Shift workers with shift work sleep disorder (SWSD) are at high risk for various comorbidities. Because of these consequences to the patient, as well as public safety concerns related to workers with SWSD, effective treatment for patients with this condition is imperative. The 2 cardinal symptoms of SWSD—excessive sleepiness and insomnia—are thought to be caused by misalignment between the scheduled sleep-wake periods and the circadian propensity for sleep alertness.¹ Patients typically attempt to sleep when their circadian signals for alertness are high, and they work when their circadian alertness levels are low.
The management of SWSD requires an individualized and comprehensive approach, incorporating various strategies targeted at either the underlying misalignment or at the 2 defining symptoms of the disorder. Other objectives of treatment are to improve the patient’s cognitive function and performance and safety on the job. In the present article, we review the physiologic mechanisms of the circadian rhythm and various alternatives for treating patients with SWSD including the level of recommendation based on the American Academy of Sleep Medicine (AASM) guidelines for the treatment of circadian rhythm disorders (Table 1).²

**Normal circadian physiology**

To better understand how available interventions correct circadian misalignment, it is necessary to understand the normal mechanisms of circadian rhythm physiology.

A circadian pacemaker, also referred to as the “biological clock,” controls the daily patterns in neuroendocrine function and behavior, such as the sleep-wake cycle and fluctuations in many physiologic processes. This central pacemaker—located in the suprachiasmatic nucleus (SCN), within the hypothalamus of human beings and other mammals—functions on a cycle of approximately 24.2 hours.³ Because the cycle of the SCN pacemaker is slightly longer than the 24-hour biological clock, it eventually will not fit into the 24-hour day if the two systems are not entrained or synchronized. Natural zeitgebers (German for “time givers” or “synchronizers”) help the circadian rhythm stay within a 24-hour window and not shift out of phase. These zeitgebers are light, melatonin, and social or physical activities.⁴ Of these agents, light and melatonin are recognized as having the greatest influence on determining the entrainment of endogenous circadian rhythms.

Light stimulates the neurons in the SCN via the retinohypothalamic tract.⁴ The timing of light exposure ultimately determines effects on the entrainment of circadian rhythms. Exposure to light in the evening causes a delay in the circadian rhythm, with the consequences of postponement of the rest period and a late awakening time. Exposure to light in the morning causes an advance of the circadian rhythm, resulting in early initiation of sleep and early awakening.

Melatonin is a hormone secreted by the pineal gland under regulation of the SCN. Melatonin levels start to increase 1 to 3 hours before an individual’s usual sleep time.⁵ This melatonin secretion essentially blocks the circadian signals for wakefulness from the SCN. Opposite to the effects of light exposure, exogenous melatonin administration in the evening shifts the circadian rhythm to an earlier time (ie, advances the circadian rhythm), and melatonin administration in the morning shifts the circadi-an rhythm to a later time (ie, delays the circadian rhythm).

The circadian system interacts with the homeostatic drive for sleep, which naturally generates pressure for sleep after several successive hours of wakefulness. As the homeostatic drive for sleep accumulates, the SCN activity increases to maintain alertness. In the evening, with decreased light exposure and secretion of melatonin, the SCN activity decreases to facilitate sleep.

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**Table 1**

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Standard</td>
<td>Generally accepted patient-care strategy that reflects a high degree of clinical certainty</td>
</tr>
<tr>
<td>Guideline</td>
<td>Patient-care strategy that reflects a moderate degree of clinical certainty</td>
</tr>
<tr>
<td>Option</td>
<td>Patient-care strategy that reflects uncertain clinical use</td>
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Table 1. Adapted from Morgenthaler TI, Lee-Chiong T, Alessi C, et al.²
Nonpharmacologic treatment

Change in work pattern

The symptoms of SWSD are directly linked to the out-of-phase shift-work schedule, and they usually resolve after the patient returns to daytime work. However, returning to daytime work is impractical for many individuals. In most cases, occupational and societal constraints prevent the implementation of this option.

For workers on night shifts, more than 4 consecutive 12-hour night shifts should be avoided because of a documented increased risk of accidents and injuries.6 There is also evidence of decreased cognitive performance and increased sleepiness in this group of workers.7,8 Individuals on rotating shift schedules should be encouraged to rotate in a clockwise, rather than counterclockwise, manner (ie, morning to evening to night, rather than night to evening to morning), because this pattern follows the natural pattern of delaying the sleep period.9

Sleep hygiene

Measures for improving sleep hygiene are recommended not only for patients with SWSD, but also for all shift workers. Patients should be advised on how to create a proper environment for sleep in terms of levels of darkness, noise, and temperature, together with how to mentally and physically prepare for sleep (eg, avoidance of large meals, caffeinated drinks, smoking, and alcohol prior to sleep). There is also evidence to support a continuous 7-hour to 8-hour sleep episode to promote better sleep, as opposed to fragmented sleep periods,10,11 because fragmentation of sleep can affect sleep architecture and accumulated sleep debt.12

Exercise has been shown to be beneficial in promoting sleep and improving perceived sleep quality13 and in facilitating phase shifting of the circadian rhythm.14 Thus, an exercise program might help in the adaptation of shift workers to their sleep-wake schedule. Further research is needed to identify the timing and type of exercise that would have the best impact on SWSD.

Scheduled naps

Napping is considered an effective strategy to counteract sleepiness in shift workers. Naps have been shown to decrease accidents15 and to improve performance in shift workers, as measured by the Maintenance of Wakefulness Test and the Psychomotor Vigilance Task, particularly when used with caffeine administration.16 Beneficial effects, such as improvements in sleepiness and performance in vigilance and neurobehavioral testing, can be seen when planned naps take place before or during night-shift work.17,18

It is important to note that no studies have evaluated outcomes of napping in patients with SWSD. Besides this limitation, implementation of napping might be difficult in the workplace, because appropriate facilities may not be available and napping might be considered unprofessional or ethically unacceptable in some work settings. Nevertheless, the AASM considers scheduled or planned naps a standard treatment of patients with SWSD.2

Light exposure

The interaction between light exposure and the endogenous circadian rhythm forms the basis for light therapy as a therapeutic option for patients with SWSD. Several studies have evaluated the effects of scheduled light exposure during the work period and its impact on the patient’s circadian physiologic mechanisms, degree of sleepiness, and mood. The outcomes of some studies indicate that light exposure causes physiologic adjustment of phase shift, resulting in improved alertness and mood.19,20 Other studies suggest that workers’ performance is improved only when light exposure is combined with caffeine intake during the night shift.21

Despite potential benefits produced by realigning circadian rhythms to night work, many workers might refuse to take such steps, preferring to preserve their natural phase and to keep a conventional diurnal waking schedule during their off-days. A strategy of “partial realignment,” resulting in a new circadian sleep-wake cycle that is considered appropriate for both workdays and off-days, has achieved positive results in healthy volunteers under simulated conditions.22 This strategy seems promising, but it requires further validation in real-world conditions and in patients with SWSD.

A variety of light regimens (different light intensities and timing) have been evaluated in studies; these studies have been conducted mostly with simulated night shifts in the laboratory, which result in limitations when interpreting the results. To our knowledge, no light-
exposure studies have been conducted in the field, and none of the studies have specifically consisted of patients with SWSD.

The AASM recommends the use of light exposure during the nighttime work period, as well as restriction of morning light (with the use of sunglasses or goggles) as a guideline in night-shift workers.2

**Pharmacologic treatment**

**Stimulants**

Caffeine is a commonly used agent to promote wakefulness among shift workers.23,24,25 A recent Cochrane Review study showed that caffeine could reduce the number of errors and improve cognitive performance in shift workers, compared to no intervention. However, no statistically significant difference in effect was found when caffeine was compared with other interventions, such as other wakefulness-promoting agents (modafinil), planned naps, and light exposure.26 The most appropriate dose and timing of caffeine intake for shift workers still needs to be determined by research studies. It should be kept in mind that the potential for hyperstimulation, toxic effects, and development of tolerance might limit the long-term efficacy of caffeine in the management of SWSD. The AASM recommends its use only as an option.2

Similarly, although there is evidence of the effectiveness of methamphetamine at improving performance and mood in individuals undergoing simulated night-shift work,27 these agents cannot be recommended for management of SWSD given their potential for abuse and adverse cardiovascular effects.

**Wakefulness-promoting agents**

Modafinil and armodafinil are wakefulness-promoting agents used in the treatment of patients with conditions associated with excessive daytime sleepiness, including narcolepsy and idiopathic hypersomnia. These agents are the only medications approved by the U.S. Food and Drug Administration (FDA) for promotion of wakefulness in patients with SWSD.28 Evidence of the efficacy of modafinil was described in a report of a randomized controlled trial using this drug at a dose of 200 mg, with improvement in wakefulness and ability to sustain attention in patients with SWSD.29 Importantantly, these effects were not sustained throughout the night despite the 15-hour half-life of modafinil. A subsequent study by the same research group, using armodafinil at a dose of 150 mg for 12 weeks, showed improved levels of wakefulness, long-term memory, and attention, as well as an improved overall clinical condition.30 Both modafinil and armodafinil are recommended by the AASM as a guideline to enhance alertness during night shift work.2

To date, there have been no studies directly comparing the efficacy and safety of modafinil and armodafinil. Given the pharmacokinetic profile of armodafinil, with once-daily dosing and longer duration of action than modafinil, this drug might be a more appropriate and convenient choice for patients with SWSD. Headache and nausea were the most common adverse effects observed in patients who participated in the clinical trials of modafinil and armodafinil. Caution should be taken when prescribing these drugs to patients who have histories of angina, recent myocardial infarction, or seizures.

**Melatonin**

Several studies have been conducted—both in simulated and in real-world shift-work conditions—evaluate melatonin administration before daytime sleep. These studies have shown mixed results. Although some melatonin studies have demonstrated decreased sleep latency and increased sleep duration,31-33 others have failed to demonstrate any subjective or objective benefits.34 Regardless, the AASM recommends the use of melatonin as a guideline in the treatment of patients with SWSD.2 Greater benefits might be obtained from melatonin administration when used as part of a phase-advancing program in individuals with SWSD. Because different melatonin formulations vary in potency and quality (as a result of lack of FDA regulation), a melatonin receptor agonist, such as
ramelteon, might be a more promising agent for treating patients with SWSD, since it is known to be more effective than regular melatonin in advancing the circadian shift.\textsuperscript{35}

**Management of insomnia**

The use of sleep-promoting agents prior to required sleep periods has been evaluated in a number of studies. Benzodiazepines, such as triazolam and temazepam,\textsuperscript{36-38} and benzodiazepine receptor agonists, such as zolpidem and zopiclone,\textsuperscript{39-41} can increase sleep duration during daytime and improve wakefulness during night-shift work. All these agents have been evaluated in simulated conditions, but zopiclone, at a dose of 7.5 mg taken before the required sleep period, has also been evaluated in volunteers working 12-hour shifts.\textsuperscript{41} In that study, zopiclone was given prior to daytime sleep (after night shift-work) and prior to nighttime sleep (on days off). It was found to improve sleep at night but not during required daytime sleep periods. It has been suggested that hypnotic agents, such as zopiclone, may be less efficacious when administered out of phase with the usual sleep period.

Benzodiazepine receptor agonists are reported to cause the adverse effects of headache, dizziness, and drowsiness. Amnesia and nonrapid-eye-movement parasomnias, such as sleepwalking and sleep-related eating syndrome, have also been reported with the use of benzodiazepine receptor agonists.

**Comorbid conditions**

Patients presenting with SWSD should receive a comprehensive evaluation to identify and address any comorbid conditions, including other sleep disorders (eg, obstructive sleep apnea), mood disorders, and medical problems that might contribute to symptoms.

**Final notes**

The treatment of patients with SWSD requires an individualized and comprehensive approach, including the diagnosis and management of comorbid sleep disorders, patient education, and behavioral interventions to optimize sleep and wakefulness at the appropriate times.

Unfortunately, few studies have been conducted among actual patients with SWSD in real-world conditions. Thus, it is unknown whether results achieved with patients in simulated conditions or with healthy shift workers in real-world conditions can be generalized to actual clinical situations. In addition, the majority of available evidence and strategies have focused on the night-shift worker. Further studies involving patients with SWSD and workers with different work schedules, such as rotating shifts or early-morning shifts, are necessary.

Effective interventions for managing SWSD include sleep and wake hygiene, planned napping, adjustments to dietary habits, an exercise program, appropriately timed light exposure, and work-hour limitations. These nonpharmacologic treatments usually need to be combined with medications. Melatonin could be used to facilitate circadian adaptation, and modafinil or armodafinil could improve persistent excessive sleepiness.

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(continued)

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