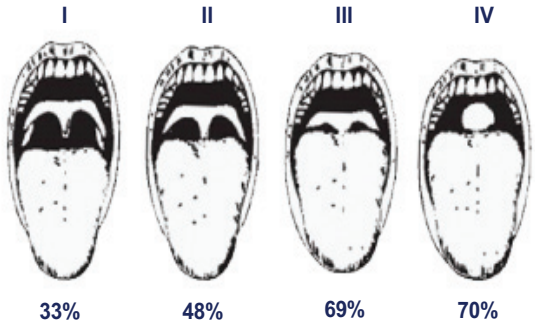
A thorough physical examination should also be undertaken including a complete head, eyes, ears, neck, and throat (HEENT) exam, as well as measurement of neck size and airway since a neck circumference of ≥16 inches in women and ≥17 inches in men is associated with an increased risk for sleep-related breathing disorders.[11] Obesity with fat distribution around the neck or midriff, nasal obstruction, mandibular hypoplasia, retrognathia enlarged tonsils and tongue, an elongated uvula and soft palate, diminished pharyngeal patency, and redundant pharyngeal mucosa suggest a diagnosis of OSA. The Mallampati Airway Classification score, based on the visibility of the soft palate and uvula, places patients into 1 of 4 classes and is an independent predictor of risk for OSA (FIGURE 2).[12]

Signs of heart failure should be noted; heart failure can cause abnormalities of breathing during sleep, which, in turn, can be associated with frequent nocturnal awakenings and unrefreshing sleep. The mental status examination should include an evaluation of affect, anxiety, psychomotor agitation or slowing, cognition, possibility of reduced alertness and slurred speech, and perceptual disturbances. Blood work can include a serum ferritin level. Low levels (ie, <50 µg/L) are suggestive of iron deficiency as an etiological factor in restless legs syndrome. General blood chemistry and metabolic tests and thyroid-stimulating hormone (TSH) should be considered.

Simple tools are available to evaluate for insomnia or excessive sleepiness. For example, the Epworth Sleepiness Scale (ESS) (TABLE 5) provides a validated assessment of the tendency to doze in 8 different situations. Using this tool, ES is defined as a total ESS score of ≥10.[8,13]

The Insomnia Severity Index (ISI) is a reliable and valid instrument that can be used to quantify perceived insomnia severity, including the next-day consequences of loss of sleep (TABLE 6). Patients are asked to rate severity of insomnia

Figure 2. Mallampati Score



During assessment, the patient is instructed to open his or her mouth as wide as possible, while protruding the tongue as far as possible. Patients are instructed to not emit sounds during the assessment.

Class I: soft palate and entire uvula visible; Class II: soft palate and portion of uvula visible; Class III: soft palate visible (may include base of uvula); Class IV: soft palate not visible.

A high Mallampati classification has been associated with an increased incidence of sleep apnea.

OSA = obstructive sleep apnea.
Source: References 8,12. *Sleep* by American Sleep Disorders Association. Copyright 2011. Reproduced with permission of American Academy of Sleep Medicine in the format Journal via Copyright Clearance Center.

over the previous week (from none to very severe on a scale of 0-4), satisfaction/dissatisfaction with current sleep patterns, interference with daily functioning, whether the sleeping problem is noticeable to others in terms of impaired quality of life, and how worried/distressed patients are about their insomnia.[14,15]

Interactive Exercise

Community pharmacies providing 24-hour services often schedule 7 10-hour days followed by 7 days off for pharmacists working the night shift. Shift-work pharmacists may work significantly more hours per week than non–shift-work pharmacists.[77,78] Community pharmacists as a group may themselves be direct beneficiaries of educational initiatives on sleep/wake health while also having particular insights into strategies that effectively address and help alleviate the health, safety, and quality of life detriments associated with SWD.

Use the ESS (TABLE 5) to calculate your score.
Use the ISI (TABLE 6) to calculate your score.

Simple sleep/wake assessment tools such as the ESS and the ISI are well suited to pharmacist-directed, patient-centered screening and provide a rapid, quantifiable assessment of subjective sleepiness (see *Part III. Role of the Pharmacist in Identification, Treatment, and Follow-up of Patients With Shift-Work Disorder)*.[8,13,16] The ESS and the ISI also are useful to assess effects of treatment for certain sleep/wake disorders, including SWD, in follow-up visits.

A sleep log/diary can be helpful in the evaluation of individuals for whom circadian misalignment is suspected and is recommended as an evaluation tool for the assessment of patients with suspected SWD (FIGURE 3).[9,10]

Use of actigraphy is an option in the diagnosis of patients with suspected SWD.[9] It involves use of a simple device, generally worn on the wrist, with movement detectors approximating sleep versus wake states. It offers a means of conveniently recording continuous 24-hour sleep/wake patterns over days or weeks. The collected data are

Table 5. Epworth Sleepiness Scale (ESS)

Situation	Chance of Dozing Off			
Sitting and reading	0	1	2	3
Watching TV	0	1	2	3
Sitting, inactive in a public place (eg, a theater or meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3
			Total Score	

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing
ESS total score ≥10 indicates ES or sleep disorder.

ES: excessive sleepiness.
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Table 6. Insomnia Severity Index (ISI)

Please rate the current (i.e., last 2 weeks) SEVERITY of your insomnia problem(s)	None	Mild	Moderate	Severe	Very Severe
Difficulty falling asleep	0	1	2	3	4
Difficulty staying asleep	0	1	2	3	4
Problem waking up too early	0	1	2	3	4
How **SATISFIED**/dissatisfied are you with your current sleep pattern?	Very satisfied 0	Satisfied 1	Neutral 2	Dissatisfied 3	Very dissatisfied 4
To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (ie, daytime fatigue, ability to function at work/daily chores, concentration anxiety, mood, etc)?	Not at all interfering 0	A little 1	Somewhat 2	Much 3	Very much interfering 4
How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?	Not at all noticable 0	A little 1	Somewhat 2	Much 3	Very much noticable 4
How **WORRIED**/distressed are you about your current sleep problem?	Not at all worried 0	A little 1	Somewhat 2	Much 3	Very much worried 4

Guidelines for Scoring/Interpretation:
Add scores for all seven items (1a+1b+1c+2+3+4+5) = ___
Total score ranges from 0-28
Total Score: 0-7: no clinically significant insomnia, 8-14: subthreshold insomnia, 15-21: clinical insomnia (moderate), 22-28: clinical insomnia (severe)
Source: Reference 14. Reproduced with permission from Charles M. Morin, PhD.

Figure 3. Two Week Sleep Diary

Patients should complete the sleep diary by filling in the date, day of the week, type of day (work, school, day off, weekend). Patient to add a "C" in a box when they had caffeine; an "M" for medications; an "A" for alcohol, and an "E" for exercise. The patient should mark a box when going to bed and shade all boxes to denote when asleep or napping.

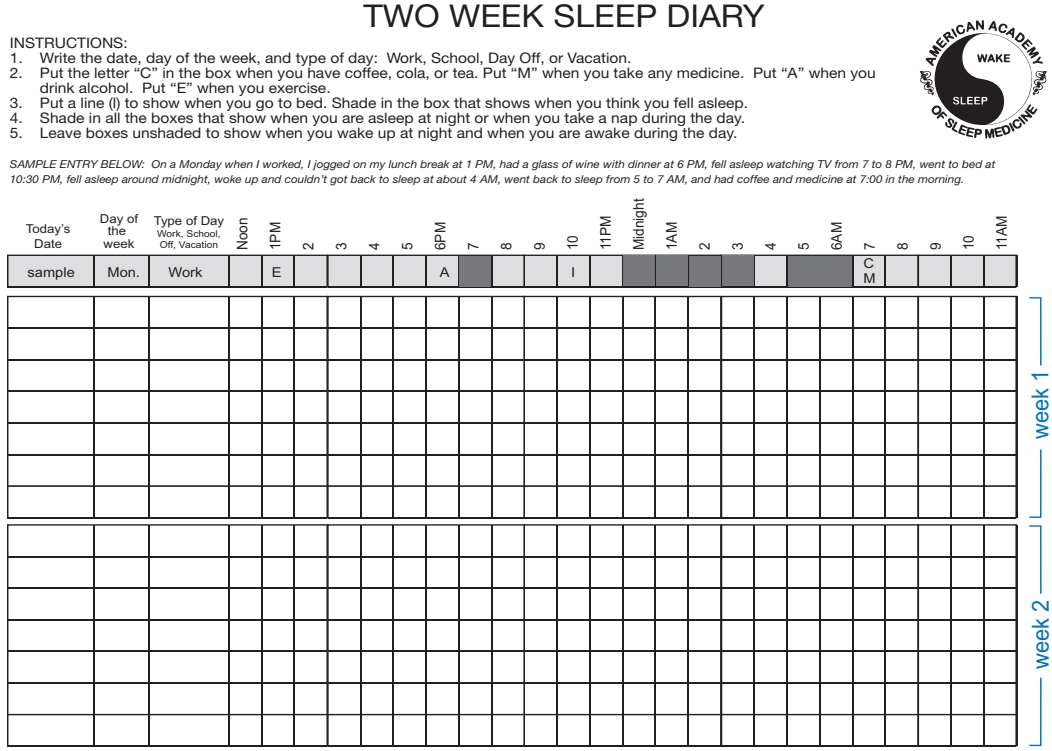

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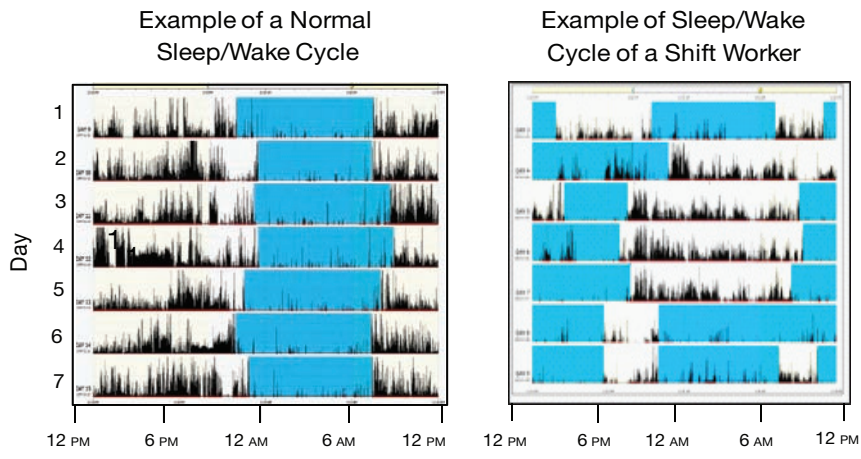
Figure 4. Diagnostic Tools for Measuring Sleep/Wake and Circadian Rhythm: Actigraphy



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downloaded into a computer for a graphic depiction of results.[5] FIGURE 4 shows representative actigraphs recorded over a 7-day period for an individual working a night shift and an individual with typical sleep/wake hours. Actigraphy is more commonly used by sleep specialists compared with primary care providers.

Polysomnography is not recommended by American Academy of Sleep Medicine (AASM) to diagnose SWD,[9] but may be useful to rule out other primary sleep/wake disorders, such as OSA, narcolepsy, or periodic limb movement disorder (PLMD), if suspected during an office-based evaluation.

MANAGEMENT OF SWD

Once the diagnosis of SWD is established, patients usually can be managed in primary care settings using behavioral and pharmacologic measures.[8,9,16-18] The AASM includes recommendations for treatment of circadian rhythm sleep disorders, including SWD (TABLE 7).[9] Each recommendation is addressed in more detail in the following sections.

Nonpharmacologic Approaches:

Patient education can help improve sleep schedule, sleep environment, and sleep hygiene (TABLE 8).[19] Short, timed naps can increase alertness and vigilance; improve reaction times; and decrease accidents during night-shift work without affecting daytime sleep following a night shift.[9,20] These naps can be taken prior to or during the night shift.[21,22]

To reduce risk of motor vehicle accidents during the commute home, patients should consider using a taxi service or car pooling (preferably with a driver who has not just completed a night shift); taking a nap before driving home; minimizing the commute time when possible; using public transportation; and, if sleepy while driving, pulling over at a rest stop to take a nap.[22]

When feasible, timed bright light exposure at night in the work environment and light restriction (eg, use of dark glasses) on the way home in the morning is indicated to decrease sleepiness and improve alertness during night-shift work. Exposure to different light intensities (2350 to 12,000 lux) for 20- to 30-minute discontinuous periods during the night shift or continuously during the first half to the entire night shift has been shown to improve performance on work-related tasks, alertness, and mood.[9] This is possibly related to the ability of light to shift the circadian phase of endogenous rhythms. Exposure to bright light at or shortly after the spontaneous wake time is associated with an advancement in circadian rhythm (eg, earlier wake time), whereas a delay in circadian rhythm is associated with exposure to bright light several hours prior to going to bed in the evening.[23] Full spectrum bright light typically is used without ultraviolet (UV) frequencies because these can interact with photosensitizing agents.[9] Ophthalmologic evaluations of normal patients have shown no impairment following bright light exposure, yet infrared

Table 7. AASM Summary of Recommendations for SWD: Therapy

Therapy	Level of Recommendation[a]
Planned sleep schedule	Indicated (Standard)
Timed light exposure	Indicated (Guideline)
Hypnotics	Indicated (Guideline)
Timed melatonin administration	Indicated (Guideline)
Stimulants (caffeine)	Indicated (Option)
Alerting agents (eg, modafinil)	Indicated (Guideline)

[a]AASM Levels of Recommendations.
Standard: generally accepted, high degree of clinical certainty; Guideline: moderate degree of clinical certainty; Option: uncertain clinical use (eg, inconclusive or conflicting evidence, conflicting expert opinion).
AASM: American Academy of Sleep Medicine; SWD: shift-work disorder.
Source: Reference 9.

Table 8. Practices Conducive to Restorative Sleep

Practice	Practical Tips
Bedroom should be dark. For shift workers, light exposure should be minimized when traveling home after work	Use curtains or blinds that block light For shift workers, consider wearing sunglasses when traveling home after work
Bedroom should be maintained at a constant, cool, comfortable temperature	Maintain room temperature at approximately 20ºC (68ºC) Limit number of blankets
Loud noise should be avoided/minimized before and during the sleep period	To minimize exposure to noise that cannot be attenuated, consider using earplugs, sleeping in a room located in a quieter area of the home To minimize exposure to noise that can be attenuated, consider avoiding loud music/TV prior to sleep period, using a telephone answering machine, informing housemates of the importance of quiet
Large meals, caffeine, smoking, and alcohol should be avoided before the sleep period	Eat main meal of the day during or prior to work period Consider having a warm noncaffeinated drink shortly before going to bed

Source: Reference 22.

and UV exposure can damage the lens, cornea, retina, and pigment epithelium. Patients with retinopathies, glaucoma, and cataracts should be excluded.[24] Although the side effects of bright light have not been systematically explored in the context of SWD, some adverse effects have been noted in the treatment of patients with seasonal affective disorder with bright light, including headache, visual difficulties, nausea and vomiting, dizziness, and sedation.[25]

A variety of shift work schedules are used, including unpredictable "on-call" shifts, variable (rotating) shifts, night shifts with weekend variation in sleep/wake times, and constant night shifts, which maintain the same sleep/wake times on weekends. It is beyond the scope of this article to discuss the relative merits and drawbacks of each of these shift types. Nevertheless, where possible, rotating shifts should take advantage of "clockwise" versus "counterclockwise" rotation, as workers adjust better to forward time shifts.[22]

Pharmacologic Approaches:

Pharmacologic agents for the treatment of patients with SWD include hypnotics and melatonin to treat SWD-associated insomnia, and stimulants, such as caffeine, as well as the wakefulness-promoting agents modafinil and armodafinil, to treat ES in patients with SWD.[9,26]

Hypnotics to treat insomnia

Placebo-controlled trials have shown that a number of hypnotic agents can favorably impact the quantity and/or quality of sleep.[27] However, few studies have evaluated hypnotic agents for the treatment of insomnia associated with SWD,[26,28-30] and none of these agents is specifically indicated by the US Food and Drug Administration (FDA) for the treatment of SWD. Hypnotic medications may be used to promote daytime sleep among night-shift workers (TABLE 7),[9] however, the risk of carryover sedation to the subsequent night shift, with the potential for adverse consequences for job performance and safety, should be balanced with benefit. The possibility that such medications might also worsen other coexisting sleep conditions, such as sleep-related breathing disorders, should be considered by clinicians so that therapy can be individualized and adverse effects closely monitored.[9] TABLE 9 summarizes available information on the mechanisms of action (MOA) of some of the agents used to treat insomnia, although the precise MOAs of many of these agents are not known. Also included in TABLE 9 are the U.S. Drug Enforcement Agency (DEA) schedules for these agents. TABLE 10 summarizes some of the dosing and pharmacokinetic parameters for these hypnotic agents.

Benzodiazepine receptor agonists

Benzodiazepines: There are 5 benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam) that are FDA-approved for the management of insomnia.[31-35] Because insomnia can be associated with problems initiating sleep and/or other sleep difficulties associated with sleep duration, consolidation, or quality, the pharmacokinetic properties of hypnotic agents need to be considered when selecting therapy (TABLE 10). For example, shorter-acting benzodiazepines, such as triazolam, may be more appropriate for patients with insomnia characterized by difficulty falling asleep, whereas longer-acting agents (eg, flurazepam, quazepam) may be better choices for patients with problems maintaining sleep. Potential side effects of these agents may include drowsiness, dizziness, interaction with alcohol, complex sleep-related behaviors (eg, sleep-driving), and/or rare cases of severe anaphylactic and anaphylactoid reactions.[31-35] Some benzodiazepines are associated with anterograde amnesia (ie, loss of ability to create new memories) of varying severity.[31,32]

Table 9. MOA of Agents Used in the Treatment of Insomnia or ES in SWD

	MOA	DEA Schedule
Benzodiazepine receptor agonists		
Benzodiazepines		
Estazolam, flurazepam, quazepam, temazepam, triazolam,	Agonists of the GABA-BZ complex; nonselective binding	IV
Selective benzodiazepine receptor agonists (ie, nonbenzodiazepines)		
Zolpidem Oral tablets Oral spray Sublingual Extended and immediate release	An agonist of the GABA-BZ receptor complex, binding BZ_1 receptor preferentially	IV
Zaleplon	An agonist of GABA-BZ receptor; acts through subunit modulation	IV
Eszopiclone	An agonist of GABA receptor complexes; believed to interact through binding domains close to or allosterically coupled to BZ receptors	IV
Melatonin receptor agonists		
Ramelteon	Melatonin receptor agonist with high affinity for MT_1 and MT_2 receptors	Not a controlled substance
Histamine H_1 receptor antagonists		
Doxepin (low dose)	Binds to histamine H_1 receptor and acts as an H_1 receptor antagonist	Not a controlled substance
Melatonin[43]		
	Acts on MT_1 and MT_2 melatonin receptors in the SCN	Over-the-counter
Alerting agents		
Caffeine[63]	Adenosine receptor antagonist	Over-the-counter
Wakefulness-promoting agents		
Modafinil Armodafinil	Likely to involve selective potentiation of CNS catecholaminergic signaling. Although not direct or indirect dopamine receptor agonist, these agents bind to the dopamine transporter and inhibit dopamine reuptake	IV

CNS: central nervous system; DEA: Drug Enforcement Agency; ES: excessive sleepiness; GABA-BZ: gamma-aminobutyric acid-benzodiazepine; IV: intravenous; MOA: mechanism of action; SCN: suprachiasmatic nucleus; SWD: shift-work disorder.
Source: References 31-44,55,63,70,71.

Selective benzodiazepine receptor agonists (nonbenzodiazepines): The nonbenzodiazepines include zolpidem in a variety of oral formulations (ie, immediate- and extended-release tablets, oral spray, sublingual), zaleplon, and eszopiclone. Whereas the immediate-release formulations of zolpidem are indicated for the treatment of insomnia characterized by sleep initiation, extended-release zolpidem, which provides extended plasma concentrations beyond 3 hours following administration, is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[36-39] Eszopiclone also may be an option for an individual who has difficulty with sleep initiation and duration because it reaches peak plasma concentration after only 1 hour but has an elimination half-life of 6 hours (TABLE 10). Zaleplon, although helpful for sleep initiation difficulties, is unlikely to be effective in prolonging sleep continuity given its short elimination half-life. Adverse effects of these agents may include drowsiness and dizziness, and use of eszopiclone may be associated with unpleasant taste. Abnormal thinking/behavioral changes, complex sleep-related behaviors (eg, sleep-driving), and/or rare cases of severe anaphylactic and anaphylactoid reactions are possible side effects of these agents.[36-41]

Melatonin receptor agonists

Ramelteon, a melatonin receptor agonist with high affinity for the melatonin MT_1 and MT_2 receptors, represents a relatively new class of hypnotic agents, although it has not been conclusively shown to have a circadian effect in SWD.[42-43] Ramelteon is indicated to treat insomnia characterized by difficulty with sleep onset.[27,42] The most commonly reported adverse effects of ramelteon include somnolence, dizzi-

Table 10. Hypnotics for Insomnia: Pharmacokinetic and Dosing Information

Agent	Dose Range	$t_{1/2}$[a]	T_{max}
Benzodiazepine receptor agonists			
Benzodiazepines			
Estazolam	1, 2 mg	10-24 h	Within 2 h
Flurazepam	15, 30 mg	47-150 h	0.5-1 h
Quazepam	7.5, 15 mg	39-73 h	≈2 h
Temazepam	7.5, 15, 22.5, 30 mg	8.8 h[b]	1.5 h[b]
Triazolam	0.125, 0.25 mg	1.5-5.5 h	Within 2 h
Selective benzodiazepine receptor agonists (nonbenzodiazepines)			
Zolpidem			
Oral tablets	5, 10 mg	≈ 2.5 h[b]	≈1.6 h[b]
Oral spray	5, 10 mg	2.7 h[b] (5mg); 3.0 h[b] (10 mg)	0.9 h[b] (5 mg); 1.0 h[b] (10 mg)
Sublingual	5, 10 mg	2.85 h[b] (5 mg); 2.65 h[b] (10 mg)	82 min[c]
Extended-release	6.25, 12.5 mg	2.8 h[b]	1.5 h[b]
Zaleplon	5, 10 mg	≈1 h	≈1 h
Eszopiclone	1, 2, 3 mg	≈6 h	≈1 h
Melatonin receptor agonists			
Ramelteon	8 mg	≈1-2.6 h	0.75 h[b]
Histamine H1 receptor antagonists			
Doxepin (low dose)	3, 6 mg	15.3 h	3.5 h

[a]Includes longest-acting active metabolite; [b]mean value; [c]median value.
$t_{1/2}$: elimination half-life; T_{max}: time to peak plasma concentration.
Source: References 31-42,44.

ness, fatigue, nausea, and exacerbated insomnia. Other potential side effects may include complex sleep-related behaviors (eg, sleep-driving), worsening of depression, central nervous system (CNS) depressant effects, and rare cases of severe anaphylactic and anaphylactoid reactions.[42]

H1 receptor antagonist

The hypnotic effects of low-dose (3 mg and 6 mg) doxepin relate to its ability to preferentially inhibit the wake-promoting activity of histamine by acting as a histamine H_1 receptor antagonist. Doxepin at low doses is indicated for the treatment of insomnia characterized by difficulties with sleep maintenance.[44] The most common side effects are somnolence/sedation, nausea, and upper respiratory infection. Other potential side effects include complex sleep-related behaviors (eg, sleep-driving), abnormal thinking, worsening of depression, and CNS depressant effects.[44]

Other agents

Trazodone, a serotonin modulator used to treat depression, also has anxiolytic and hypnotic effects and is sometimes prescribed for insomnia at low doses in nondepressed individuals, although not indicated for this use by the FDA.[45] It is also a blocker of 5-HT_2 and alpha-1 adrenergic receptors. A few studies suggest trazodone improves sleep in patients without mood disorder, although it does increase total sleep in patients with major depressive disorder.[46] There are virtually no dose-response data for trazodone vis-à-vis sleep and, similarly, no available data on tolerance to its possible hypnotic effects. Daytime sedation, induction of cardiac arrhythmias, and priapism are some of the considerations in its use, and a review of its adverse effects is in order prior to use.[47]

Limited evidence is available for the safety and efficacy of oral nonprescription treatments for insomnia, despite popular and extensive use of such products.[48] A double-blind, placebo-controlled crossover trial of the first-generation histamine-1-receptor antagonist diphenhydramine hydrochloride in 111 patients found that at a dose of 50 mg, the agent was significantly more effective than placebo in improving sleep latency, frequency of awakenings, wake time after sleep onset, sleep duration, and quality of sleep, with physician ratings of efficacy similar to patient responses.[49] Side effects may include residual drowsiness,[48] as well as an increased risk of delirium and urinary side effects in older individuals.[50]

Valerian, derived from plants of the species Valeriana (*V officinalis L*), is used as a sedative and anxiolytic. Results of several randomized, placebo-controlled trials of valerian in

doses ranging from 400 to 3600 mg administered before bedtime suggest efficacy as a mild hypnotic over short-term use; however, the studies are limited by small sample sizes and lack of objective sleep parameters.[48,51,52] In addition, there is a lack of standardization and quality control for these types of dietary/herbal products.

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine), a naturally occurring neurohormone primarily synthesized by the pineal gland discovered in 1958,[53] has been described as a "pill form of dark" when administered exogenously.[54] Most studies evaluating the pharmacokinetic properties of exogenously-administered melatonin have reported half-life and time to reach peak plasma concentration ranging from 0.54 to 0.8 hours and 0.5 to 1.0 hours, respectively.[55]

Data from clinical studies evaluating the impact of exogeneously administered melatonin in insomnia are limited and conflicting in the setting of SWD.[43,55] Three major findings resulted from analysis of several studies comparing administration of melatonin with placebo prior to daytime sleep after night-shift work: (1) daytime sleep quality and duration was improved; (2) some—but not all—subjects had a shift in circadian phase; and (3) alertness at night was not enhanced. Doses of exogenous melatonin in these studies ranged from 0.5 mg to 10 mg, although mostly lower doses have been studied; effectiveness was not correlated with dosage strength or form. The 2 shift-work simulation studies that used melatonin in dosages ranging from 1.8 mg to 3 mg found a positive effect on sleep quality,[9] although blood levels of melatonin following a 3 mg dose are at least 10-fold higher than physiological peak blood levels in adults (ie, ≈100 pg/mL).[55] A double-blind, placebo-controlled crossover trial of melatonin 5 mg taken 30 minutes before nighttime sleep in shift-work nurses to determine whether sleep improved during recovery from night work found that sleep onset latency was significantly reduced compared with placebo and baseline. Total sleep time was not altered.[56] Additional studies conducted in more homogeneous shift-worker populations involving standardized dosing and timing of melatonin administration are needed.[9]

Endogenous melatonin levels typically reach maximal values several hours after the onset of sleep.[52] In nocturnal sleepers, when melatonin is taken in the early afternoon or evening, the circadian clock can be advanced; if taken in the early morning, the clock is delayed, although morning administration in shift workers is not recommended because this can produce inordinate sedation during wake times.[57]

Exogenous melatonin is classified by the FDA as a dietary supplement, and its unregulated status has raised concerns regarding quality, purity, and variability in stated dose. Although no serious side effects have been reported with melatonin use, the adverse effects of this agent have not been well studied. It has been suggested that exogeneous melatonin should not be used by patients taking immunosuppressants or corticosteroids, pregnant or lactating women, and patients with certain vascular disorders.[58-61] In addition, exogenous melatonin may impact fertility by suppressing ovulation.[58,60]

Stimulants and wakefulness-promoting agents to treat SWD-associated ES

Caffeine

Caffeine is available in a variety of beverages such as colas, tea, coffee, and in the form of an over-the-counter (OTC) agent alone or in combination with pain relievers.[62] Caffeine doses in these preparations vary widely. The stimulant effects of caffeine are believed to relate, in part, to its antagonist activity at adenosine receptors, thereby interfering with the buildup of the homeostatic sleep drive associated with increasing adenosine concentrations (**TABLE 9**) (see *Part I. Shift-Work Disorder: Pathophysiology and Health-Related Consequences*).[63,64] In a study using measurements of caffeine in saliva following consumption of a capsule containing 400 mg of caffeine, the elimination half-life and the time to peak plasma concentration of caffeine in healthy individuals was determined to be 4.0 hours and 2.0 hours, respectively.[65]

Timed ingestion of caffeine may be helpful in alleviating ES associated with SWD.[9,20,26] A laboratory study found that caffeine (4 mg/kg administered 30 minutes prior to start of night shift), napping (2.5 hour nap opportunity prior to night shift), and a combination of caffeine and napping improved performance and alertness in night-shift workers.[20] In one of the first demonstrations of objectively measured benefits of a countermeasure for night work–related performance impairment in shift workers in the workplace, the same investigators conducted a field study that examined the effectiveness of caffeine and napping. The field study data documented that combined intervention had positive effects on performance and subjective sleepiness in the early morning hours, although the study led to speculation that effective use of caffeine to increase alertness in shift workers may require low social consumption of caffeine in such individuals.[20] Although caffeine dependence has been identified as a risk factor for insomnia,[66] recent data in non–shift workers suggest that low to moderate doses of caffeine consumed at home early in the day do not interfere with sleep.[67] Excessive use of caffeine (>250 mg/d) should be avoided and can be associated with

restlessness, nervousness, insomnia, diuresis, muscle twitching, among other symptoms.[68] Caffeine use has been associated with rapid development of tolerance, and abrupt discontinuation of caffeine consumption is associated with a mild withdrawal syndrome, characterized by fatigue, sedation, and, with higher doses of caffeine, headache.[69]

Modafinil and armodafinil

Modafinil and armodafinil are the only FDA-approved wakefulness-promoting agents for patients with ES due to SWD.[70,71] Although the precise MOA of these wakefulness-promoting agents is unknown, it has been proposed that selective potentiation of CNS catecholaminergic signaling is involved (TABLE 9).[17] In addition, although armodafinil is not a direct or indirect dopamine receptor agonist, it has been shown to bind to the dopamine transporter and inhibit dopamine reuptake. Results of 1 study showed administration of modafinil to be associated with increased levels of dopamine in the brain.[72] Dosage and administration recommendations for these agents are included in TABLE 11.

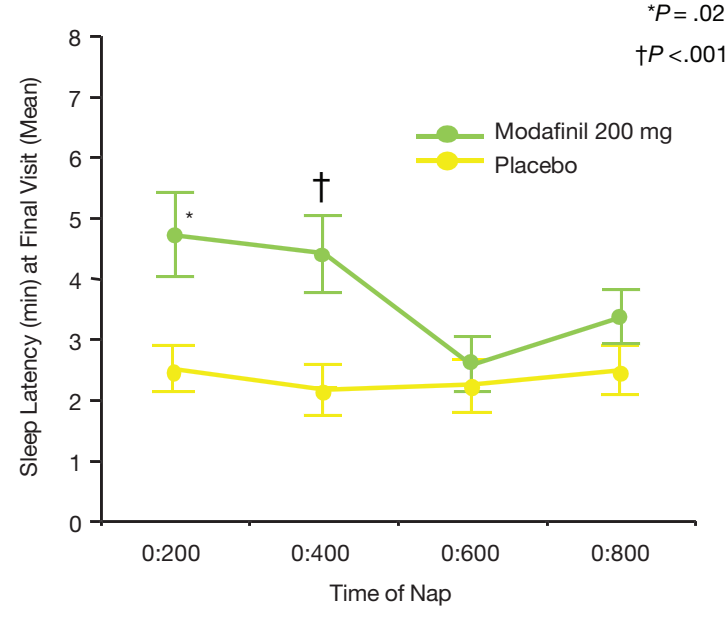
Modafinil is a racemic mixture of S- and R-modafinil, the latter enantiomer referred to as armodafinil. Pharmacokinetic studies of these agents have shown the S-enantiomer to be cleared 3 to 4 times faster than the R-enantiomer; hence, the concentration versus time profile of modafinil is biphasic.[73] However, the elimination half-lives and times to peak plasma concentration of the 2 agents have been reported to be similar—approximately 15 hours and 2 hours, respectively.[70,71]

Although the efficacy of these 2 agents has not been compared in a head-to-head randomized study, results from 2 large randomized clinical trials comparing either modafinil or armodafinil to placebo have shown these agents improve Multiple Sleep Latency Test (MSLT) sleep latency and reduce sleepiness in populations of night-shift workers during the work period without affecting planned sleep.[74,75] The MSLT is an electrophysiologically-based sleep disorder diagnostic tool that measures in minutes the latency to the onset of sleep during 5 nap opportunities, each 2 hours apart. It is a validated measure of sleepiness during the day and is used for the diagnosis of narcolepsy. The test is scored from 0 to 20; sleep latencies of less than 10 minutes generally have been regarded as indicating a high level of daytime sleepiness, although normative data have not been systematically gathered for this test. According to one author, ranges are 0 to 5 minutes (severe; "extreme sleep tendency" or "twilight zone," in which physical and mental reactions often are very impaired), 5 to 10 minutes ("borderline" or troublesome), 10 to 15 minutes ("manageable sleep load"), and 15 to 20 minutes ("excellent alertness").[76]

In a 12-week, randomized, double-blind, placebo-controlled study comparing modafinil to placebo, 209 participants with SWD were randomly assigned to 200 mg of modafinil or placebo 30 to 60 minutes prior to the laboratory night shift. Significant differences were seen in the MSLT from baseline to the final visit at the 2 AM and 4 AM nap opportunities, but not at the 6 AM or 8 AM nap opportunities (FIGURE 5). The Clinical Global Impressions of Change (CGI-C), used to evaluate changes in symptom severity compared to baseline showed significant improvement in the modafinil group compared with the placebo arm.[74]

The effect of armodafinil also was assessed in a 12-week randomized, double-blind, placebo-controlled study in individuals with SWD (87% of whom were permanent night-shift workers and 13% rotating-shift workers) using the MSLT. Study participants were randomized to armodafinil 50 mg on the first night, 100 mg on the second and third nights, and 150 mg on all

Figure 5. Management of Shift-Work Disorder (SWD): Wakefulness-Promoting Agents: Modafinil



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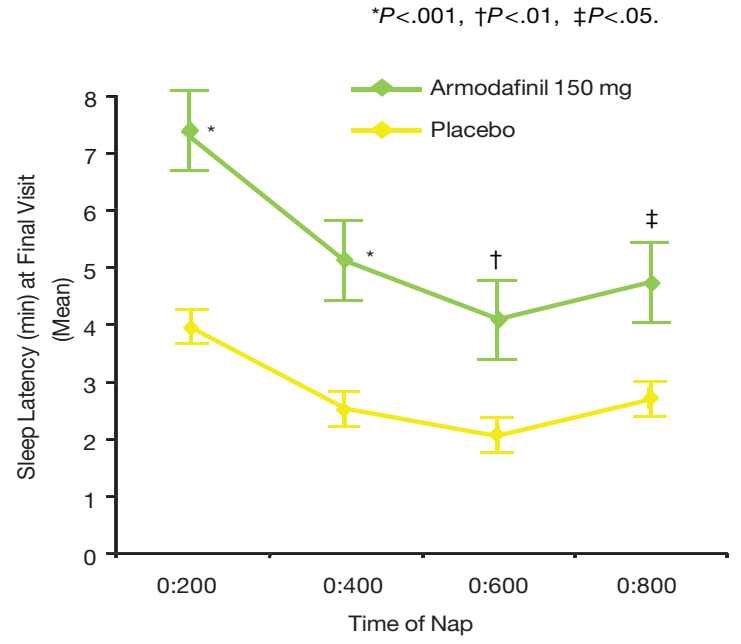
subsequent nights, or matching placebo 30 to 60 minutes before each night shift. The CGI-C scale was used to assess changes from baseline in symptom severity.[75] Armodafinil was found to significantly improve mean nighttime MSLT sleep latency at all 4 time points (2 AM-8 AM) (FIGURE 6). Of the 216 patients included in the efficacy analysis, 79% of those in the armodafinil group had improved CGI-C ratings compared with 59% in the placebo group. Compared with placebo, significant improvement with armodafinil was evident beginning at week 4 and continued through study end at week 12.[75]

Pooled safety data indicate modafinil and armodafinil are well tolerated (TABLE 11). Headache is the most commonly reported adverse event, which is dose-related with armodafinil.

Figure 6. Management of Shift-Work Disorder (SWD): Wakefulness-Promoting Agents: Armodafinil



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SUMMARY

A number of effective interventions are available to help individuals with SWD; nevertheless, at-risk individuals must first be identified, and SWD must be diagnosed in the context of a comprehensive assessment of sleep/wake health before it can be addressed clinically. Most patients with SWD can be managed effectively in primary care settings using individualized behavioral and pharmacologic measures to counteract misalignment in circadian rhythm and sleep deprivation associated with SWD.[8,9,17,18] Pharmacists can play an important role in screening, counseling, managing medication, and following individuals undergoing treatment for SWD.

Table 11. Modafinil and Armodafinil: Dosing, Administration, and Safety Issues

Characteristic	Modafinil	Armodafinil
Dosage/administration	200 mg/d approximately 1 h prior to start of work shift	150 mg/d approximately 1 h prior to start of shift work
Warnings	Serious rash, including Stevens-Johnson syndrome Not approved for use in pediatric patients for any indication Angioedema and anaphylactoid reactions Multiorgan hypersensitivity reactions Persistent sleepiness Psychiatric symptoms	
Treatment-emergent adverse events (≥5%)	Headache (34%) Nausea (11%) Nervousness (7%) Rhinitis (7%) Back pain (6%) Diarrhea (6%) Anxiety (5%) Dizziness (5%) Dyspepsia (5%) Insomnia (5%)	Headache (17%) Nausea (7%) Dizziness (5%) Anxiety (5%)

Source: References 70,71.

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Advances in the Management of Shift-Work Disorder

Part III: General Role of the Pharmacist in Identification, Treatment, and Follow-Up of Patients With Shift-Work Disorder

Introduction

Sleep/wake disorders, such as shift work disorder (SWD), are common and associated with many health, safety, and quality of life detriments, but remain largely undiagnosed (see *Part I. Shift-Work Disorder: Pathophysiology and Health-Related Consequences*).[1] Reasons for this discrepancy are likely to include a low level of awareness among the general public and healthcare providers about sleep/wake disorders, underestimation of the clinical impact of sleep/wake disorders by healthcare professionals, and the fact that sleep health is a relatively new field of medicine.[2,3]

Community pharmacies are often the first point of entry into the healthcare system, and it is not uncommon for individuals to seek help from a pharmacist before consulting with a primary or specialty care provider.[4] The community pharmacist, a highly trusted healthcare provider with a high degree of public exposure,[4] is uniquely positioned to identify individuals with possible sleep/wake disorders and provide key educational and therapeutic interventions to improve sleep/wake health. The community pharmacist also is well situated to reinforce changes in health practices and lifestyle at regular intervals.[2,5] Although there are data suggesting there is a high degree of interest in additional education on sleep/wake health among community pharmacists,[2] there is also evidence of frequent "missed opportunities" to provide help and share information about sleep/wake disorders.[2]

This article addresses the important roles that community pharmacists can play in helping to alleviate the burdens of sleep/wake disorders in general, with a particular emphasis on SWD, a circadian rhythm sleep/wake disorder associated with excessive sleepiness and/or insomnia for at least 1 month in an individual working a nontraditional shift (see *Part II. General Approach to Screening, Diagnosis, and Management of Shift-Work Disorder*).[6]

These roles include: recognizing individuals at risk for a sleep/wake disorder through the use of simple screening tools; evaluating drug regimens as potential contributors to sleep/wake disorders; providing education on nonpharmacologic and pharmacologic options for treating SWD; providing clients with a referral to a primary care provider for a comprehensive assessment of sleep/wake health, if needed; and managing medication therapy in patients receiving pharmacologic treatment for SWD. FIGURE 1 describes the central role the community pharmacist can play in helping individuals with a sleep/wake disorder, such as SWD, receive the counseling and support needed to address this critically important, yet frequently ignored, area of health management.

As pharmacy practice continues to transition from a product-centered to a patient-centered focus, these roles are being expanded to place a greater emphasis on direct patient care, thereby providing the opportunity for more active involvement of the pharmacist in the multidisciplinary management of individuals with sleep/wake disorders.

POP QUIZ

All of the following strategies are reasonable next steps in addressing a client's concerns about having problems sleeping *except*:

A. Refer client to a primary care provider.
B. Ask additional questions about sleep/wake patterns.
C. Provide assurance that such symptoms are unlikely to be a cause for concern.
D. Administer a sleep/wake screening tool.

Recognition of a Possible Sleep/Wake Problem Is the First Step in Getting Help

Several recent studies have investigated the effectiveness of using simple sleep/wake health screening tools in the pharmacy setting to facilitate identification of patients at risk of a sleep/wake disorder. In 1 study conducted in 804 pharmacies in Switzerland, customers were invited to use an online computer program to complete 2 validated questionnaires related to sleep/wake health: the Epworth Sleepiness Scale (ESS), a tool designed to detect excessive sleepiness based on the tendency of an individual to doze in 8 different situations,[7] and

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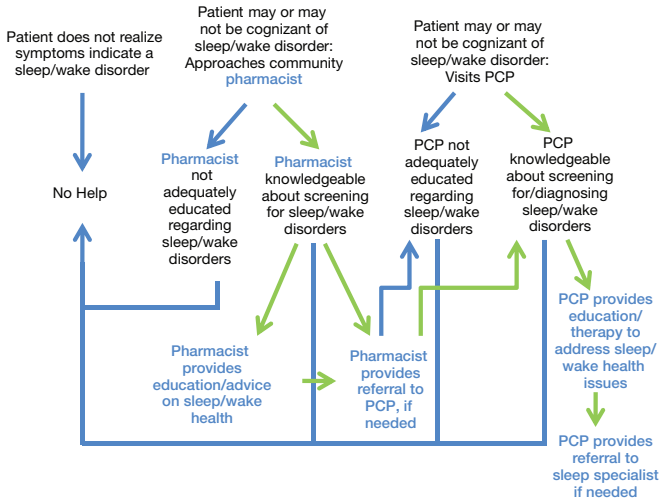
Figure 1. Healthcare Pathways for Patients With a Sleep/Wake Disorder



PCP: primary care provider. Source: Adapted from Reference 2.

the Stanford Sleep Disorders questionnaire, which is designed to classify symptoms of sleep/wake problems into 1 of 4 prevalent sleep/wake disorder categories: sleep apnea syndrome; insomnia in psychiatric disorders; periodic leg movement disorders/restless legs syndrome; and narcolepsy.[8,9] In this study, the medical and/or psychological history of the study participants were not used as selection criteria for study participation. Interestingly, the prevalence of an ESS score of >11, an indicator of excessive sleepiness (defined as an ESS score of ≥10), was 16.5% in females and 23.9% in males (FIGURE 2),[9] and a sleep/wake disorder was suspected in 32% of the individuals undergoing screening.[10] More than half of the pharmacies participating in this study indicated that they would like to continue to use these screening tools, suggesting the use of these tools was feasible and beneficial.[10] Feedback from such screening can facilitate intervention by the pharmacist to provide an individual with direction for addressing the underlying sleep/wake disorder (FIGURE 1).

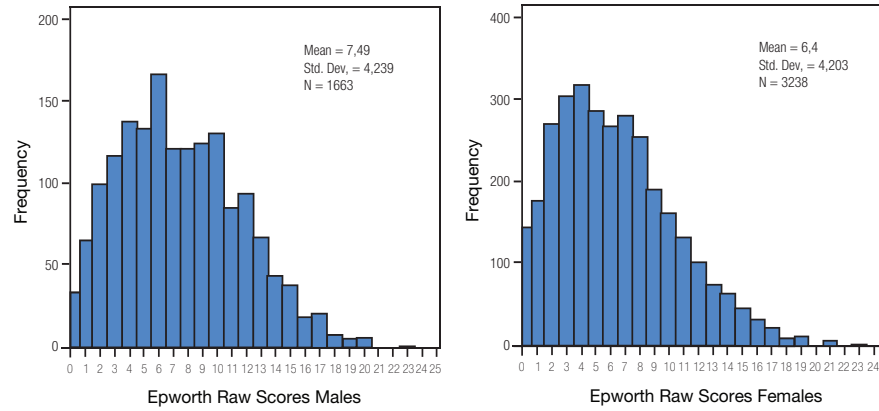
In a study of a sleep/wake disorder screening program conducted in community pharmacies in Australia, 4 validated screening tools were administered: the ESS, the Insomnia Severity Index (ISI), the Multiple Apnea Prediction Index (MAPI), and the International Restless Legs Syndrome Study Group Screening Criteria (IRLS). Participants also were asked questions regarding lifestyle, medical history, and demographic information.[11] In particular, the ISI, which included 7 questions related to problems falling and staying asleep as well as the impact of insomnia on quality of life, provided a useful assessment of the risk of clinical insomnia.[12,13] Of the 167 patients participating in this study, 62% were found to be at risk of at least 1 sleep/wake disorder. Excessive sleepiness measured by the ESS and insomnia measured by the ISI were detected in 7.1% and 33.3% of this group, respectively.[11] In addition, shift work was associated with higher odds (odds ratio = 8.4; 95% confidence interval [CI] =1.6-43.2) of having insomnia as measured by the ISI. The results of these studies evaluating the use of sleep/wake screening tools further support previous findings that the prevalence of sleep/wake disorders is influenced by the clinical setting under investigation,[14] with symptoms of sleep/wake disorders among pharmacy customers particularly prevalent.

POP QUIZ

All of the following classes of pharmacologic agents have been associated with disruptions in *both* sleep and wakefulness *except*:

A. Angiotensin-converting enzyme (ACE) inhibitors
B. Selective serotonin re-uptake inhibitors (SSRIs)
C. Statins
D. Tricyclic antidepressants

Figure 2. Histogram of Epworth Score Distributions Among Male and Female Pharmacy Customers



Source: Reference 9. Reprinted with permission from EMH Swiss Medical Publishers Ltd.

Medications That Impact Sleep and Wakefulness

Multiple factors can contribute to sleep/wake disorders, necessitating a comprehensive assessment prior to diagnosis. Moreover, sleep/wake disorders are not mutually exclusive.[3] With respect to pharmacologic factors, it is well known that many medications can disrupt sleep and wakefulness. In a study by Tran and coworkers, approximately half of the patients undergoing screening for sleep/wake disorders in an Australian pharmacy were taking ≥1 of these types of medications, with the majority of patients unaware of potential side effects.[11] These results, however, may include selection/participation bias. TABLES 1 and 2 list some of the common medications/agents that can impact sleep and wakefulness, many of which are not directly associated with the treatment of sleep/wake disorders.[3,15-17]

In addition to the contribution of some prescription medications to the disruption of sleep and wakefulness, the impact of social drugs, such as alcohol, should be considered. Although many people believe alcohol will help them sleep, its use can cause sleep maintenance insomnia (TABLE 1). Furthermore, the caffeine content of drug and herbal products may be high. An assessment of total daily caffeine consumption from food and over-the-counter (OTC) products should be done to evaluate the acute effects of this agent as well as possible effects from caffeine withdrawal.[3] Hidden sources of caffeine are present in dietary aids and supplements, herbal products, OTC stimulants, and OTC pain relievers.[18]

Additionally, prescription drugs Fioricet (combination of acetaminophen, butalbital, caffeine) and Fiorinal (combination of aspirin, caffeine, butalbital) contain caffeine in amounts sufficient to impact sleep. TABLE 3 lists the caffeine content of commonly ingested foods, OTC medications, and some prescription medications.[18,19]

POP QUIZ

Systemic exposure of which of the following agents is *not* increased by concomitant administration of ketoconazole?

A. Triazolam
B. Doxepin
C. Ramelteon
D. Armodafinil

Drug-drug Interactions

Beyond a general evaluation of drugs and foods that can impact sleep and wakefulness, the community pharmacist is at the front line for identifying potential drug interactions within

Table 1. Selected Common Medications With Potential to Disrupt Sleep

Drug Class	Patient Complaint												
	Restless Legs Symptoms	Sleep Onset Insomnia	Insomnia	Sleep Maintenance Insomnia	Non-restorative Sleep	Dream Enactment Behavior	Abnormal Dreams	Nightmares	Nocturnal Cough	Nocturnal Breathlessness	Worsening Sleep Apnea	Frequent Awakenings	Muscle Pain
SSRIs	✔		✔		✔	✔[15]							
Tricyclic antidepressants	✔		✔										
ACE inhibitors									✔		✔[17,a]		
Norepinephrine and dopamine reuptake inhibitors		✔			✔	✔[16]							
Beta-2 agonists		✔		✔									
Beta blockers								✔					
Corticosteroids		✔		✔			✔						
Non-nucleotide reverse transcriptase inhibitors (antiretroviral)						✔	✔						
Statins		✔										✔	✔
Opiates					✔					✔		✔	
CNS stimulants		✔										✔	
Social drugs (eg, caffeine, tobacco)		✔		✔							✔		
Social drugs – alcohol				✔							✔		

ACE: angiotensin converting enzyme; CNS: central nervous system; SSRIs: selective serotonin re-uptake inhibitors.
[a]The association between cough and use of ACE inhibitors is stronger.
Source: References 3,15-17.

Table 2. Selected Common Medications With Potential to Disrupt Wakefulness

DRUG CLASS	PATIENT COMPLAINT						
	Daytime Sleepiness	Morning Grogginess	Daytime Fatigue	Nonrestorative Sleep	Poor Exercise Tolerance Due To Muscle Pain	Poor Attention and Concentration	Headaches/ Depression/Anxiety
SSRIs	✔						
Tricyclic antidepressants	✔	✔		✔			
Benzodiazepines	✔	✔		✔			
Anticonvulsants	✔						
Neuroleptics	✔						
Beta blockers			✔				
Statins			✔		✔		
Antihistamines	✔		✔			✔	
Social drugs (alcohol)			✔				✔

SSRIs = selective serotonin reuptake inhibitors.
Source: Reference 3.

the prescription medication profiles of clients. Based on recommendations from the American Academy of Sleep Medicine (AASM), prescription hypnotic agents (eg, ramelteon, doxepin, benzodiazepines, eszopiclone, zaleplon, zolpidem) and/or prescription agents that promote wakefulness (eg, modafinil, armodafinil—the *R*-enantiomer of racemic modafinil) may be indicated for treatment of SWD.[20]

Because the benzodiazepine drug class, as well as eszopiclone and zaleplon, are metabolized, at least in part, by the cytochrome P (CYP) 450 isozyme, CYP3A, the systemic exposure of these drugs is increased by CYP3A inhibitors, such as ketoconazole, and decreased by inducers of this enzyme, such as rifampin.[21-25] Zaleplon, modafinil and armodafinil are also metabolized by the CYP3A enzyme, but broken down by other non–CYP-related pathways as well. In the case of modafinil and armodafinil, the non–CYP pathways are more rapid in the metabolism of this drug, suggesting the impact of CYP3A inhibition/induction by concomitant medications is likely to be low.[23,26,27] Modafinil and armodafinil, which are metabolized in the liver, also are inducers of the CYP3A4 enzyme, and can decrease systemic exposure of agents, such as cyclosporine and ethinyl estradiol, which are substrates for this enzyme. The latter interaction is especially important to take into consideration when patients are using oral contraceptives. In such a situation, an additional form of contraception or a switch to a different form of contraception is recommended.[26,27] In addition, because modfanil and armodafinil are inhibitors of the CYP2C19 enzyme, administration of either of these agents is associated with increased systemic exposure of substrates for CYP2C19, such as phenytoin.[26,27] Results from 3 open-label studies evaluating the potential for drug interactions when armodafinil is given concomitantly with drugs metabolized by enzymes CYP1A2, CYP3A4, and CYP2C19 showed that armodafinil generally was well tolerated when administered with caffeine, midazolam, or omeprazole.[28] Although systemic exposure to caffeine, metabolized by the CYP1A2 enzyme, can be increased or decreased by concomitant administration of an inhibitor or inducer of this enzyme, and there are in vitro data suggesting that modafinil and armodafinil can induce the CYP1A2 enzyme, this effect was not observed clinically when armodafinil and

Table 3. Caffeine Content of Foods and Drugs

Caffeinated Product	Service Size	Caffeine Content (mg)
Coffee	8 oz	133 (range: 102-200)
Espresso	1 oz	40 (range: 30-90)
Tea	8 oz	53 (range: 40-120)
Soft drinks (FDA official limit is 71 mg)	12 oz	35-72
Energy drinks	8 oz-20 oz	48-300
Frozen desserts	8 oz	50-84
Chocolates/candies/other	Various	9-33
OTC drugs: examples		
NoDoz (Maximum Strength)	1 tablet	200
Vivarin	1 tablet	200
Excedrin (Extra Strength)	2 tablets	130
Anacin (Maximum Strength)	2 tablets	64
Prescription drugs: examples		
Fioricet (acetaminophen, butalbital, caffeine)	1 tablet	40
Fiorinal (aspirin, butalbital, caffeine)	1 capsule	40

FDA: Food and Drug Administration; OTC: over-the-counter.
Source: References 18,19.

Table 4. Agents Used in the Treatment of SWD: Drug Interactions[d]

	Metabolized By:	Systemic Exposure May Be Increased By:	Systemic Exposure May Be Decreased By:	Inducer/Inhibitor of CYP450 Isozyme(s)	May Increase Systemic Exposure of:	May Decrease Systemic Exposure of:	Other Adverse Interactions
Agents Used to Treat Insomnia							
Benzodiazepines (eg, estazolam, temazepam, triazolam)	CYP3A	Ketoconazole,[a] itraconazole,[a] nefazodone,[a] cimetidine, macrolide antibiotics, isoniazid, oral contraceptives, ranitidine[b]					Ethanol, anticonvulsants, antihistamines, other psychotropic medications
Doxepin (low-dose)	CYP2C19, CYP2D6, and to a lesser extent CYP1A2 and CYP2C9	Cimetidine, sertraline					Ethanol,[a] monoamine oxidase inhibitors,[a] CNS depressants, sedating antihistamines, tolazamide[a]
Eszopiclone	CYP3A4, CYP2E1	Ketoconazole	Rifampin				Ethanol
Melatonin	CYP1A2, CYP2C19 to a lesser extent[29]						
Ramelteon	CYP1A2, CYP2C and CYP3A4 to a lesser extent	Fluvoxamine,[a] ketoconazole, fluconazole, donepezil, doxepin			Zolpidem		Ethanol[a]
Zaleplon	Aldehyde oxidase, CYP3A4 to a lesser extent	Erythromycin, ketoconazole, cimetidine	Rifampin, phenytoin, carbomazapine, phenobarbital				Ethanol, imipramine, thioridazine, promethazine
Zolpidem	CYP3A	Ketoconazole, itraconazole, sertraline	Rifampin				Ethanol,[a] imipramine, chlorpromazine
Agents Used To Promote Wakefulness							
Armodafinil	Amide hydrolysis, S-oxidation, aromatic ring hydroxylation, glucuronide conjugation, CYP3A4/5 to a lesser extent	Ketoconazole, erythromycin	Rifampin, carbamazepine, phenobarbital	CYP3A4 (possible inducer), CYP1A2 (inducer), CYP2C19 (inhibitor)	Phenytoin, diazepam, propanolol, omperazole, clomipramine	Cyclosporine, ethinyl estradiol,[c] midazolam, triazolam	Monoamine oxidase inhibitors, ethanol (potential)
Modafinil	Amide hydrolysis, S-oxidation, aromatic ring hydroxylation, glucuronide conjugation, CYP3A4	Ketoconazole, itraconazole	Rifampin, carbamazepine, phenobarbital	CYP219 (inhibitor), CYP2C9 (inhibitor), CYP3A4 (inducer), CYP2B6 (inducer), CYP1A2 (inducer)	Phenytoin, diazepam, propanolol, clomipramine	Cyclosporine, ethinyl estradiol[c], triazolam	Monoamine oxidase inhibitors, ethanol (potential)
Caffeine	CYP1A2 CYP3A4	Cimetidine, ciprofloxacin, clarithromycin, enoxacin, erythromycin, fluvoxamine	Barbiturates, nicotine				

[a]Avoid; [b]Other agents that may increase systemic exposure include: fluvoxamine, diltiazem, verapamil, sertaline, paroxetine, ergotamine, cyclosporine, amiodarone, nicardipine, nifedipine; [c]Includes oral contraceptives; [d]List of drugs interaction is representative and not all-inclusive.
CNS = central nervous system.
Source: References 21-33.

caffeine were given concomitantly.[27] The pharmacokinetics of caffeine was not affected by prolonged administration of armodafinil.[28] Melatonin is metabolized, in part, by CYP1A2 and CYP2C19 enzymes, although interactions between melatonin and specific drugs have not been well investigated.[29]

Other adverse interactions with hypnotics and wake-promoting agents can occur through other pathways. Most notably, ethanol should be avoided when many of the hypnotic agents are administered. TABLE 4 provides a summary of the metabolic properties of these agents as well as a list of representative drugs/substances that may interact with them when used concomitantly.[21-33]

Given their knowledge of pharmacotherapy and their access to the prescription histories of their clients, community pharmacists are in a key position to provide individualized counseling on the potential impact of drugs and foods on sleep/wake health as well as the effect of sleep/wake therapy within the context of an individual's overall medication treatment regimen.[11] Such counseling may extend to alerting primary care providers on the potential for adverse drug interactions. Furthermore, an ongoing review of all medications is a central component of recent medication therapy management initiatives.[34]

Pharmacist's Role in Patient Education

The characteristics of high accessibility and approachability associated with the community pharmacist are likely to foster an environment conducive to education on sleep/wake health (FIGURE 1).[35] In the study evaluating the effectiveness of screening for sleep/wake disorders in 804 Swiss pharmacies, targeted counseling was provided to the study participants. Such counseling included education on strategies for improving sleep hygiene, demonstrating the feasibility of providing this type of information in the pharmacy setting.[10] Good sleep hygiene practices, recommended by the AASM and described in detail in *Part II. General Approach to Screening, Diagnosis, and Management of Shift-Work Disorder* are an important component of helping patients with SWD obtain sufficient/restful sleep.[20] Pharmacists can help individuals understand that sleep time should be protected time and educate them on how to create an appropriate sleep environment in terms of noise, temperature, and mental preparation for sleep.[36]

Other nonpharmacologic strategies that may benefit individuals with excessive sleepiness or insomnia related to shift work include timed light therapy and planned napping, and recommendations for timed administration of caffeine or melatonin (see *Part II. General Approach to Screening, Diagnosis, and Management of Shift-Work Disorder*).[20]

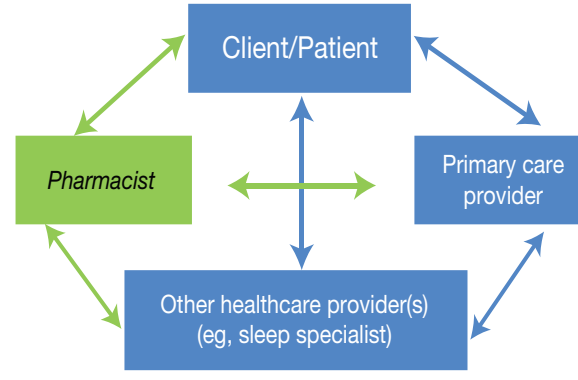
OTC sleep aids are commonly used to self-treat insomnia,[10] although there are limited data on the efficacy and safety of many of these products, including most herbal supplements (eg, valerian), diphenhydramine, and melatonin (see *Part II. General Approach to Screening, Diagnosis, and Management of Shift-Work Disorder*).[37-40] In 1 case study of pharmacy clients not receiving medical care from a physician, 22% and 49% were taking an OTC sleep aid on a regular or occasional basis, respectively.[10] This result is consistent with other findings that consultation with a physician or primary care provider about sleep/wake disorders often is neglected.

When It's Time to Refer

Delivery of targeted counseling by the community pharmacist may include recommendations to consult a primary care provider (FIGURE 1). In the study evaluating the community pharmacist as a provider of sleep/wake health evaluation and intervention, 26% of study participants were counseled to see a physician to further address their sleep/wake health problems.[10]

In addition to providing referrals, direct interaction between the community pharmacist and other healthcare providers may be necessary to ensure safe and effective administration of medication therapy. The community pharmacist may need to alert other healthcare providers to the potential for adverse drug interactions. Beyond the need to communicate safety concerns, there is evidence that more direct participation of the community pharmacist in the multidisciplinary management of patients with chronic health problems may be feasible and beneficial.[41,42] Results of a randomized controlled study of patients with hypertension showed collaborative intervention between pharmacists and physicians to be significantly more effective in controlling mean blood pressure and rates of overall blood pressure control compared with a control group of patients treated under usual care.[43] Such a multidisciplinary approach (FIGURE 3) to the management of patients with sleep/wake disorders has the potential to improve patient outcomes.

Figure 3. Managing Patients With Sleep/Wake Disorders in a Multidisciplinary Setting



Medication Therapy Management

As the pharmacy profession continues to move from a product-focused to a patient-focused practice, it is anticipated that opportunities for the community pharmacist to favorably impact sleep/wake health will increase. The federal Medicare Prescription Drug Improvement and Modernization Act of 2003 recognized that medication therapy management (MTM) allows pharmacists to offer direct patient care services and to receive reimbursement for those services.[34,44] MTM encompasses many of the more traditional aspects of medication monitoring performed by pharmacists, but goes beyond these services. TABLE 5 describes the components of MTM as described by the Minnesota state legistature.[45] These components are consistent with MTM consensus statements accepted nationally[46,47] and are focused on fostering improved patient outcomes through private face-to-face consultations with patients to identify and resolve problems associated with drug therapy. Direct contact with the patient's primary care provider is an integral part of MTM, making the pharmacist, as the coordinator of MTM interventions provided to the patient, an integral member of the interprofessional team involved in the patient's care. Several studies have shown the effectiveness of pharmacist-led interventions focused on improving medication use in patients with diabetes and heart failure, and in high-risk Medicare beneficiaries.[48-52] Some health insurers and large employers already pay for MTM programs and in 2011 approximately 25% of individuals covered by Medicare Part D prescription drug plans will be eligible.[53]

Table 5. Medication Therapy Management

- Performing or obtaining necessary assessments of the patient's health status
- Formulating a medication treatment plan
- Monitoring and evaluating the patient's response to therapy, including safety and effectiveness
- Performing comprehensive medication review to identify, resolve, and prevent medication-related problems, including adverse drug events
- Documenting the care delivered and communicating essential information to the patient's primary care provider
- Providing verbal education and training designed to enhance patient understanding and appropriate use of the patient's medications
- Providing information, support services, and resources designed to enhance patient adherence with the patient's therapeutic regimens
- Coordinating and integrating medication therapy management services within the broader healthcare management services being provided to the patient

Source: Reference 45.

A recent report of a clinic for patients with hypertension, dyslipidemia, and/or diabetes conducted in a community pharmacy setting described an initiative that combined lifestyle interventions with MTM services.[5] There were 7 individualized programs, including sleep success, that were components of the lifestyle medicine program. These personalized programs, a form of pharmacist-led patient self-management, involved fostering active patient participation in monitoring and documenting adherence to lifestyle modifications, frequent follow-up encounters between pharmacist and patient, and communication between the pharmacist and the patient's primary care provider. The future success of pharmacy-based MTM and lifestyle initiatives to optimize sleep/wake health are likely to be facilitated by pharmacist access to a centralized electronic patient record system.[54-56] In addition, similar pharmacy-based programs focused on sleep/wake health, such as the management of SWD, may be well suited to occupational/employee health settings.

Summary

Healthy People, an initiative from the US Department of Health and Human Services, describes the public health burden of sleep disorders as "substantial," and in its 2020 version for the first time includes several goals related to sleep health.[57,58] These goals are focused on increasing the proportion of adolescents and adults obtaining adequate sleep, decreasing the number of motor vehicle incidents attributed to drowsy driving, and increasing the proportion of adults with apnea symptoms seeking medical treatment.[58] The Healthy People 2020 initiative also emphasizes the importance of "increasing public knowledge of how adequate sleep and treatment of sleep disorders improves health, productivity, wellness, quality of life, and safety on the roads and in the workplace."[57,58]

According to the Institute of Medicine, sleep/wake disorder "awareness among the general public and health professionals is low, given the magnitude of the burden."[1] In that report, many of the patient contacts with healthcare professionals were described as "missed opportunities" to provide help and share information about sleep/wake disorders, and it was stated that "the current situation necessitates a larger more interdisciplinary workforce."

The scope of pharmacy practice continues to evolve from one that is product-oriented to one that is patient-centered.[2,59,60] Interventions including screening for sleep/wake disorders (eg, SWD), MTM, patient education, including lifestyle interventions with regular follow-up to promote sleep/wake health, and active participation within the patient healthcare team have the potential to close many of the gaps in patient sleep/wake healthcare.

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