Support for the publication of this supplement was provided by Cephalon, Inc. It has been edited and peer reviewed by *The Journal of Family Practice*.

SUPPLEMENT TO
THE JOURNAL OF FAMILY PRACTICE

Available at jfponline.com VOL 59, NO 1 / JANUARY 2010

Shift-work disorder

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Dr Thorpy reports that he serves as a consultant to and on the speakers bureaus of Cephalon, Inc., and Jazz Pharmaceuticals, Inc.

Support

Support for the publication of this supplement was provided by Cephalon, Inc. Editorial assistance was provided by Anthemis Consulting Ltd and supported by Cephalon, Inc.

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This material was submitted by Anthemis Consulting Ltd on behalf of the authors. It has been edited and peer reviewed by *The Journal of Family Practice*.

The social and economic burden of shift-work disorder

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Practice recommendations

- Shift-work disorder (SWD) and its defining symptoms can negatively affect health, quality of life, and work performance. The gravity of these consequences necessitates vigilance for the symptoms of SWD by primary care physicians (**SOR: B**).
- The threshold for treatment intervention for emergency service workers, such as firefighters, who make crucial decisions under shift-work conditions and who are experiencing SWD should be lower than for shift workers in general (**SOR: B**).
- The economic costs of untreated SWD are likely to be high. Early diagnosis and treatment of SWD may reduce these costs in addition to reducing the human burden of this circadian rhythm sleep disorder (**SOR: C**).

Dr Culpepper reports that he serves as a consultant to AstraZeneca, Eli Lilly and Company, Pfizer Inc, Wyeth, sanofi-aventis, and Takeda Pharmaceuticals North America, Inc, and on the speakers bureau of Wyeth.

Shift work is a fundamental component of working patterns across the US workforce and is therefore an integral part of the lifestyle of a large proportion of the population. However, shift workers are at risk of developing the circadian rhythm sleep disorder shift-work disorder (SWD), a clinically recognized condition that develops in some individuals who work at night, start work early in the morning (4 to 7 AM), or work according to a rotating-shift schedule. SWD is more severe than—and distinct from—the sleep disturbances commonly associated with shift work. Provided other sleep/wake disorders can be discounted, SWD is diagnosed by the presence of excessive sleepiness (ES) and/or insomnia for ≥1 month during which the individual is performing shift work.[1]

Shift work poses a serious public health risk, as it can impair an individual's ability to perform effectively and may lead to occupational or traffic accidents. Furthermore, shift work has numerous negative health effects and infringes on an individual's ability to sleep, eat normally, exercise, and develop relationships. However, SWD is underrecognized in the clinical setting,[2] and data regarding its epidemiology and etiology are scarce in the scientific literature. Published information regarding shift work in general has therefore been used as the foundation for informing the clinical community on the potential burden of SWD. It is incumbent on primary care physicians to be vigilant for SWD in shift workers, make an accurate diagnosis, and initiate appropriate treatment in order to relieve—and prevent—the acute consequences and long-term health sequelae of this disorder, as well as to ensure public safety.

This supplement describes the burden of SWD, discusses the current understanding of the processes that cause this and other circadian rhythm sleep disorders, and describes the recognition and available management strategies for SWD. This article reviews the prevalence of SWD and examines the scale of its social and economic burden, including associated comorbidities. In the second article, Dr Chris Drake explains the causes of SWD and other circadian rhythm sleep disorders by describing the circadian and homeostatic systems and detailing how lifestyle factors, individual susceptibility, morbidity, and genetic components can result in circadian rhythm pathology.

The diagnosis of SWD is particularly challenging because its defining symptoms of ES and/or insomnia are demonstrated by numerous morbidities, including other sleep disorders. Furthermore, normal and abnormal responses to the challenge of shift work are not easily differentiated, and current diagnostic criteria require additional validation.[3] Identification of SWD relies on detailed discussion of a patient's medical history, knowledge of relevant risk factors, and differential diagnosis to rule out other potentially causative medical conditions. Dr Jonathan Schwartz provides a comprehensive guide to recognizing and diagnosing patients with SWD in the third article of this supplement. In the final article, Dr Michael Thorpy discusses the behavioral and pharmacologic options available for patients with SWD in order to address ES and insomnia as well as comorbidities. He also supplies a useful algorithm to assist with the treatment of SWD in the primary care setting.

Epidemiology of SWD, insomnia, and ES in shift workers

For approximately 22 million US adults, shift work is an integral part of their professional life.[4] Of these individuals, about 3.8 million regularly work night shifts, and an additional 3.3 million perform night-shift work on a rotating basis.[5]

Drake and colleagues[6] used a telephone questionnaire to conduct a study of the prevalence of SWD in the general population of Detroit, MI; 2036 day-shift, 360 rotating-shift, and 174 night-shift workers participated. This study used minimum *International Classification of Sleep Disorders 2* (ICSD–2) criteria to define SWD[1]; namely, subjects with ES and/or insomnia who had been working either a night-shift or a rotating-shift schedule for the past 2 weeks were diagnosed with SWD. In this study, ES was defined by an Epworth Sleepiness Scale (ESS)[7] score of the total sample mean + 1 standard deviation (effectively, an ESS score of ≥13, compared with the more commonly applied ES diagnostic score of ≥10). Insomnia was diagnosed using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria,[8] ie, the subject had experienced periodic recurrences of difficulty in falling asleep, staying asleep, or nonrestorative sleep for at least 1 month, with a self-reported severity of at least 6 points out of a possible score of 10 on a visual analog scale.

Drake and colleagues[6] reported that 32.1% and 26.1% of night-shift and rotating-shift workers, respectively, met their prespecified ES and/or insomnia criteria, compared with 18.0% of day workers. The differential "true" prevalence of ES and insomnia—and therefore SWD—in night-shift and rotating-shift workers was reported to be approximately 14.1% and 8.1%, respectively. When it is considered that approximately 6% of all workers in the United States perform night- or rotating-shift work, the overall prevalence of SWD in the general population was estimated to be approximately 1%.[6] This result is lower than the 2% to 5% estimated in the ICSD–2 coding manual,[1] and some sleep specialists have argued that the figure put forward by Drake and colleagues[6] is conservative.[3] However, Drake and colleagues[6] also applied the more usual ES diagnostic measure of an ESS score of ≥10 and, using this criterion, found a much higher prevalence of ES in their study population: 44.8% of night-shift workers and 35.8% of rotating-shift workers were found to have ES and therefore would also be considered to have SWD, provided their symptoms persisted for ≥1 month.

A recent study of 4471 US police officers reported that 2.0% of this population had SWD, which was defined by the occurrence of both insomnia and ES in association with a recurrent schedule of work that overlapped the normal rest period.[9]

Epidemiologic data for SWD are sparse and additional studies are warranted. Few overt data exist for the prevalence of SWD. Although the occurrence of insomnia and/or ES has been studied in various shift-working populations, frequently only one symptom is analyzed. Shift-working individuals who have either symptom for ≥1 month should be regarded as meeting the diagnostic criteria for SWD even if this is not stated explicitly by the respective study investigators.

For example, the Helsinki Heart Study examined the occurrence of insomnia and/or ES over a 3-month period in a population of approximately 3000 middle-aged men participating in a coronary heart disease prevention trial.[10] Persistent insomnia was reported by approximately 50% of rotating- and night-shift workers, whereas persistent ES was reported by approximately 25% of shift workers overall; those with ES and/or insomnia therefore met the diagnostic criteria for SWD.[10]

By contrast, a study using the Multiple Sleep Latency Test in a population of shift-working, long-haul bus drivers reported that the criteria for ES were met by 38% to 42% of subjects.[11] However, as the time frame over which patients experienced ES was not measured in this study, these patients should be viewed as being at risk of developing SWD, as opposed to having SWD per se.[11]

Similarly, in a study of police officers, insomnia or hypersomnia were reported by a significantly higher proportion of shift-working personnel compared with their day-working colleagues (insomnia, 25.9% vs 15.8% [$P < .001$]; hypersomnia, 4.9% vs 2.2% [$P < .02$]).[12] The absence of data regarding persistence of these symptoms precludes diagnosis of SWD in these patients.

Other studies have reported the prevalence of unplanned napping at work, which may be indicative of ES or sleep deprivation. For example, in a study of almost 700 registered female nurses, approximately 35% and 32% of participants working rotating or night shifts, respectively, reported episodes of unplanned sleep at work and may therefore have been at risk for developing SWD.[13]

Comorbidities associated with shift work and SWD

There are few reported studies regarding comorbidities in patients with SWD, although a large epidemiologic study has reported that patients with SWD are significantly more likely to experience comorbidities than are day workers or shift workers without SWD ($P < .05$).[6] Shift work has adverse effects on health even in the absence of SWD, although to date there is no evidence that shift work directly affects longevity.[14,15]

Metabolic disturbance and gastrointestinal issues

The relationship between sleep disturbance and obesity is well documented but poorly understood due to its complexity.[16] Sleep deprivation in particular has been implicated in the pathogenesis of weight gain and diabetes, and it may be that recognition and treatment of sleep disorders in general may assist with curtailing the current obesity epidemic.[17]

In a study of 500 male municipal workers in Italy, 3 of the 5 diagnostic symptoms of metabolic syndrome—obesity, elevated cholesterol, and raised triglyceride levels—were found significantly more frequently in night-shift workers than in day workers ($P < .001$, $P < .01$, and $P < .001$, respectively), indicating that shift work is associated with significant metabolic disturbance.[18] This report extended the findings of an earlier study that demonstrated that shift workers at a chemical plant in Italy had a significantly higher mean body mass index (BMI) than their day-working colleagues (27.7 kg/m^2 vs 26.5 kg/m^2, respectively; $P < .01$).[19] In addition, the prevalence of diabetes increased with duration of exposure to shift work, and markers of insulin resistance were more common in shift workers than in day workers.[20,21]

Compared with day workers, shift workers also have higher rates of peptic ulcers and gastrointestinal problems, such as constipation and diarrhea.[22,23] These findings were confirmed by a large trial of US workers, which reported that night-shift workers (odds ratio [OR], 3.13; 95% confidence interval [CI], 1.62-6.05), rotating-shift workers (OR, 2.32; 95% CI, 1.32-4.06), and subjects diagnosed with symptoms of SWD (OR, 4.55; 95% CI, 2.47-8.37) experienced increased rates of peptic ulcers compared with day workers ($P < .001$ for all comparisons).[6] Furthermore, both the effects of shift work and the symptoms of SWD contributed cumulatively to the increased likelihood of developing an ulcer among patients with SWD.[6]

Metabolic disturbance and gastrointestinal symptoms in shift workers and patients with SWD may arise in response to eating at unusual times of day, as food intake acts as a cue for the synchronization of the circadian clock. Moreover, gastric secretions in the middle of the night oppose the intrinsic circadian rhythm of enzymatic activity set by the light/dark cycle. The increased consumption of caffeine and alcohol used as coping strategies by many shift workers may also lead to gastrointestinal sequelae.[24]

Cardiovascular issues

Heart rate and blood pressure vary throughout the day due to circadian control; however, persistent nocturnal activity due to night work reportedly limits or abolishes the normal nocturnal reductions in blood pressure and decreases heart rate variability.[25,26] Individuals who do not experience circadian-driven fluctuations in blood pressure are likely to develop hypertension, which may lead to further cardiovascular sequelae.[27] In addition, there is some evidence that ES may be a risk factor for hypertension.[28] Shift workers have a 40% increased risk of developing cardiovascular disease compared with day workers.[29] Interestingly, a large study of the general population in Detroit, MI, reported that while night-shift (OR, 2.57; 95% CI, 1.24-5.30) and rotating-shift work (OR, 2.01; 95% CI, 1.06-3.83) were associated with an increased risk of heart disease ($P = .01$), the symptoms of SWD per se did not additionally exacerbate heart disease.[6] However, a cohort study of nearly 6000 participants (the Cardiovascular Health Study) reported that ES is linked with increased rates of myocardial infarction, total and cardiovascular mortality, and congestive heart failure,[30] although differences between the study populations in this and the study by Drake and colleagues[6] preclude direct comparison of their results.

Changes in hormone secretion, autonomic and sympathetic cardiac control, metabolism, and heart rate while working at night are implicated in shift-work-related cardiovascular problems.[18,31] Other factors, such as heightened levels of stress relating to work dissatisfaction and an absence of social support, may also play a part.[29,32] Furthermore, increased rates of smoking and more frequent rates of overweight contribute to the increased risk of developing cardiovascular problems in this patient population.[18,29]

Cancer

Increased rates of breast, prostate, and colorectal cancer have been reported in occupations typically associated with night-shift work, such as firefighting, health care, and law enforcement.[33-39] For example, a study of long-term shift-working nurses reported that this population was at a moderately increased risk of breast and colorectal cancer. Nurses who had worked for ≥20 years on a rotating night-shift schedule had a relative risk of breast cancer of 1.79 (95% CI, 1.06-3.01) compared with non–shift-working nurses.[39] The risk of developing breast cancer increased with longer working hours and increased duration of night-shift working.[34] The relative risk of colon cancer in nurses who had worked a rotating night-shift for ≥15 years compared with nurses who never worked night shifts was 1.35 (95% CI, 1.03-1.77).[38]

Women who are awake during what would normally be the period of peak melatonin production (ie, at night) due to work commitments or poor sleep habits have been shown to have an increased risk of developing breast cancer (OR, 1.14 for each night per week; 95% CI, 1.01-1.28).[34] It may be that increased rates of cancer in shift-working populations are due to a reduction in night-time melatonin production, which has been shown to increase the incidence of tumors in animal models.[40,41] Dysregulation of circadian genes in cancer-related pathways or altered hormone production have also been implicated in raising the risk of cancer in shift-working individuals.[42,43]

Reproductive health

In addition to an increased risk of developing breast cancer, shift-working women are also more likely than day workers to experience irregular menstruation, reduced fertility, and problems during pregnancy.[44-46] Moreover, women working rotating shifts have more difficulty becoming pregnant than night-shift working women.[47,48]

Sleep disorders

The chronic sleep deprivation experienced by individuals with insomnia, including shift workers and those with SWD, is linked to reduced serum iron levels, which in turn leads to additional sleep problems such as restless legs syndrome or periodic limb movement disorder.[12,49] Periodic limb movement disorder occurs in 8.5% of shift workers, compared with 4.2% of non–shift workers ($P < .005$).[12] Fatigue (weariness without feeling sleepy) is frequently reported by shift workers and is often a manifestation of an underlying sleep disorder that is disrupting sleep quality.[50] The reported prevalence of sleep disorders other than SWD in shift workers is approximately 30%.[51]

Mood and anxiety disorders

High rates of depression have been reported in shift workers, particularly in women.[52] Furthermore, depression and SWD can both manifest as impairment in memory and concentration and may also result in apathy and lethargy. It is therefore vital that shift-working patients who present with symptoms of depression are asked about their sleep habits in order to avoid misdiagnosis of a mood disorder.

Shift work is thought to exacerbate existing mood disorders; this may be due to a lack of bright light exposure, as is the case with patients who experience seasonal affective disorder.[53] A large epidemiologic study has reported that symptoms of SWD were associated with elevated rates of depression (OR, 2.57; 95% CI, 2.01-3.27).[6] Interestingly, rates of depression did not differ between day, night-shift, and rotating-shift workers who did not have SWD. The findings indicate that, although SWD may be associated with depression, shift work alone does not elevate the risk of developing this mood disorder.[6] Assessment of shift-working radar controllers in the US Air Force using the Zung Anxiety and Depression Scales showed that shift workers with SWD had a greater likelihood of experiencing anxiety than did their shift-working colleagues without SWD ($P < .01$), and they were also significantly more prone to depression ($P < .01$).[54]

Cognitive effects associated with shift work and SWD

Memory consolidation, learning, alertness, and performance are severely affected by sleep deprivation, even in the absence of circadian misalignment.[55,56] Moreover, ES has detrimental effects on memory, impedes concentration, and impairs learning and work performance, regardless of its etiology.[57-59] A recent study has assessed learning in healthy patients who lived under shift-work conditions in a laboratory devoid of time cues by measuring improvements in the Mathematical Addition Test and the Digit Symbol Substitution Task.[60] Circadian misalignment was found to be detrimental to learning in subjects who failed to adapt to their imposed schedule of sleep and wake.[60] Thus individuals who experience ES, sleep deprivation, and sleep/wake synchronization issues as a result of SWD are likely to be particularly affected in this respect.

ES can be severe in night-shift workers (defined by an ESS score ≥18)[7] and becomes most pronounced in terms of impaired performance between 3 and 6 AM.[55] Reductions in sleep duration of between 1 and 4 hours per day have been reported in night-shift populations, and this sleep deprivation may account for a large proportion of the ES associated with SWD.[61-63] Moreover, the quality of night-shift workers' sleep is often poor due to premature awakening and reductions in rapid eye movement and stage 2 slow wave sleep, which is associated with memory consolidation and learning.[62-66] Restriction of sleep time by as little as 2 hours per night for 1 week has been shown to significantly affect scores on vigilance tasks.[67] Furthermore, the persistent sleep debt incurred by shift workers may lead to reduced attention and performance equivalent to that demonstrated by intoxicated persons or study subjects required to remain awake continuously for 24 hours.[67,68] Of concern, significantly lower levels of alertness and performance have been recorded in nuclear power plant night-shift workers vs day- and evening-shift workers.[69,70]

Alertness and cognitive processes may be especially impaired during the transition from day work to a series of night shifts, as many individuals will attempt to stay awake throughout the whole first day and night.[71] Response times in tests of visual selective attention were significantly ($P < .05$) affected on the first night shift in a shift-work simulation study.[71] These results indicate that the potential for accidents is increased in affected night-shift workers from as early as their first shift; productivity is also likely to be affected almost immediately in such workers.[71]

Social and quality of life burden of SWD

Shift work negatively affects quality of life. In a study of Air Force radar controllers, shift workers in general experienced higher levels of anxiety ($P < .001$) and irritability ($P < .05$) and demonstrated a greater tendency to ignore stress ($P < .001$) than did day workers.[54] Importantly, this study also demonstrated that SWD imparts a significantly greater detriment to quality of life than does shift work alone. Quality of life for shift workers with SWD was significantly poorer than that of shift workers without this disorder for the Sickness Impact Profile domains of sleep and rest ($P < .001$), emotional behavior ($P < .001$), home management ($P < .05$), mobility ($P < .05$), social interaction ($P < .01$), ambulation ($P < .05$), alertness behavior ($P < .001$), work ($P < .05$), and recreational pastimes ($P < .01$).[54] Subjects with SWD also experienced greater impairments, compared with other shift workers, for the Illness Behavior Questionnaire domains of general hypochondriasis ($P < .001$), disease conviction ($P < .001$), affective inhibition ($P < .001$), affective disturbance ($P < .001$), and the Whiteley Index of Hypochondriasis ($P < .001$).[54]

Moreover, a large epidemiologic study of the general US population found that individuals with SWD are more likely to be unable to attend social and family interactions due to sleep problems than those without SWD.[6] Permanent night workers with SWD missed 8.6 days of family or social activity per month compared with 1.5 days in those without SWD; rotating-shift workers with SWD missed 10.1 days of family or social activity each month vs 1.0 day in their colleagues without SWD.[6]

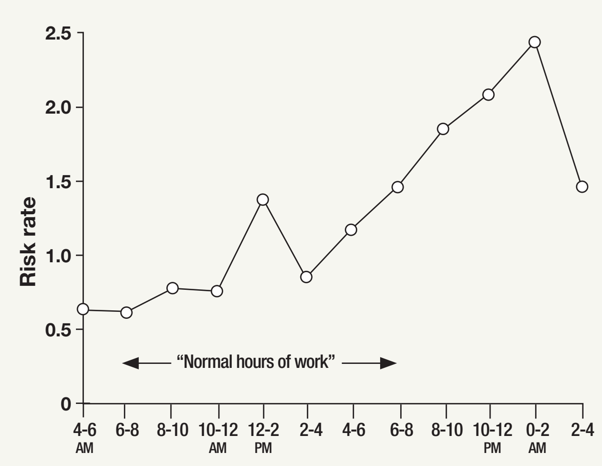
A set of self-report questionnaires—the Standard Shiftwork Index (SSI)—was developed specifically to monitor problems relating to shift work, including changes in alertness, coping, job satisfaction, sleep, psychological well-being, and physical health.[72] A number of studies have used the SSI in shift-work populations and have demonstrated that this measure can differentiate between shift schedules of differing types and length.[73-79] However, a number of analyses have intimated that several of the scales incorporated in the SSI are psychometrically weak, and further evidential support for this set of questionnaires may be required.[80,81]

Accidents

Shift workers are more likely to have work-related accidents than are day workers.[82] Considering that the shift-work population includes nurses, physicians, firefighters, police officers, military personnel, pilots, and drivers, the potential ramifications of SWD are disconcerting. Early treatment intervention should be considered in emergency workers presenting with SWD symptoms so that they can continue to perform their roles safely. Transportation accidents due to ES, suboptimal treatment of patients under the care of shift-working clinicians, and injuries to the clinicians themselves are commonplace, yet SWD remains a poorly documented condition.[2]

The likelihood of a medical resident experiencing a percutaneous injury (with a scalpel or needle) was

FIGURE 1 Risk rate and periods of driving



The risk of a truck driver experiencing a traffic accident is high during times of postprandial drowsiness but is greatest outside normal working hours and, in particular, at the end of the night.

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found to be twice as high during a night shift than during a day shift (OR, 2.04; 95% CI, 1.98-2.11).[83] The odds of reporting an accident or error due to ES were twice as high among nurses on a rotating-shift schedule compared with nurses on a fixed day or evening shift.[13]

Other workers with vital roles are also affected by the demands of shift work. Police officers required to work shifts were reported to be significantly more likely to experience a sleep-related accident at work or at home than were their non–shift-working colleagues (OR, 2.24; $P < .0005$); data concerning the types of accidents experienced by these police officers were not collected in this study.[12]

More accidents are reported by workers commuting home after the night shift than by day workers.[84,85] For example, 40% of motor vehicle accidents experienced by medical residents in their first postgraduate year occurred during the commute home after shift work.[86] Moreover, 74% of motor vehicle crashes involving emergency medicine residents occurred after they had worked a night shift, compared with 12% after a day shift.[85] Among night-shift working nurses, 79% reported experiencing at least one episode of drowsiness on the commute home in a 4-week study.[87]

Driving as part of a shift-based occupation also presents risks for accidents, with approximately 25% of police officers reporting that they have fallen asleep at the wheel while driving at work.[88] It is not surprising that the vast majority of single-vehicle accidents occur early in the morning, when drivers are sleepiest[89,90] (**FIGURE 1**).

Early-morning sleepiness is also thought to be responsible for the increased rate of military flight accidents at this time of day.[91] Twelve percent of US Air Force non-aircrew shift workers admit that they have experienced a fatigue-related operational error, although only 31% of those affected officially reported such an event. Of concern, work/rest guidelines used by shift-working US Air Force aircrew do not appear to greatly improve matters, as fatigue was found to be a factor in 13% of serious aviation mishaps recorded between 1972 and 2000.[92]

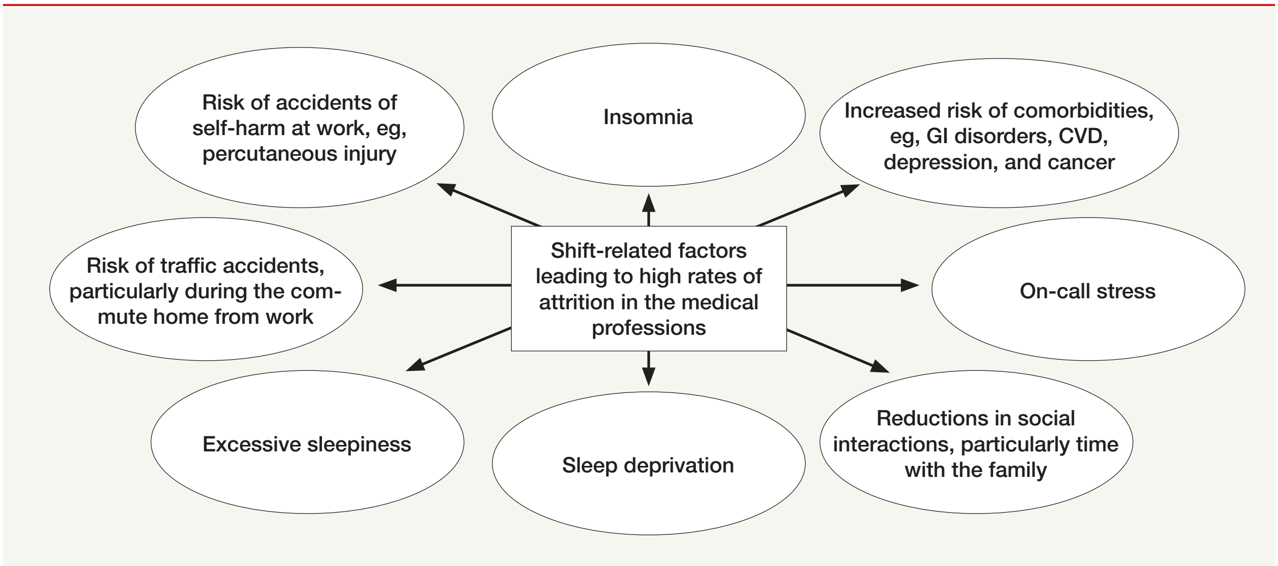
Although these data are illuminating, it is apparent that very few studies have been published on the rate of accidents specifically caused by SWD. Considering that patients with SWD are particularly vulnerable to the circadian issues created by shift work, it seems likely that they must make up a significant proportion of the shift-working population that experiences work-related and traffic accidents. However, until further studies are performed that specifically analyze accidents involving patients with SWD, we can only anticipate that the incidents that these individuals experience are more harmful and occur more frequently compared with the general shift-working population.

Economic impact of SWD

As described in "Cognitive effects associated with shift work and SWD" on page S6 of this article, shift work is associated with significant neurocognitive deficits and reduced efficiency at work. The costs due to lost productivity and accidents associated with shift workers performing at suboptimal level are, therefore, likely to be substantial. To date, studies of the direct and indirect costs of shift work and SWD have not been published; however, an indication of the scale of the economic burden can be gained by looking at the costs associated with the 2 key symptoms of SWD: ES and insomnia.

A study of the economic consequences of ES (performed using 1988 data) reported that ES of any etiology was responsible for motor vehicle accidents costing between \$29 billion and \$38 billion annually (\$53 billion and \$69 billion, when adjusted to 2009 values) and work-related accidents (including deaths and disabling injuries) costing between \$10 billion and \$13 billion annually (\$18 billion and \$24 billion when adjusted to 2009 values).[93]

FIGURE 2 **Shift-related factors likely to affect attrition in the emergency medical professions**



CVD, cardiovascular disease; GI, gastrointestinal.

Studies of patients with insomnia of unspecified etiology reveal the extent of the cost burden of this symptom. An observational US study found that average 6-month total costs (ie, direct and indirect costs) were approximately $1253 higher for an adult (age 18–64 years) with insomnia than for a matched control without insomnia.[94]

A recently reported Canadian study highlighted the large contribution of indirect costs to the total costs associated with insomnia.[95] Direct costs included those for doctors' visits, transportation to the visits, and prescription and over-the-counter drugs. Indirect costs associated with insomnia included those for lost productivity and job absenteeism; these accounted for 91% of all costs. On average, the total annual costs incurred by a patient with insomnia syndrome (defined as those who used a sleep-promoting agent ≥3 nights per week and/or were dissatisfied with sleep, had insomnia symptoms ≥3 nights per week for ≥1 month, and experienced psychological distress or daytime impairment)[95] were C$5010 (C$293 direct and C$4717 indirect). For a patient with insomnia symptoms, average annual total costs were calculated to be C$1431 (C$160 direct and C$1271 indirect). By comparison, a good sleeper (ie, a study subject who reported being happy with his or her sleep, did not report symptoms of insomnia, and did not use sleep-promoting medication) was found to incur average annual costs of C$421.[95]

More detailed assessment is required of the costs incurred specifically in patients with SWD, but there is clearly an economic rationale for early diagnosis and treatment of the symptoms of SWD.

Summary

What is clear from this review is that, while information on shift work is relatively abundant, data concerning SWD are meager. For example, epidemiologic data on SWD are sparse, in part because many investigators in studies of shift workers do not take the seemingly logical step of assessing SWD in their subjects. However, differentiating between shift workers who experience transient symptoms associated with adapting to a new shift schedule and individuals with SWD is complex and may lead to underrecognition of this condition. Similarly, there are few data on the comorbidities experienced by individuals diagnosed with SWD and further studies are warranted. The increased risk of illness demonstrated by shift-working individuals may be even greater in patients with SWD due to their intrinsic—and poorly understood—vulnerability to the effects of shift work.

The studies described here show that the burden of SWD is multifactorial, and it includes impairment of patients' relationships and health and reduces their efficiency at work.[6] Again, there are very few data on the economic burden of SWD, although reduced productivity and the cost of accidents in the workplace and while driving are likely to be high. Additional research is needed in this area.

Shift workers, including public service workers, must make difficult decisions during times of day when they are not functioning optimally. Emergency clinicians in particular have great responsibility and must work under these trying conditions. In addition to the increased rates of traffic and workplace accidents encountered by such clinicians, many will also have difficulty adapting to shift and on-call work, lose recreation time with their families, and experience insomnia, ES, sleep deprivation, and comorbidities (**FIGURE 2**). Not surprisingly, these factors lead to high rates of dissatisfaction and attrition in specialized roles,[96] including health care workers, air traffic controllers, and power-plant workers. A lack of support for shift workers dealing with such issues has economic and safety consequences for society in general; recognition and treatment of SWD are therefore vital. ■

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The characterization and pathology of circadian rhythm sleep disorders

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Practice recommendations

- Being alert to excessive sleepiness and/or insomnia in shift workers may prevent comorbidities and accidents that can occur as a consequence of shift-worker disorder (SWD) (**SOR: B**).
- Not all shift workers develop SWD. Thus, identification of sensitivity to shift work may be facilitated by asking patients whether they find it difficult to function in the absence of consolidated sleep, prefer to be active early in the day, or have previously experienced insomnia due to sleep challenges (**SOR: B**).

Dr Drake reports that he has received research support from Cephalon, Inc., Takeda Pharmaceuticals North America, Inc, and Zeo, Inc., and has served on the speakers bureaus of Cephalon, Inc., and as a consultant to sanofi-aventis.

Organisms demonstrate predictable daily patterns in neuroendocrine function and behavior. The archetypal example is the sleep/wake cycle, although daily fluctuations are evident in nearly all physiological processes, including heart rate, blood pressure, and the release of digestive enzymes.[1,2] Such characteristics are controlled by circadian rhythms under the command of the organism's circadian pacemaker, also referred to as the "biological clock." The word *circadian* is taken from the Latin *circa dies*, meaning "around a day" and, in this instance, refers to the endogenous free-running clock within the hypothalamus. This clock functions on a cycle of approximately 24.2 hours,[3] although daylight and social cues serve to entrain (synchronize) the circadian pacemaker to the 24-hour day ascribed by the rotation of the Earth. This article aims to characterize the current understanding of the mammalian circadian system and describes the features of the 6 recognized circadian rhythm sleep disorders (CRSDs), including shift-work disorder (SWD).

The circadian system

The circadian system consists of 3 parts: (1) input pathways, (2) a central oscillator, and (3) output pathways.[4] The mammalian sleep/wake cycle is governed by the circadian clock as follows: (1) light is transferred from the retina via melanopsin in ganglion cells of the retinohypothalamic tract to (2) the 2 suprachiasmatic nuclei (SCN) in the hypothalamus, which interpret these data regarding day length and signal them to (3) the pineal gland, which secretes melatonin nocturnally for a duration corresponding to the habitual period of darkness (scotoperiod) experienced by the organism[5-8] (**FIGURE 1**). The SCN also activate further output pathways, including the adrenal gland, which releases the stress hormone cortisol in the morning prior to waking; production of cortisol assists with arousal from sleep.[9]

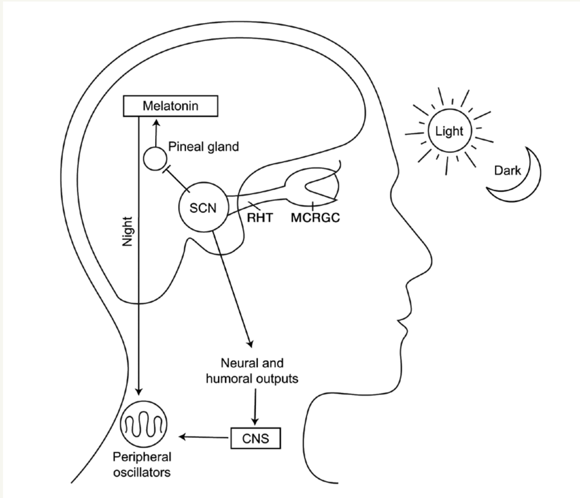
The SCN are capable of maintaining oscillatory patterns of rhythmic gene expression and electrical and metabolic activity even when cultured in vitro.[10-13] Ablation of the SCN results in disruption of activity/rest cycles in some mammals.[14] These findings demonstrate the robustness of the central oscillator and its vital role in preserving important mammalian behaviors such as the sleep/wake cycle. Each of the 2 SCN comprises approximately 10,000 neurons, a proportion of which fire rhythmically to synchronize cellular activity throughout the body via the neuroendocrine and autonomic nervous systems.

Target cells and the SCN rhythmically transcribe clock genes. Expression of such genes is controlled by autoregulatory feedback, ensuring that the circadian rhythm of each cell can work autonomously while remaining capable of responding to entrainment from extrinsic cues—predominantly the light/dark cycle. Examples of clock genes that have been characterized in humans are *hPer* (period homolog)*1*, *hPer2, hPer3, hCLOCK* (circadian locomotor output cycles kaput), *hCK* (casein kinase)*1*δ, and *hCK1*ε. Mutations in these genes are thought to be responsible for a variety of intrinsic CRSDs and also confer individual preferences for activity early or late in the day (morningness or eveningness, respectively). For example, a single nucleotide polymorphism in the *hCLOCK* gene is associated with a more delayed, evening-type, individual-phase preference, whereas a polymorphism in the *hPer2* gene is associated with more of an advanced-phase preference characterized by going to sleep and awakening earlier.[15,16]

The homeostatic system

The sleep/wake cycle is not governed solely by the circadian system; successive hours of wakefulness produce an increasing sleep pressure referred to as the homeostatic sleep drive. These 2 systems typically interact in a synergistic way, with the homeostatic system increasing the drive to sleep as the day progresses, while the circadian signal counteracts this process by promoting wakefulness (**FIGURE 2A**). The circadian alertness signal dissipates in the evening, making way for homeostatic sleep pressure to give rise to sleep onset.[17,18] However, when the internal circadian phase is shifted or behaviors change relative to circadian timing—as occurs in individuals with a CRSD—the homeostatic and circadian systems no longer interact synergistically to maintain appropriate sleep/wake behavior. For example, shift workers may struggle to stay awake at night in the face of increased homeostatic pressure for sleep, without the benefit of a wake-promoting signal from the SCN (**FIGURE 2B**) (see "Shift-work disorder" on page S15 of this article for a more detailed explanation of the sleep challenges that give rise to this CRSD).[19] This situation is diametrically opposed to normal sleep/wake behaviors in terms of the circadian timing of physiological processes and has potentially dire consequences. Indeed, circadian desynchronization in animals has been shown to decrease survival rate,[20] and numerous studies in humans have demonstrated increased morbidity associated with circadian misalignment (see "The social and economic burden of shift-work disorder" on page S3 of this supplement).

FIGURE 1 **Entrainment of the sleep/wake cycle by light**



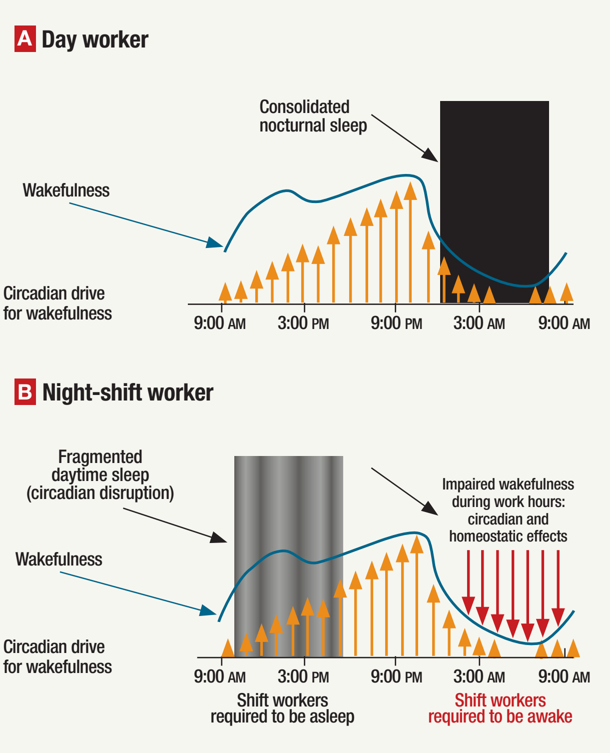
CNS, central nervous system; MCRGC, melanopsin-containing retinal ganglion cells; RHT, retinohypothalamic tract; SCN, suprachiasmatic nuclei.

Types of circadian rhythm sleep disorder

The 6 main CRSDs can be broadly classified into 2 types: intrinsic and extrinsic (**TABLE 1**).[21] Intrinsic CRSDs are characterized by asynchrony between the patient's sleep/wake cycle and the external day/night cycle, due to dysregulation within the internal circadian system. Some intrinsic CRSDs have a heritable component, while other intrinsic CRSDs are caused by the absence of the transmission of light/dark signals to the brain or by maturational changes.[22-25]

Extrinsic CRSDs result from an imposed change in the behavioral timing of sleep and wakefulness relative to internal circadian timing. Not everyone who is

FIGURE 2 **Sleep/wake patterns of day and night-shift workers**



(A) A schematic of the typical sleep/wake patterns in a diurnally entrained day worker. The circadian drive for wakefulness increases throughout the day to maintain alertness and then declines with the start of melatonin secretion in the early evening, facilitating sleep onset. Here circadian and homeostatic factors work synergistically to promote the normal cycle of sleep and wakefulness. **(B)** A schematic of a diurnally entrained night-shift worker. Sleep that is initiated during the day is in conflict with the internally generated circadian signal for wakefulness, thereby producing fragmented daytime sleep. During night-time work hours, the circadian signal for wakefulness dissipates in conjunction with an increasing homeostatic drive for sleep. Thus, in the shift worker, both circadian and homeostatic factors that promote sleep occur at times when the worker is attempting to remain awake and alert. Maladjustment to these challenges contributes to the occurrence of shift-work disorder.

exposed to changes in their sleep/wake pattern will develop an extrinsic CRSD; rather, these conditions act as a trigger for individuals who are susceptible to the circadian challenges of shift work or jet lag. (Factors that may cause a vulnerability to extrinsic CRSDs are discussed in detail in “Shift-work disorder” on page S15 of this article.)

In addition to the CRSDs listed above, the second edition of the *International Classification of Sleep Disorders* also recognizes CRSDs that occur due to a medical condition, or drug or substance abuse, or are not otherwise specified.[21] Potential causes/triggers of CRSDs include stroke, depression, intracranial infection, or head injury. Central nervous system stimulants and depressants may also contribute to drug-induced circadian phase disturbances.[22]

Intrinsic circadian rhythm sleep disorders

Delayed sleep-phase disorder

Delayed sleep-phase disorder leads to a postponement of the rest period and a late awakening compared with societal norms, and is the most common intrinsic CRSD.[23] An overwhelming majority (90%) of these patients report that the onset of their symptoms occurred before or during adolescence.[23] Functional alterations in some clock genes may lead to maladaptation of the sleep/wake cycle to entrainment by light,[26] and several different mutations in the *hPer3* gene have been found to result in the delayed sleep-phase disorder phenotype.[27,28] Individuals with this heritable form of delayed sleep-phase disorder may have a lengthened intrinsic circadian period even in the presence of normal entrainment cues. Other patients with delayed sleep-phase-disorder demonstrate hypersensitivity to light.[29]

Advanced sleep-phase disorder

Individuals with advanced sleep-phase disorder experience a circadian pressure for early initiation of sleep and early awakening.[30] This disorder is uncommon, being diagnosed in <2% of patients with an intrinsic CRSD.[23] Patients with advanced sleep-phase disorder tend to be elderly.[23,24] As sleeping and awakening early are less likely to interfere with work and social interactions than consistently sleeping and rising later in the day, it may be that advanced sleep-phase disorder is underreported. Advanced sleep-phase disorder has a heritable pathology in some individuals (familial advanced sleep-phase disorder). Two different gene mutations (in *hPer2* and *hCK1*δ) in separate families have been reported to result in a shortened circadian pacemaker oscillation period in the presence of normal entrainment, resulting in advanced melatonin, temperature, and sleep/wake rhythms.[31-34]

Free-running disorder

Patients with free-running disorder—also referred to as non–24-hour sleep/wake syndrome—demonstrate a progressive pattern of 1- to 2-hour delays in the onset of sleep and the subsequent waking time. Free-running disorder is diagnosed in <2% of individuals with an intrinsic CRSD[23] and most often occurs in totally blind individuals with no light perception due to the absence of photoentrainment of the sleep/wake cycle.[25] Without entrainment, the behavioral sleep/wake cycle persists with a period similar to that of the internal circadian period of slightly more than 24 hours, resulting in a small but continual off-setting of sleep/wake times compared with the 24-hour day/night cycle.[35]

Irregular sleep/wake rhythm

Individuals with irregular sleep/wake rhythm experience disorganized and variable rest and wake times, sleeping multiple times throughout the day and night. This disorder is diagnosed in 12% of patients with an intrinsic CRSD and occurs most frequently in the neurologically impaired who have damage to the SCN.[23,30] In addition, older age is associated with irregular sleep/wake rhythm due to the increasing prevalence of neurologic conditions such as dementia.[30]

Extrinsic circadian rhythm sleep disorders

Jet lag disorder

The circadian clock cannot adjust quickly enough to accommodate long-distance travel across multiple time zones, often leading to jet lag disorder. Symptoms of jet lag disorder include difficulty in initiating or maintaining sleep, excessive sleepiness, and gastrointestinal disturbances, as the body struggles to accommodate sudden shifts in the timing of activities relative to internal circadian rhythms.[21] Because environmental cues at the flight destination support phase adaptation of the circadian clock to local time, symptoms of jet lag disorder are usually transitory; however, objective measurements of hormone levels, sleep architecture, and body temperature have indicated that a complete phase shift after a long-haul flight can take up to 2 weeks.[36]

The characteristics and severity of jet lag disorder are largely dependent on the direction of travel and the number of time zones crossed.[37] Westward travel is more easily accommodated by the circadian system, as it allows the passenger to delay the onset of sleep instead of advancing sleep times, as required when traveling east. This occurs because the human circadian system runs at an internal period (tau) of slightly longer than 24 hours, a period that is conducive to phase delays in circadian timing.[3] Older age and individual vulnerability to phase shifts also affect sensitivity to jet lag disorder.[37,38]

Shift-work disorder

SWD is an extrinsic circadian rhythm sleep disorder with far-reaching implications in terms of associated morbidity, occupational and traffic accidents, and reduced work productivity (see "The social and economic burden of shift-work disorder" on page S3 of this supplement).[39] SWD occurs when an individual's occupation requires that he or she function at times that are in opposition to the body's normal circadian-controlled periods of sleep and wake. Most individuals will experience some degree of difficulty in attempting to work at unusual times within the 24-hour day, and current diagnostic criteria do not clearly differentiate this group from individuals who have a pathologic response to shift work and develop SWD.[37] Broadly, workers with SWD can be defined as those experiencing persistent insomnia when trying to sleep and/or excessive sleepiness when trying to remain awake. Sleep in patients with SWD is typically fragmented, with frequent awakenings during the daytime rest period. Although appropriate scheduling of light exposure can improve circadian adaptation, even permanent night workers find it difficult to adapt their

TABLE 1 Circadian rhythm sleep disorders (CRSDs) recognized in the ICSD-2[21]

Intrinsic	Extrinsic
• Delayed sleep-phase disorder • Advanced sleep-phase disorder • Free-running disorder (non–24-hour sleep/wake syndrome) • Irregular sleep/wake rhythm	• Shift-work disorder • Jet lag disorder

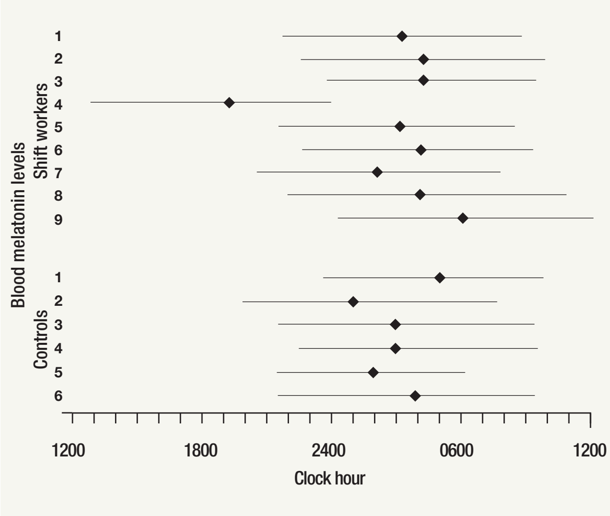
ICSD–2, International Classification of Sleep Disorders, 2nd edition.
The ICSD–2 also recognizes CRSDs that are secondary to medical conditions and drug or substance abuse as well as CRSDs that are not otherwise specified.

TABLE 2 Innate factors that may trigger shift-work disorder

Factor	Supporting evidence
Predisposition to developing insomnia	An increased chance of developing insomnia has been shown to have a heritable component; this vulnerability to insomnia is then unmasked by sleep challenges such as shift work.[42-44]
Genetic vulnerability to sleep-loss induced performance decrement	Reductions in waking performance as a result of sleep loss vary in healthy individuals with different polymorphisms of the *hPer3* gene.[45]
Circadian variation	Genetic polymorphisms result in individual morningness or eveningness preferences; morning-type individuals are more likely to develop SWD.[15,16] Wide intersubject variation has been reported in the expression of genes related to the circadian system after a simulated night shift.[46]

SWD, shift-work disorder.

FIGURE 3 Blood plasma levels of melatonin in individual shift workers and control subjects



Lines indicate nocturnal melatonin elevation (onset, offset, and duration) and diamonds represent the peak of the rhythm (acrophase) in individuals.

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internal circadian rhythms to the timing of their new sleep/wake schedule.[40]

Accumulated sleep loss over successive nights as a result of shift work creates a growing sleep debt that increases the homeostatic sleep drive.[41] Over a series of night shifts, the natural circadian drive for sleep during the night interacts with this increasing sleep debt (**FIGURE 2B**), resulting in further exacerbation of excessive sleepiness, impaired work performance, and increased risk of accidents in individuals with SWD.[19] Thus, both sleep loss as well as circadian pressure for sleep independently contribute to excessive sleepiness in patients with SWD.

Although a change in sleep/wake relative to circadian timing can trigger SWD, not all shift workers develop this CRSD. The high degree of variation between individuals in terms of the severity of symptoms associated with shift work is a complex issue that has not yet been fully elucidated. However, it seems likely that there are a number of innate factors that may increase an individual's susceptibility to SWD, including vulnerability to insomnia, sensitivity to sleep loss, or variation within the circadian system (**TABLE 2**).[15,16,42-46]

Studies of melatonin rhythms in night-shift workers have shown that many workers do not completely adapt their circadian rhythms to their new pattern of sleep and wake[47,48] (**FIGURE 3**). This may be due to an inherent inability to adapt their circadian rhythms or due to behaviors that preclude adaptation. A recent study has shown that a significantly greater ($P < .0001$) number of shift-intolerant vs shift-tolerant workers have a circadian period that is longer or shorter than 24 hours, indicative of circadian desynchronization and an inability to adapt to their new work schedule.[49] In addition, adaptation cannot occur in night-shift workers who persistently revert to a night-time sleep schedule on their days off and who, therefore, do not experience consistent circadian sleep/wake alignment with the light/dark cycle. Night-shift workers who do not adapt to their new shift schedule have been reported to experience reduced sleep during the daytime, putting them at increased risk of developing SWD compared with colleagues who demonstrated a rapid phase shift to accommodate their new work schedule.[50]

The presence of noise in the home, poor sleep hygiene, and social obligations may make it difficult for some shift workers to obtain a sufficient amount of sleep. In these instances, it may be that shift work is incompatible with the patient's lifestyle, resulting in behaviorally induced insufficient sleep syndrome. In patients with SWD, however, insomnia and/or excessive sleepiness persist despite attempts to fully accommodate the altered work schedule.

Summary

The mammalian circadian clock is complex and is responsible for ensuring the rhythmic nature of numerous behaviors and processes. In recent years, there have been frequent and impressive advances in our understanding of the structure and properties of the mammalian central circadian oscillator—the SCN—and the molecular machinery that it controls.

Of the 6 main CRSDs recognized by the *International Classification of Sleep Disorders* (**TABLE 1**),[21] 4 are due to intrinsic problems with the circadian pacemaker, caused by damage to the SCN, maturational changes, lack of appropriate entrainment, or genetically inherited traits. The 2 remaining CRSDs—jet lag disorder and SWD—are triggered by behavioral changes, as they occur as a direct result of human activity, ie, long-distance air travel in a short time and working outside usual hours, respectively. However, not everyone develops jet lag disorder or SWD under these conditions, and the interindividual variation in susceptibility to intrinsic and extrinsic CRSDs is an area of ongoing research.

In a round-the-clock, global society, shift-working individuals perform vital tasks, so it is imperative to find simple ways to diagnose and treat SWD. The following articles discuss how this may be achieved. ■

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Recognition of shift-work disorder in primary care

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Practice recommendations

- To recognize shift-work disorder (SWD), primary care physicians can screen for persistent excessive sleepiness (ES) and insomnia in patients who work night or rotating shifts (**SOR: B**).
- If SWD is suspected, a differential diagnosis should be generated, as ES and insomnia are commonly associated with other morbidities. Ask patients about symptoms of other common sleep/wake disorders, such as obstructive sleep apnea and periodic limb movement disorder (**SOR: B**).
- The Epworth Sleepiness Scale is a useful tool for subjectively evaluating ES (**SOR: A**).

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Shift-work disorder (SWD) is experienced by individuals whose work schedule overlaps with the normal sleep period, causing misalignment between the body's endogenous circadian clock and the time at which the worker is able to rest. The *International Classification of Sleep Disorders, 2nd edition* (ICSD-2) defines SWD as the presence of excessive sleepiness (ES) and/or insomnia for at least 1 month, in association with a shift-work schedule.[1]

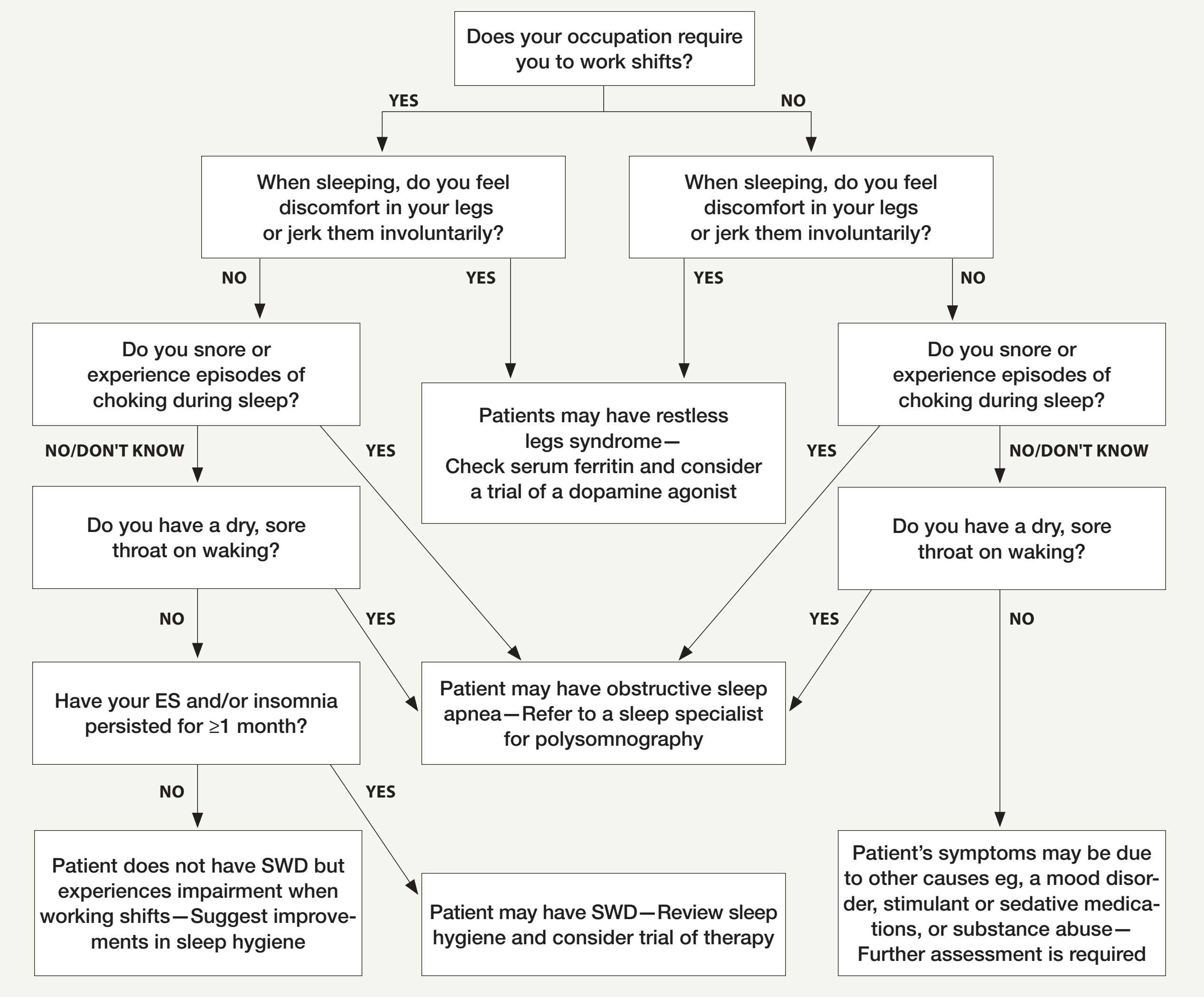
This classification results in the shift-work population being separated into 3 distinct groups: those who have no impairment; those who have impairment but do not meet the ICSD-2 criteria for the diagnosis of SWD; and those who have SWD. Individuals in the last 2 groups are less likely to be able to meet the demands of shift work and, therefore, often return to non–shift-work schedules or retire from the workforce. This creates a "healthy worker effect," whereby workers remaining on night- or rotating-shift patterns are the best suited for this type of work.[2,3] However, retirement or changes to shift-work schedules are not an option for many workers, and patients with SWD must be recognized and treated in order to preserve their health and livelihood.

This article aims to characterize the symptoms and risk factors associated with SWD, with a view to assisting primary care physicians in the diagnosis and recognition of this consistently underrecognized sleep/wake disorder.[4]

Symptoms of SWD

Insomnia and ES (drowsiness and a propensity to sleep) are the defining symptoms of SWD and can result in fatigue (weariness and depleted energy), difficulty concentrating, reduced work performance, headache, irritability or depressed mood, and feeling unrefreshed after sleeping.[4,5] The consequences of insomnia and ES may, therefore, also be useful warning signs for SWD, and patients presenting with one or more of these sequelae should be evaluated for risk factors for SWD and asked about their symptoms using the differential diagnosis described below and in the **FIGURE**.

FIGURE Questions to ask patients who present with insomnia and/or ES (as assessed by an ESS score ≥10)



ES, excessive sleepiness; ESS, Epworth Sleepiness Scale; SWD, shift-work disorder.

These questions aim to aid in differentiating between common sleep/wake disorders in shift-working patients who present with sleepiness or have trouble sleeping and should not be viewed as an exhaustive or definitive list of potential questions or potential diagnoses.

Risk factors for SWD

Vulnerability to SWD is dependent on certain predisposing and precipitating factors, including shift characteristics, circadian preference, job satisfaction, and susceptibility to sleep disturbance (see "The characterization and pathology of circadian rhythm sleep disorders" on page S12 of this supplement). The effects of some physiological and lifestyle factors, such as age and gender, on an individual's propensity to develop SWD have not been well quantified to date.

Shift type and pattern

Night-shift workers are reportedly most susceptible to SWD, with an estimated 32.1% of this group experiencing symptoms that meet the minimum diagnostic criteria for SWD compared with 26.1% of rotating-shift workers.[6] A recent study by Waage and others[7] found that 23.3% of oil rig swing-shift workers (2 weeks working 12-hour day/night shifts followed by 4 weeks off) met ICSD-2 criteria for SWD. The relatively high prevalence of SWD in night-shift workers is thought to be due to exposure to light during rest periods and dark during the hours when the workers are attempting to be most productive.[6] Morning-shift workers are more susceptible to SWD than evening-shift workers, as delaying sleep appears to be more easily achieved than attempting to advance the rest period.[8]

The timing of shifts and changes to the shift schedule have been shown to significantly affect sleep, with individuals on rotating shifts experiencing the greatest detriments to their sleep quality.[8] In one study, workers on rotating shifts experienced significantly more difficulty sleeping than those on a stable shift schedule: 20.4% of rotating-shift workers reported a sleep latency >30 minutes vs 11.5% of fixed- or night-shift workers ($P < .001$).[8] Furthermore, while rotating-shift workers experienced a similar frequency of disrupted nights' sleep to that of other shift workers, they also reported a significantly higher number of night-time awakenings during each disrupted night's sleep ($P < .05$). In addition, approximately one-third of rotating-shift workers reported experiencing ES compared with 19% of night- or other shift workers and 12% of daytime workers ($P < .001$). Therefore, it is probably not surprising that rotating-shift workers were absent from work significantly more often than individuals on fixed day-shift schedules (62.8% vs 38.5%, respectively; $P < .001$) and had a significantly higher annual frequency of work-related accidents (19.5%) than those on fixed daytime (8.8%) or night-time shifts (9.6%) ($P < .001$).[8]

Advancing the rest period is reportedly more difficult than delaying sleep and is thought to be responsible for making counterclockwise shift rotation a risk factor for maladaptation to shift-work conditions.[9] Forward-rotating shift patterns have long been considered more beneficial to workers than backward-rotating patterns.[9] A rapidly forward-rotating shift system has been shown to have positive effects on sleep, to reduce ES, and to improve overall perceptions of general well-being compared with a slower backward-rotating shift pattern.[10] However, this study did not elucidate whether the new shift pattern reduced the negative effects of shift work to the level of those experienced by day workers.[10] The forward-rotating system was found to be particularly helpful to older workers, who experienced larger improvements in ES compared with younger workers.[10]

Shift timing in relation to "zeitgebers"

Bright light is the strongest "zeitgeber"—a cue responsible for the entrainment (synchronization) of the circadian clock. The body's natural circadian rhythms, and therefore the likelihood of developing ES and/or insomnia, will persist as long as shift workers continue to expose themselves to light at times that are inappropriate for re-entrainment (for example, exposure to light in the morning in night-shift workers).[11,12] One study found that workers who ensured that they slept in a darkened bedroom, wore dark glasses when commuting home, and avoided bright light on their days off were least affected by a night-shift schedule.[13] There is some evidence that shift workers respond to relative changes in light intensity over a 24-hour period rather than absolute light intensity, and bright light on the commute home in the morning from a night shift is enough to prevent re-entrainment of the circadian clock toward night working.[13] Interestingly, any degree of re-entrainment to the new rhythm is sufficient to confer significant benefits. Patients who either completely or partially re-entrained their circadian phase with respect to their night shift through the use of a fixed dark daytime sleep episode, sunglasses, melatonin, and bright light at night experienced substantial benefits in ES, performance, and mood (see "Managing the patient with shift-work disorder" on page S24 of this supplement).

Job satisfaction

Poor job satisfaction is associated with higher levels of ES in shift workers[14,15] and may therefore predispose an individual to SWD. Workers on rapidly rotating shifts who had poor job satisfaction did not have shorter sleep times but were sleepier at work compared with their satisfied colleagues ($P < .001$) and had poorer quality of sleep.[14] In a 3-year study, workers on a backward-rotating shift schedule who had poor job satisfaction had a higher likelihood of experiencing ES than individuals who were satisfied with their work ($P = .026$).[15] In addition, ES significantly increased in dissatisfied workers ($P < .05$) over the duration of the study compared with workers who were content with their jobs.[15]

Individual physiological and lifestyle factors

AGE. There is some disagreement in the literature as to the degree to which age affects adjustment to shift-work conditions, but the weight of current evidence suggests that advancing age is a risk factor for developing an intolerance to shift work.[2,3,16-19] Older individuals (ages 53–59 years) appear to adapt better initially to acute sleep deprivation than younger individuals (ages 19–29 years); however, older individuals show a reduced capacity for circadian adaptation when exposed to a series of night shifts.[17] Thus, although younger individuals are initially sleepier in response to a new shift pattern, they are capable of rapidly adapting to these changes. After 3 consecutive night shifts, younger workers were less sleepy than older workers[17]; therefore, older workers are more likely to experience impairment while working night shifts even if they do not meet all of the ICSD-2 criteria for a diagnosis of SWD.

GENDER. Shift work may affect men and women differently. In a study of crane operators, women working night shifts or afternoon shifts slept approximately 30 minutes less than their male counterparts,[20] although this is unlikely to translate into an increased propensity to develop SWD in women. However, less sleep in female shift workers may reflect differences in the familial and/or social obligations of the male and female members of this worker population. The tendency for female shift workers to sleep less also emphasizes that extrinsic factors, such as childcare requirements, may have an impact on sleep during a shift-work schedule even in the absence of any innate circadian issues.[20] A more recent study found few gender-related differences in sleepiness and performance in workers on rapidly rotating shifts.[14] More detailed epidemiologic data are needed before any firm conclusions can be drawn on the influence of gender in SWD; currently it does not appear that gender is a risk factor for SWD.

CIRCADIAN PREFERENCE. It has been suggested that adults can be divided into "morning" or "evening" types[21] and the Morningness–Eveningness Questionnaire (MEQ) can be used to assess into which category an individual falls.[21] Morning-type individuals, or "larks," are most alert early in the day and are thought to be more susceptible to SWD, as they obtain less sleep (on average 86.8 minutes fewer) after a night shift than evening-type workers, or "night owls."[22] However, use of the MEQ is unproven in the evaluation of SWD.[23] Currently, there are no studies regarding whether there is a genetic component to SWD susceptibility[19]; however, a number of reports have indicated that a preference for "morningness" or "eveningness" is genetically determined (see "The characterization and pathology of circadian rhythm sleep disorders" on page S12 of this supplement). In addition, an inherent vulnerability to insomnia or sensitivity to sleep loss may also lead to an innate susceptibility to SWD.

LIFESTYLE FACTORS. A number of lifestyle factors and choices can cause ES and insomnia in shift workers. These include the presence of other people in the home who may disrupt the attempted rest period; social obligations during the normal waking day that require the patient to be awake when he or she should be resting; patients attempting to sleep at "normal" times during days off and the weekend, thus lowering the chances of adapting to the shift-work pattern during the week; and deliberately staying awake or being unable to sleep during transitions between shift patterns, leading to sleep deprivation. These factors should be discussed with the patient at presentation, with a view to improving sleep hygiene. Such factors may trigger SWD in patients who are predisposed to developing this sleep/wake disorder; addressing poor sleep habits in patients who do not have SWD may help resolve their sleep problems.

Shift work can prevent individuals from enjoying a healthy lifestyle, with lower levels of physical exercise and higher levels of smoking seen in shift workers compared with non–shift workers.[15,24] Poor diet and lack of exercise as a result of social constraints or coping mechanisms associated with shift work may lead to metabolic imbalance, which can exacerbate symptoms of ES and insomnia.[24]

Habits adopted to cope with shift work may actually exacerbate the problems associated with night- or rotating-work schedules. For example, consumption of caffeinated drinks to enhance wakefulness or napping at inappropriate times may worsen insomnia when trying to rest.[25] Consumption of alcohol to induce sleep may increase ES during the next shift.[25] Alcohol also interacts with certain shift characteristics to increase the risk of developing SWD and was found to be particularly detrimental to workers on a 3-shift rotation, with 51% vs 42% of regular alcohol consumers and nondrinkers experiencing insomnia, respectively. Although alcohol did exacerbate insomnia in the other shift workers studied, the effect was not as pronounced, with 48% of workers on a 2-shift rotation who consumed alcohol experiencing insomnia compared with 46% of their nondrinking counterparts.[24]

Differential diagnosis of SWD in the primary care setting

The American Academy of Sleep Medicine notes that the boundary between a "normal" response and a pathologic response to shift work is not clearly defined and that the validity and reproducibility of diagnostic criteria need testing.[19] To add to the challenges inherent in defining SWD, ES, insomnia, and a number of their sequelae (see "Symptoms of SWD" on page S18 of this article) are also indicative of a variety of disorders other than SWD. For example, ES and/or insomnia are also symptoms of other sleep/wake disorders, sleep deprivation, pre-existing medical conditions (including mood disorders and central nervous system issues such as narcolepsy and brain injury), the use of sedative or stimulant medications, and substance abuse. The discussion of a patient's full medical history should assist in ruling out other potential causes for his or her symptoms, but it is also vital to generate a differential diagnosis to exclude the other potentially causative conditions. (Examples of how mood disorders and other sleep/wake disorders can be differentiated from SWD appear below.)

Mood disorders and sleep/wake disorders often present in the primary care setting and can at first seem indistinguishable. For example, patients with ES as a result of a sleep/wake disorder may superficially appear to have depression, as a lack of energy, poor memory, reduced concentration, and a loss of interest in life are common features of both ES and mood disorders. In such instances, asking the patient about his or her sleep habits and the use of simple depression questionnaires such as the Patient Health Questionnaire-9 (www.patient.co.uk/showdoc/40025272/) are vital to avoid misdiagnosis and prescription of inappropriate medication.

ES is also a symptom of the sleep/wake disorders obstructive sleep apnea (OSA) and restless legs syndrome (RLS), which are commonly reported in shift workers.[26,27] Patients with OSA have poor quality sleep, as they experience repeated full or partial blockages of their airway, resulting in snoring and episodes of choking or gasping during sleep.[28] Recurrent partial or complete obstruction of the upper airway leads to repeated arousals and disturbed sleep, which can cause ES.[29,30] Night-shift work has been shown to aggravate OSA,[31] possibly due to the increased potential for weight gain and metabolic disturbance in this population[24]; overweight and metabolic syndrome are risk factors for and comorbidities associated with OSA.[28] It is imperative that patients with suspected OSA are referred to a sleep specialist as well as counseled about appropriate therapies and lifestyle changes.[32]

RLS may develop in shift workers due to low serum iron levels induced by chronic sleep deprivation.[33] Patients with symptoms of RLS should have their serum ferritin levels checked and, if found to be <50 mcg/mL, a trial of oral iron therapy may be of benefit.[34] If serum ferritin is normal or symptoms of RLS persist, patients can be treated with a dopamine agonist such as pramipexole or ropinirole.[34] If therapy with a dopamine agonist is not successful, the patient should be referred to a sleep specialist for further treatment and given guidance regarding sleep hygiene. The **FIGURE** provides a suggested set of questions that could form the basis of a differential diagnosis of sleep/wake disorders in shift-working individuals presenting with symptoms of ES and/or insomnia.

Further assessment of patients with suspected SWD

Further assessment for SWD is advised if the patient works shifts, has been experiencing symptoms of ES and insomnia for ≥1 month, and does not have the signs and symptoms of other sleep/wake disorders. Recent practice parameters from the American Academy of Sleep Medicine recommend the use of a sleep diary for ≥7 days to aid in the diagnosis of SWD and to rule out other sleep/wake disorders.[19,23] At present, there are no standard sleep diaries, and many clinicians create their own so that patients can capture data on the quantity and quality of their sleep.

The Epworth Sleepiness Scale (ESS) is helpful in measuring ES in the primary care setting.[35] This brief questionnaire, which can take as little as 2 minutes to complete, asks the patient about his or her chances of dozing in 8 sedentary situations, such as when reading a book or sitting in a meeting. A score of ≥10 out of a possible 24 is indicative of clinically significant ES.[35] However, as the situations described in the ESS are more oriented toward activities of day to day living, they may not be completely appropriate for the measurement of ES in a shift-work situation. Furthermore, the ESS is not validated in night- or rotating-shift workers. Nonetheless, the ESS is useful both as a screen for ES and for follow-up of therapy.

Because the diagnosis of SWD is based on patient history, it does not require confirmation with a sleep study. However, if the patient has symptoms suggestive of OSA or another sleep/wake disorder, then further evaluation, including a sleep study or polysomnogram, is warranted.

Summary

The difference between a "normal" and a pathologic response to shift work is not clearly defined. As a result of this uncertainty, SWD is underrecognized, underdiagnosed, and underrepresented in published clinical studies. The main symptoms of SWD—ES and insomnia—are also characteristic of a number of other conditions, including a variety of sleep/wake disorders. For this reason, exclusion of other potential causes of ES and insomnia is necessary before a firm diagnosis of SWD can be given. Further research is required to establish the physiologic basis of individuals' vulnerability to SWD. Such studies would be helpful in identifying risk factors for SWD and delineating normal and pathologic responses to shift-work conditions. ■

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Managing the patient with shift-work disorder

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Practice recommendations

- Behavioral measures, eg, exercise and improved sleep hygiene, can enhance sleep quality and combat insomnia and excessive sleepiness (ES) in shift workers and individuals with shift-work disorder (SWD) (**SOR: B**).
- Napping before a shift followed by consumption of a caffeinated drink and, if appropriate, scheduled naps at work, may improve ES in patients with SWD (**SOR: C**).
- Use of bright light therapy to partially re-entrain the circadian clock should be explored for all night-shift workers—particularly those with SWD (**SOR: B**).
- The wakefulness-promoting agents armodafinil and modafinil are FDA approved for the treatment of ES in patients with SWD. Alongside nonpharmacologic interventions, they can be included in a comprehensive management plan for SWD (**SOR: A**).
- Melatonin or other sleep-promoting agents may help shift workers achieve sleep during required rest periods and when adjusting to night-shift work; studies are needed in patients with SWD to better evaluate the utility of these agents in this population (**SOR: C**).

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The goals of treatment for individuals with shift-work disorder (SWD) are to ensure sustained wakefulness when wakefulness is required and to facilitate restorative sleep when sleep is required. Several nonpharmacologic interventions are available for the treatment of SWD, such as the improvement of sleep hygiene, exercise, and timed exposure to light. Although these treatments are recommended as part of the Practice Parameter Guidelines for the Evaluation and Treatment of Circadian Rhythm Sleep Disorders from the American Academy of Sleep Medicine,[1,2] most have been evaluated in shift workers generally, rather than specifically in those with SWD. However, the current definition of SWD requires further validation, and while the delineation between workers who do not thrive under shift-work conditions and individuals who develop SWD remains indistinct, it is likely that literature specific to SWD will remain sparse.[2]

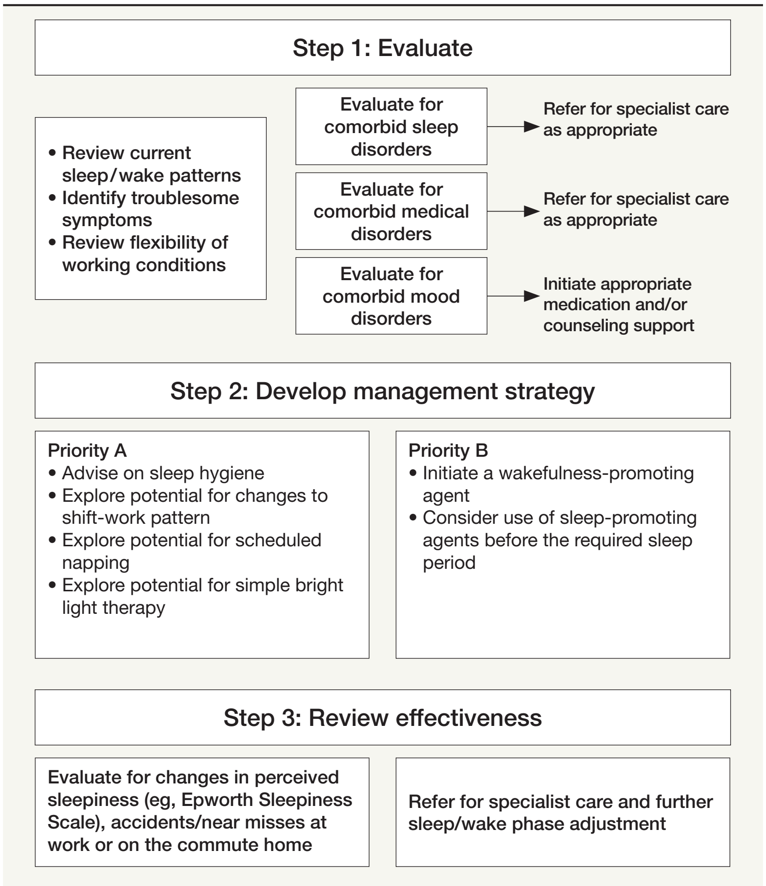
Regardless, such nonpharmacologic interventions should be introduced for all individuals presenting with SWD. Pharmacotherapy may also be required. Two pharmacologic agents—modafinil and its *R*-enantiomer armodafinil—have been evaluated specifically in patients with excessive sleepiness (ES) associated with SWD and are approved as wakefulness-promoting agents for this indication by the US Food and Drug Administration (FDA).

This article reviews appropriate management strategies and specific interventions—both nonpharmacologic and pharmacologic—that primary care physicians can offer to individuals diagnosed with SWD.

Addressing comorbid conditions

For the individual presenting with SWD, it is essential to identify and address any comorbid conditions that might contribute to poor sleep hygiene and/or cause ES or fatigue during required periods of wakefulness. Perhaps the most relevant comorbidities are other sleep disorders, such as obstructive sleep apnea (OSA), and mood disorders, such as depression. Referral to a sleep specialist may be necessary for individuals with a suspected or confirmed comorbid sleep disorder (see "Recognition of shift-work disorder in primary care" on page S18 of this supplement). An algorithm for the management of SWD in the primary care setting, including steps to evaluate comorbid disorders, appears in **FIGURE 1**.

FIGURE 1 **Primary care management algorithm for the individual with shift-work disorder**



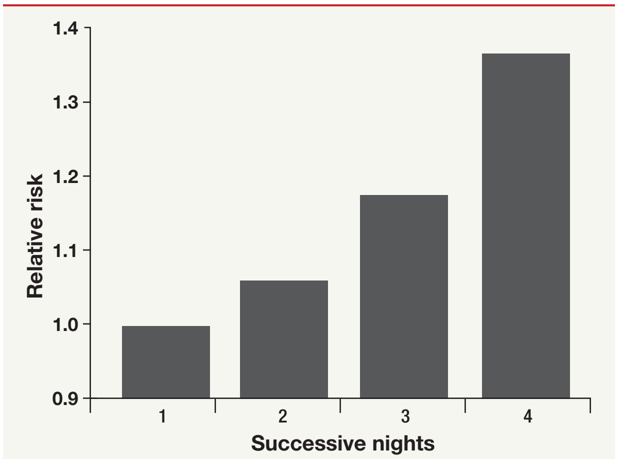
Nonpharmacologic interventions

A range of nonpharmacologic options have been evaluated to relieve the ES often reported by shift workers. These interventions include steps to improve sleep hygiene, scheduled nap times, exercise, and timed exposure to light. Although not all of these interventions have been specifically evaluated among individuals with SWD, such approaches may prove useful as part of a wider management program alongside pharmacotherapy.

Evaluating the work pattern

Certain shift patterns have been shown to be more detrimental than others in terms of their effects on performance.[3] For example, Folkard and Tucker[3] analyzed data from 7 studies that evaluated the risk for incidents (including accidents and injuries) during successive night shifts. They found that the risk approximately doubled with each shift worked, from ~6% during the second night shift to 17% during the third night shift and 36% during the fourth night shift (**FIGURE 2**). Additional studies evaluating the effects of >4 consecutive night shifts, which were not included in the analysis by Folkard and Tucker,[3] confirm the risk for decreased cognitive performance and increased severe ES.[4,5] The observed marked increase in the risk for incidents during working hours suggests that working more than 4 consecutive 12-hour night shifts should be avoided. Individuals should also be counseled to avoid work shifts that are longer than 12 hours due to the risk accumulated on an hourly basis.[3] Individuals on a rotating shift schedule should be encouraged to rotate their shifts in a clockwise rather than a counterclockwise manner (morning to evening to night shift as opposed to night to evening to morning shift) (**FIGURE 3**). It is easier to change the sleep/wake cycle to a clockwise shift rotation, as this follows the natural adaptive pattern of delaying the sleep period.[6,7] However, a change of rotation direction does not eliminate the risks associated with SWD.

FIGURE 2 **Risk for incidents during successive night shifts**



Reprinted from Occupational Medicine (London), Volume 53, Issue 2, Folkard S and Tucker P. Shift work, safety and productivity; pp 95–101, Copyright © 2003, with permission from Oxford University Press.[3]

FIGURE 3 Optimal and least beneficial shift rotation patterns

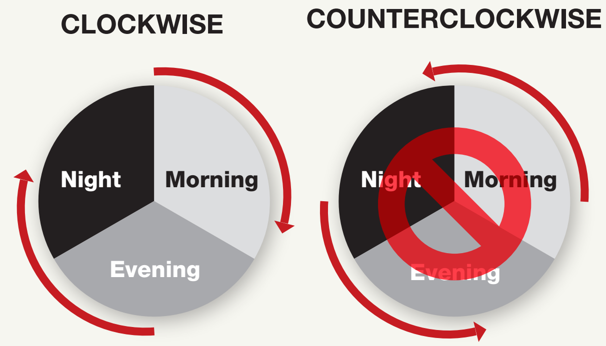


TABLE 1 Steps to achieve an appropriate environment for restorative sleep

Step	Practical advice
Ensure the room is dark if sleep is required during daylight	• Ensure the room has sufficiently well-lined curtains, or install black-out blinds on all windows
Ensure a constant temperature in the bedroom	• Aim for a temperature of around 20°C (68°F) • Avoid too many bedclothes
Reduce noise exposure before and during the required sleep period	• Avoid watching television or listening to loud music immediately before the required sleep period • Use a room at the rear of the house if near a busy road • Consider ear plugs if the ambient noise is intrusive • Put telephones on an answering machine • Ask family members to be quiet
Avoid large meals, caffeine-containing drinks, smoking, and alcohol before the required sleep period	• Schedule meal times so that the main meal of the day is eaten during or before the work period • Consider having a warm, milky drink before the required sleep period

Improving sleep hygiene

Insomnia during periods when sleep is required is a key feature of SWD. When persistent, the chronic sleep debt such individuals incur may contribute to long-term health detriments, eg, cardiovascular disease and ongoing ES, during periods when wakefulness is required. (See "The social and economic burden of shift-work disorder" on page S3 of this supplement.)

Advice on steps to improve sleep hygiene is relevant to all shift workers—including those with and those without SWD—and should be among the first steps in managing any individual presenting with sleep disturbances. Individuals should be advised on how to create an appropriate environment for sleep in terms of noise, temperature, and mental preparation for sleep (**TABLE 1**). They should also be encouraged to ensure a single 7- to 8-hour sleep episode during a 24-hour period, as opposed to, for example, two 4-hour sleep periods.[8,9] There is now good evidence to suggest that sleep fragmentation of this type can adversely affect sleep architecture (ie, the natural stages of sleep), which leads to an accumulated sleep debt.[10] Incurring a sleep debt can exacerbate the negative effects of shift work on cognitive performance and may also aggravate any underlying sleep disorder by adding to the ES experienced during periods of wakefulness.

Exercise

Exercise has been shown to be helpful in promoting sleep onset and improving the perceived quality of sleep.[11] Exactly how exercise promotes sleep remains unclear, but the beneficial effects of exercise on mood and anxiety may contribute.[11,12] In addition, exercise has been shown to facilitate phase shifting of the circadian system[13] and thus may help in the adaptation process to shift work.[14] The most appropriate timing and type of exercise to support individuals with SWD remain to be defined, although there is no evidence to suggest that short bouts of exercise during a work period would be beneficial. In one study of 12 volunteers undergoing a period of sleep deprivation, short bouts of exercise increased alertness for a short time, but this benefit was lost in less than an hour.[15]

Further research is needed to fully define the benefits of exercise among individuals with SWD and to define the optimal timing and regimen to facilitate phase adaptation and reduce the symptom burden among this population.

Scheduled naps

Several studies have indicated that scheduled napping for shift workers may be useful in relieving ES during work periods.[16-22] The optimal duration and timing of such naps have yet to be defined, although one study suggested a longer nap during a night shift (120 minutes vs 60 minutes) was better in terms of sustaining cognitive performance in the early hours of the morning

TABLE 2 Reducing the risk for motor vehicle accidents during the commute home

Steps to recommend	To be avoided
• Consider using a taxi service and/or car pooling, preferably with a driver who has not just completed a night shift • Consider taking a nap before driving home • Try to minimize the commute time, eg, move closer to the workplace • Consider using public transportation • If sleepy while driving, pull over at a rest stop and take a nap	• Avoid traveling at high speeds on highways • Do not rely on rolling down the window and turning up the radio—these actions will only relieve sleepiness very briefly • Do not continue to drive when feeling sleepy; pull over at a rest stop and take a nap

and that sleep efficiency was greater when the nap was taken later in the work shift.[18] Even short naps of <1 hour appeared to improve alertness among experienced night-shift workers.[21] Finally, napping before a night shift may also be beneficial in improving performance, particularly when combined with subsequent caffeine intake.[22]

No studies to date have evaluated napping in subjects with SWD. Furthermore, introducing such an intervention may not be practical for all individuals with SWD. Appropriate facilities may not be generally available in the workplace, and napping while "on duty" may be considered unprofessional or ethically unacceptable in some work settings. For example, concerns regarding continuity of care for patients may impede the implementation of scheduled napping among health care workers.[16]

Additional studies evaluating the health, safety, and performance benefits of scheduled nap times for shift workers and among those with a diagnosis of SWD will be required if any cultural change to allow napping is to be achieved.

Light exposure

The human endogenous circadian rhythm is closely linked to the external light/dark cycle; this interaction involves the receipt of daylight-stimulated nerve activity via the retinal ganglion and the retinohypothalamic tract and is controlled by the suprachiasmatic nuclei of the hypothalamus (see "The characterization and pathology of circadian rhythm sleep disorders" on page S12 of this supplement).[23] Consequently, bright light can incrementally reset (re-entrain) the innate sleep/wake cycle[24,25] and can promote wakefulness by suppressing the production of the sleep-mediating hormone melatonin.[26,27] The interaction between light exposure and the endogenous circadian rhythm forms the basis for bright light therapy as a countermeasure for sleep disturbance among night-shift workers.[28]

Evidence suggests that light therapy can entrain the circadian pacemaker to suit night-shift work and so can be used to support night-shift workers in adapting to their shift pattern.[29,30] Bright light (~2500 lux vs normal lighting of ~150 lux) during the work period, combined with regular sleep periods in a darkened room between shifts, significantly ($P < .05$) delayed the dim-light melatonin-onset response in 54 subjects undergoing a simulated night-shift work pattern, indicating a physiologic phase shift.[31] Such partial re-entrainment improved performance, alertness, and mood during the work period among healthy adults.[32]

A separate study, again using a simulated night-shift work pattern, suggested that brief (1-hour) bright light (~3000 lux) exposure combined with caffeine intake during a night shift maintained cognitive performance throughout the work period in 11 subjects, but that brief bright light exposure alone could, in fact, degrade performance.[33] Reducing light exposure on the commute home from work using sunglasses (or goggles) has been shown to assist with achieving sleep when the worker arrives home[34,35] and to support the partial circadian re-entrainment attained with bright light therapy.[34,36]

The optimal bright light exposure to facilitate partial re-entrainment of the circadian rhythm among night-shift workers has yet to be established. The above studies used a variety of regimens, from constant bright light throughout the work period[31] to intermittent delivery of bright light.[32] A recent study has suggested that a combination of afternoon/evening sleep (between 2 PM and 10 PM) and phase-advancing light therapy (between 3 AM and 7 AM) may be optimal for maintaining alertness in individuals undergoing a simulated night-shift (11 PM to 7 AM) work pattern comprising 4 day and 3 night shifts over 10 days.[37] However, none of these studies have been conducted specifically in patients with SWD.

Reducing the effects of ES when commuting

ES is a well-established risk factor for motor vehicle accidents.[38,39] The potential for motor vehicle accidents on the commute home from work is of considerable concern among shift workers, as they are at greater risk for such an event following a night shift.[40-43] Individuals with SWD should be counseled to minimize their risk for a motor vehicle accident during the commute home. Practical steps are summarized in **TABLE 2**.

Attention to diet

One study has suggested that attention to dietary composition may have an impact on alertness and performance among individuals working night shifts in a hospital setting.[44] The study suggested that a diet with a carbohydrate-to-protein ratio of around 3:1 is optimal in terms of benefits for both mood and psychometric performance.

Pharmacologic interventions

Wakefulness-promoting agents

The wakefulness-promoting agents modafinil and armodafinil (the *R*-enantiomer of modafinil) are currently the only agents specifically approved by the FDA for the treatment of ES associated with SWD. Approval of modafinil for this indication was based on the results of 2 controlled clinical trials (**TABLE 3**).[45,46] Modafinil significantly improved wakefulness, as measured using patient-reported diary data and changes on the Multiple Sleep Latency Test ($P < .001$ and $P = .002$, respectively) in those who had ES as a consequence of SWD.[45] Attention was also significantly improved in the modafinil group compared with placebo ($P < .001$), and significantly fewer participants treated with modafinil reported accidents or near misses during the commute home than did those who received placebo ($P < .001$).[45] Additionally, modafinil significantly improved self-reports of functioning (in terms of productivity and vigilance; $P < .05$) and quality of life ($P < .05$) in individuals with SWD.[46]

In these 2 studies, headache was the most commonly reported adverse event, and nausea was the next most prominent adverse effect with modafinil. In the study by Czeisler and colleagues[45] more modafinil-treated patients experienced insomnia compared with the placebo group (6% vs 0%, respectively; $P < .01$).

Armodafinil has been shown to improve wakefulness in individuals with ES associated with SWD in a controlled clinical trial (**TABLE 3**).[47,48] This study showed armodafinil to be significantly better than placebo at improving wakefulness, reflected by a significantly prolonged sleep latency throughout the night among night-shift workers with SWD ($P < .0001$). Compared with placebo, treatment with a single dose of armodafinil 150 mg, 30 to 60 minutes before the start of the shift, significantly reduced ES at work ($P < .0001$) and during the commute home ($P = .0027$) and did not adversely affect daytime sleep.[47,48] As observed for modafinil, headache and nausea were the most common treatment-emergent adverse events in patients with SWD who took part in these 2 studies.

To date, no studies have been performed that directly compare the efficacy of armodafinil and modafinil; however, the 2 wakefulness-promoting agents do have different pharmacokinetic profiles.[49,50] Compared with modafinil, armodafinil takes longer to reach its peak plasma concentration and is present at higher concentrations for a longer period after administration, resulting in its wakefulness-promoting effects lasting throughout the day.[49,50] The longer duration of armodafinil's effects and its potential for once-daily dosing make it an appropriate and convenient choice for patients with SWD.

Stimulants

Stimulants, such as methamphetamine, have been shown to enhance wakefulness in individuals undergoing simulated night-shift work.[51,52] However, amphetamines can induce rebound insomnia and this, combined with their adverse cardiovascular effects and their abuse potential, makes them less than ideal options for an often chronic condition such as SWD.[53] Methamphetamine has not been evaluated as an intervention for individuals with a diagnosis of SWD and, although it is effective at improving performance and mood during one or more night shifts after single doses, its usefulness in managing SWD on numerous sequential nights is questionable.

A number of studies among individuals undergoing simulated night-shift work suggest that caffeine may be useful to promote wakefulness during the work period, although there may be some residual effects on daytime sleep depending on the caffeine drink selected.[54-56] One study suggested that low-dose repeated caffeine administration may improve performance at the expense of increasing subjective ES during periods of extended wakefulness.[57] As discussed above, caffeine in combination with other wakefulness-promoting strategies, including scheduled napping and bright light therapy, has proved to be a promising intervention under simulated shift-work conditions.[22,23] However, the appropriate dose and timing of caffeine intake to optimize performance and mood during a night shift have not yet been determined. Higher caffeine doses may induce a state of hyperstimulation and can even be toxic.[58] Moreover, habitual caffeine intake can lead to the development of tolerance to its effects,[59] abrogating the efficacy of caffeine intake in the long-term management of an often chronic condition such as SWD. To date, regular

TABLE 3 **Improved wakefulness and reduced ES associated with FDA-approved wakefulness-promoting agents**[45-48]

Citation	Population	Regimens	N (evaluable efficacy population)	Key findings
Modafinil				
Czeisler et al[45]	Adults (18-60 years) with SWD working ≥5 night shifts/month with ≥3 worked consecutively	Modafinil 200 mg Placebo *Taken 30-60 minutes before the start of the work shift for 12 weeks*	89 104	• Mean sleep latency change from baseline ± SD: – Modafinil: 1.7 ± 0.4 minutes – Placebo: 0.3 ± 0.3 minutes (P = .002) • Change from baseline in the median frequency of reported attention lapses: – Modafinil: Reduced by 2.6 – Placebo: Increased by 3.8 (P < .001) • Reported accidents/near accidents while commuting home: – Modafinil: 29% – Placebo: 54% (P < .001)
Erman et al[46]	Adults (18-60 years) with SWD working ≥5 night shifts/month with ≥3 worked consecutively	Modafinil 200 mg Modafinil 300 mg Placebo *Taken 30-60 minutes before the start of the work shift for 12 weeks*	87 90 86	• Modafinil 300 mg significantly improved overall patient functioning vs placebo as measured using the FOSQ: – Increase from baseline in FOSQ score: 2.3 vs 1.6 points, respectively (P < .05) • Modafinil 200 mg and 300 mg both significantly improved quality of life vs placebo as measured using the SF-36 mental health component score: – Mean change from baseline of 3.2, 3.7, and 0.7 points, respectively (P < .05 for both doses vs placebo)
Armodafinil				
Drake et al,[47] **Roth et al**[48]	Adult permanent or rotating night-shift workers with SWD working ≥5 night shifts/month	Armodafinil 150 mg Placebo *Taken 30-60 minutes before the start of the work shift for 12 weeks*	112 104	• Mean sleep latency change from baseline: – Armodafinil: 3.1 ± 4.5 minutes – Placebo: 0.4 ± 2.9 minutes (P < .0001) • Reported ES levels on the KSS were significantly reduced with armodafinil vs placebo (P < .005). • Change in the maximum level of sleepiness (electronic diary data) – During the work shift: 2.0 vs 1.1 points, respectively (P < .0001) – During the commute home: 1.2 vs 0.6 points, respectively (P = .0027)

ES, excessive sleepiness; FOSQ, Functional Outcomes of Sleep Questionnaire; KSS, Karolinska Sleepiness Scale; SD, standard deviation; SF-36, Medical Outcomes Study Short-Form (36-item) Health Survey; SWD, shift-work disorder.

moderate caffeine intake has not been specifically assessed among individuals with SWD.

Other pharmacologic options for SWD

Administration of the sleep-mediating hormone melatonin can promote daytime sleep.[60] However, while some studies have reported that melatonin is helpful for inducing daytime sleep in simulated and real-world shift-work conditions,[61-64] others have failed to demonstrate any objective or subjective benefit.[65] Single doses of melatonin taken before the required sleep period in simulated shift-work studies of healthy subjects have been shown to decrease sleep latency and increase sleep duration.[62] Melatonin may be most beneficial as part of a phase-advancing program to support individuals in adjusting to night-shift work rather than as a chronic therapy for SWD.[61,63,64,66]

Hypnosedatives, or sleep-promoting agents, taken before required sleep periods have also been evaluated in simulated shift-work conditions. Zolpidem, zopiclone, triazolam, and temazepam have all been shown to increase sleep duration during the day and to improve wakefulness during the night shift.[52,67-70] Only zopiclone has been evaluated among shift workers.[70] In a study of 12 healthy male volunteers working 12-hour shifts, a single dose of zopiclone 7.5 mg taken before the required sleep period significantly improved sleep at night, but this improvement did not reach statistical significance when the required sleep period was during the day. No studies of hypnosedatives have been conducted among individuals with SWD. The greater effect of hypnotics on night-time sleep suggests that they are less efficacious at improving disturbed sleep when given out of phase with the usual sleep period.

Summary

Although few interventions have been studied specifically among individuals with SWD, there are a range of practical steps that clinicians can offer to relieve its adverse effects and to reduce a patient's risk of experiencing the potentially fatal consequences of this disorder.

Appropriate interventions include steps to improve sleep hygiene, and evaluation and appropriate referral for comorbid conditions, with particular emphasis on comorbid sleep disorders. Strategies to promote adaptation to the required sleep/wake cycle should also be implemented. These can include bright light therapy (before or during a night shift), reduction of exposure to daylight on the commute home from work, and/or medication with melatonin before a required sleep period, or combinations thereof.[32,34,36,66] These strategies have proved useful among shift workers in general, and further investigation of such strategies would be valuable among those with SWD. Steps to improve shift schedules (eg, the use of clockwise-rotating shifts and avoiding shifts longer than 12 hours), and measures to improve shift-work conditions, such as bright light exposure and appropriately timed naps, may also be helpful.

The wakefulness-promoting agents modafinil and armodafinil are the only interventions with FDA approval for use in patients with SWD and have been evaluated specifically among individuals with ES associated with SWD. These agents have been proven to reduce ES during the work period, with associated benefits in terms of a reduced incidence of accidents or near misses during the commute home. Initiation of wakefulness-promoting therapy should be considered early in the management of individuals with SWD.

Future research should focus on the potential of interventions known to promote wakefulness or sleep specifically among individuals with SWD. In the meantime, clinicians caring for individuals with SWD should develop individualized management strategies that incorporate both nonpharmacologic interventions and pharmacologic therapies, such as a wakefulness-promoting agent before the work period with or without a sleep-promoting agent before the required sleep period. ■

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SUPPLEMENT TO
THE JOURNAL OF
FAMILY PRACTICE
Available at jfponline.com VOL 59, NO 1 / JANUARY 2010

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