Circadian Rhythm Disorders in Primary Care
Causes, Consequences, and Clinical Management

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CASE STUDY INTRO
Martin is a 44-year-old, single father of 2 teenage sons, whom he supports financially by working as a correctional officer in the local prison...

ACTIVITY GOAL
This continuing medical education (CME) activity is intended to improve the recognition, continuous assessment, and multimodal treatment of patients with circadian rhythm disorders (CRDs).

INTENDED AUDIENCE
This activity is intended for primary care providers.

STATEMENT OF NEED
CRDs are prevalent, underrecognized, and inadequately treated, due in part to their varied symptomatology and to the lack of assessment skills among clinicians in the primary care setting (AAASM, 2005; Drake et al., 2004; NSF, 2005; Schwartz and Roth, 2006). CRDs reflect misalignment between the biologic sleep/wake cycle and environmental demands, and/or between the biologic clock and societal norms for bedtime and wake time (AAASM, 2005). Characterized by excessive sleepiness and insomnia, circadian dysynchrony is debilitating across numerous cognitive, affective, and physiologic domains (Culpepper, 2010). CRDs comprise several distinct subtypes, including shift work disorder (SWD), the most clinically significant and prevalent, jet lag disorder (JLD), delayed sleep phase disorder (DSPD), and advanced sleep phase disorder (ASPD) (AAASM, 2005). Short-term consequences stemming from CRDs can be severe, including impaired cognition, motor vehicle accidents, and medical errors among healthcare professionals (Chen et al., 2008; DeArmond and Chen, 2009; NSF, 2008). More alarming perhaps are findings from several studies suggesting a link between CRDs and cardiometabolic dysfunction, gastrointestinal disturbances, and/or mood/affective disorders (Drake et al., 2004; Scheer et al., 2009). Primary care clinicians are faced with the need to provide an accurate diagnosis and initiate appropriate treatment for CRDs to avoid the long-term health implications associated with these disorders, and to ascertain patient and public safety.

LEARNING OBJECTIVES
At the conclusion of this activity, participants will be better prepared to:
• Formulate a comprehensive and accurate approach to initial assessment of CRDs based on the pathophysiology of circadian rhythm dysynchrony and its consequences on sleep symptoms, as well as on metabolism, cardiac function, cognition, and mood
• Perform focused initial assessments in patients identified to have SWD and other CRDs based on their telltale symptomatology
• Formulate initial treatment plans for SWD, JLD, DSPD, and ASPD based on etiology, pathophysiology, and assessment of patient comorbidities, age, medical history, and level of functional impairment
• Monitor treatment responsiveness (improved ES3 score and/or sleep log, affect, cognition, and function) for patients with SWD and other CRDs at 1-month follow-up from initial visit, and as needed, for improved long-term management and patient outcomes

ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Albert Einstein College of Medicine and Montefiore Medical Center, and Asante Communications, LLC. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION
Albert Einstein College of Medicine designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
Circadian rhythms describe biochemical, physiologic, and behavioral events that cycle approximately every 24 hours. One of the most apparent circadian rhythms is the sleep/wake cycle, the timing of which is determined by interactions among endogenous alerting and sleep-promoting signals, and external factors (eg, light exposure, work schedules). Importantly, regular uninterrupted or consolidated periods of sleep are vital to a broad array of physiologic processes, including cardiovascular homeostasis, memory consolidation, affective responses, and vigilance (Ellenbogen, 2005; Mostaghimi et al, 2005; Sabanayagam and Shankar, 2010; Walker, 2010). Chronic misalignment between endogenous sleep/wake rhythms and external demands on sleep timing may result in circadian rhythm disorders (CRDs), a group of conditions associated with wide-ranging symptomatology.

CRDs comprise several distinct subtypes, including shift work disorder (SWD), jet lag disorder (JLD), delayed sleep phase disorder (DSPD), and advanced sleep phase disorder (ASPD), among others (AASM, 2005). Characterized by excessive sleepiness (ES) and insomnia, chronic circadian dysynchrony is often seen in various patient populations. CRDs have serious consequences for patients and markedly affect public health. ES, for example, is associated with increased risk for motor vehicle accidents (MVAs), medical errors, and work-related injuries (Chen et al, 2008; DeArmond and Chen, 2009; NSF, 2008). Moreover, studies of patients with circadian dysynchrony have revealed links with cardiometabolic abnormalities, cancer, depression, and gastrointestinal disorders (Drake et al, 2004; Duez and Staels, 2010; Enren et al, 2008). The prevalence and diverse manifestations of CRDs place primary care providers (PCPs) in a critical position to screen for and treat these conditions. Importantly, inquiries into patients’ sleep habits, work schedules, and functional impairment provide a foundation for diagnosing sleep disturbances (AASM, 2005). Further, appropriate treatment of CRDs—often encompassing combinations of nonpharmacologic and pharmacologic modalities—is likely to improve outcomes across various biologic and psychosocial domains (Morgenthaler et al, 2007a).

**KEY INSIGHTS**

- Circadian rhythms describe biochemical, physiologic, and behavioral events that cycle approximately every 24 hours
- Chronic misalignment between endogenous sleep/wake rhythms and external demands on sleep timing may result in CRDs
- Circadian rhythm misalignment is associated with debilitating symptoms, such as ES and insomnia, as well as a number of serious medical and psychiatric conditions (eg, SWD, mood disorders, cardiovascular disease)

**Etiology and Clinical Consequences of CRDs**

Synchronization of various circadian rhythms relies on entrainment, which is primarily accomplished by appropriate exposure to light and darkness. As light enters the eye, activated retinal photoreceptor neurons generate a neurochemical signal that travels via the retinohypothalamic tract, down the optic nerve, across the
Case Study. Shift Work Disorder

Martin is a 44-year-old, single father of 2 teenage sons, whom he supports financially by working as a correctional officer in the local prison. Nine months ago, state budget cuts resulted in the layoff of several employees and restructuring of work schedules. To avoid being fired, Martin reluctantly agreed to change his work schedule from the day to the night shift.

Martin has scheduled an appointment for his yearly checkup with the primary care provider (PCP) he has been seeing for several years. Martin’s PCP is currently prescribing him medication for type 2 diabetes, hypertension, and dyslipidemia. At the appointment, the PCP conducts a comprehensive physical examination and reviews laboratory results obtained prior to the scheduled visit. The PCP notices no significant changes from the previous year’s assessment with the exception of a worsened lipid profile.

When asked how he has been feeling lately, Martin asserts that he has felt extremely “tired” since starting the night shift. He further contends that he is so tired and irritable that he often gets into unnecessary arguments with his children, and believes that these arguments are putting a significant strain on their relationship. Patients often report feeling “tired” to indicate sleepiness or fatigue, for example. Thus, a focused patient evaluation is necessary to characterize the nature of the patient’s symptoms.

The PCP administers the Epworth Sleepiness Scale (ESS) questionnaire and Martin scores 14 (scores >10 indicate excessive sleepiness [ESS]) of a possible 24, suggesting moderate sleepiness. The PCP inquires further into Martin’s daily schedule, sleep quantity, and sleep quality. Martin reports that it usually takes him approximately 1 hour to fall asleep after he goes to bed at 9:30 am. Once asleep, Martin frequently awakens, although he often requires an alarm to get up at 5:00 am. When the PCP asks about sleep problems on days off from work, Martin states that he eagerly anticipates weekends when he can sleep on a regular schedule and as late as he wants to “recharge his battery.” Holidays are even better; Martin reports that he slept well over the Christmas holiday going to bed around 11:00 PM, falling asleep shortly thereafter, and waking up between 7:30 AM and 8:00 AM every day, usually without an alarm. When the PCP inquires about snoring, choking, or gasping after falling asleep, characteristics associated with obstructive sleep apnea (OSA), Martin reports never being told that he snores and never waking with a sore or dry throat. The clinician also takes particular note of the patient’s neck circumference and BMI, because large neck circumference (>17 inches in men and >16 inches in women) and high BMI are important risk factors for OSA.

Martin then states that he is sleepy and forgetful most of the time and is particularly sleepy around 4:00 AM. At that hour, Martin always buys a large cup of coffee and continues to refill his cup through the end of his shift, although the effects are minimal. In fact, Martin admits to dozing off twice at work, an infraction that is grounds for immediate termination if he is caught. Martin denies dozing off while driving home, but he reports being extremely sleepy during his commute. Based on the patient’s medical and sleep history, which include ES, insomnia, and impairment (emotional lability, forgetfulness) associated with shift work, Martin receives a diagnosis of SWD.

The PCP makes several adjustments to Martin’s anti diabetic, lipid-lowering, and antihypertensive medication regimen. In addition, the PCP encourages Martin to exercise, promotes adherence to a low-fat/low-sodium diet, and emphasizes potential consequences of sleepiness during the commute to and from work. Martin is educated on good sleep practices: take naps when possible, avoid caffeine at least 6 hours before bedtime, avoid large meals before bedtime, minimize light exposure as much as possible at the end of his shift, and maximize light exposure as much as possible during his shift. The PCP instructs Martin to return for follow-up in 1 month and to keep a sleep diary for at least 2 weeks prior to his next appointment.

At the 1-month follow-up appointment, Martin reports reduced emotional lability; however, he mentions that he continues to feel as if he is going to doze off at work. Further, he reports ongoing difficulty falling asleep when he goes to bed. Martin scores a 12 of 24 on the ESS, an improvement from his previous score of 14 of 24. The clinician encourages adherence to the initially prescribed treatment regimen and recommends 3 mg melatonin 1 hour before bedtime to promote sleep onset. In addition, the PCP considers the use of alerting agents to reduce the likelihood of dozing off during work.

**Laboratory Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>107.4</td>
</tr>
<tr>
<td>Serum HbA₁c, %</td>
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</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
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<tr>
<td>LDL, mg/dL</td>
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<tr>
<td>HDL, mg/dL</td>
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<td>Triglycerides, mg/dL</td>
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</tr>
<tr>
<td>TSH, mIU/L</td>
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</tr>
<tr>
<td>Serum thyroxine, μg/dL</td>
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</tr>
<tr>
<td>Serum T₃, ng/dL</td>
<td>112</td>
</tr>
</tbody>
</table>

**Medications**

- Metformin ER, 1000 mg qd
- Pioglitazone hydrochloride, 30 mg qd
- Atorvastatin, 10 mg qd
- Lisinopril/hydrochlorothiazide, 10 mg/12.5 mg qd

**Physical Examination**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
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</tr>
<tr>
<td>Weight, lb</td>
<td>242</td>
</tr>
<tr>
<td>BMI</td>
<td>33.7</td>
</tr>
<tr>
<td>Neck circumference, in</td>
<td>15.5</td>
</tr>
<tr>
<td>BP, mm Hg (systolic/diastolic)</td>
<td>153/110</td>
</tr>
</tbody>
</table>

BMI = body mass index; BP = blood pressure; HbA₁c = hemoglobin A₁c; HDL = high-density cholesterol; LDL = low-density cholesterol; TSH = thyroid-stimulating hormone; T₃ = triiodothyronine. Abnormal values indicated in **bold** font.
optic chiasm, and into the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (Dibner et al., 2010). A cluster of approximately 20,000 neurons, the SCN serves as the body’s “master clock,” using neuroendocrine and autonomic neural pathways to entrain and synchronize peripheral clocks in virtually all organ systems (Cermakian and Boivin, 2009; Klerman, 2005; Paul et al., 2009; Reppert and Weaver, 2002; Schulz and Steimer, 2009). The result is daily molecular, cellular, and system-wide cycles in numerous physiologic and behavioral parameters (eg, core body temperature, systolic blood pressure, hormone levels, alertness). Collapse of this tightly regulated, hierarchical process derails circadian rhythms and may cause or exacerbate cardiovascular, endocrine, and psychiatric pathologies, among other domains (Klerman, 2005).

As master clock and regulator of peripheral circadian rhythms, the SCN controls the sleep/wake cycle (Moore, 2007). Sleep/wake function can be explained by the 2-Process Model comprising 2 interacting regulators: the circadian alertness signal and homeostatic sleep-promoting drive (Figure 1) (Borbely, 1982; Moore, 2007). Under normal conditions, the pressure to sleep exerted by the homeostatic sleep drive increases as the day progresses. Simultaneously, a circadian alerting signal rises to maintain wakefulness, counteracting the homeostatic sleep drive throughout the day. Sleep pressure reaches a tipping point in the late evening when the circadian alerting signal dissipates and the brain switches from a state of wake to sleep. When the sleep debt has been paid and the sleep drive reduced, the increasing circadian alertness signal induces the individual to awaken, and the sleep/wake cycle begins again (Borbely, 1982; Moore, 2007).

In an individual whose endogenous circadian rhythms function normally, misalignment between conventional or socially acceptable sleep, and the individual’s sleep and wake times may result in a CRD, such as SWD and JLD (AASM, 2005). The most prevalent of the CRDs, SWD is diagnosed based on symptoms of ES and/or insomnia that are associated with a shift schedule and persist at least 1 month (AASM, 2005). Notably, shift work schedules include not only night shifts, but also rotating, early morning, and irregular shifts (McMenamin, 2007). Some patients with SWD may exhibit ES—that is, difficulty staying awake during work when the circadian alerting signal is low and sleep pressure, exerted by the homeostatic sleep drive, is relatively high. Conversely, others may experience insomnia—characterized by difficulties staying asleep—after completing a work shift in the morning, when the circadian wake-promoting signal is increasing (AASM, 2005). In addition to the adverse consequences associated with these 2 symptoms, patients with SWD may experience pathophysiologic effects of circadian misalignment in many of the body’s systems (AASM, 2005). Importantly, not all shift workers meet diagnostic criteria for SWD (AASM, 2005). A study by Drake and colleagues estimated that 1 of every 4 rotating workers and one-third of night workers met the criteria for SWD (Drake et al., 2004). While the exact patient characteristics that confer susceptibility to SWD are not known, studies suggest a possible underlying genetic component (Drake, 2010; Viola, 2007). Additional research is ongoing.

Unlike SWD and JLD where external factors play a significant role, DSPD and ASPD result from abnormal endogenous rhythms that originate in the SCN and conflict with expected sleep and wake times. Consequently, affected patients have difficulty adhering to a conventional sleep/wake schedule. In patients with DSPD, most of whom are adolescents and young adults, circadian rhythms are delayed, usually more than 2 hours relative to conventional times (AASM, 2005). Patients therefore find it difficult to fall asleep until late night/early morning (insomnia) and experience ES in the morning.

Figure 1. Two-Process Model of Sleep/Wake Regulation

when they are required to wake up. In ASPD, which is most prevalent in older adults, endogenous rhythms cause habitual sleep onset and wake-up times several hours earlier than desired. As a consequence, patients with ASPD experience ES in the late afternoon/early evening and sleep maintenance insomnia in the early morning, often waking without being able to fall back asleep (AASM, 2005).

Besides ES and insomnia, as noted above, circadian misalignment can cause or exacerbate most important sleep-related risk factors for MVAs (Crummy and sleepiness-related MVAs (Drake et al, 2004). In fact, shift work is SWD were 4 times more likely to have ulcers and had significantly higher blood pressure and than shift workers without SWD. Compared with counterparts without SWD, individuals who met diagnostic criteria for circadian misalignment in patients with SWD and JLD included heterogeneous populations of shift workers or frequent travelers who may or may not have met the diagnostic criteria for CRDs. To replicate sleep/wake patterns that typically result in SWD or JLD, many studies have induced dyssynchrony in the laboratory setting. Scheer and colleagues, for example, maintained healthy subjects for 10 days on a sleep/wake schedule that misaligns circadian rhythms (Scheer et al, 2009). Study subjects showed 6% and 22% postprandial increases in glucose and insulin levels, respectively, compared with individuals with normal circadian rhythms. Of note, glucose levels increased despite a concomitant increase in insulin, suggesting either decreased insulin sensitivity or increased insulin resistance. Also important, several individuals displayed prediabetic or diabetic postprandial glucose levels, suggesting that circadian misalignment may contribute to the development of chronic metabolic diseases. Mean arterial blood pressure significantly increased by 3% in subjects with circadian misalignment, an elevation that is associated with increased risk of cardiovascular disease and associated mortality (Scheer et al, 2009). While the study did not address chronic circadian dyssynchrony, the findings do suggest that the high rates of cardiometabolic abnormalities observed in patients with SWD may be due, at least in part, to misaligned circadian rhythms (Antunes et al, 2010; Scheer et al, 2009).

Some studies suggest that CRDs contribute to occupation-related performance deficits as well. For example, offshore shift workers on oil rigs experience more frequent and severe work-related injuries, which likely result from reduced alertness and performance (Ross, 2009). Aviation pilot errors have been shown to increase by almost 50% during the midnight to 6:00 am shift relative to the 6:00 am to noon shift (de Mello et al, 2008). Also striking, performance deficits among shift working healthcare workers result in more frequent medical errors and poor outcomes for patients (Keller, 2009). These and other findings highlight the role of circadian dysynchrony in cognitive and performance deficits.

Drake and colleagues investigated direct relationships between chronic circadian misalignment and associated adverse effects by evaluating shift workers with and without SWD. Compared with counterparts without SWD, individuals who met diagnostic criteria for SWD were 4 times more likely to have ulcers and had significantly higher rates of depression, absenteeism, missed social appointments, and sleepiness-related MVAs (Drake et al, 2004). In fact, shift work is one of the most important sleep-related risk factors for MVAs (Crummy et al, 2008; Keller, 2009). Similarly, patients with DSPD and ASPD also experience associated cognitive, mood, and performance impairments even though they try to maintain a conventional sleep/wake schedule (AASM, 2005; Kripke et al, 2008; Wolfson and Carskadon, 2003). Intriguingly, individuals with SWD show abnormal brain activation in response to alertness and memory tasks, suggesting that neurologic changes may underlie the adverse performance and cognitive effects of circadian dysynchrony (Gumienyuk et al, 2010).

Current research efforts are attempting to identify the molecular mechanisms underlying circadian control of physiologic and neurobehavioral activity. Genetic loci involved in the regulation of cognition and mood have also been implicated in the etiology of circadian dysregulation and related symptoms (Mendlewicz, 2009; Takahashi et al, 2008). For example, a mutation in the circadian gene Per3 is associated with circadian phase dysregulation and susceptibility to sleep deprivation-induced executive impairment. Characterization of this and other genetic polymorphisms may help explain the observed relationship between CRDs and cognitive, mood, and performance abnormalities (Mendlewicz, 2009; Takahashi et al, 2008). Identifying genetic and biochemical factors that explain relationships between CRDs and other morbidities—cardiovascular disorders, for instance—is certainly an active area of research. PCPs should consider the potential effects of circadian dys synchrony on all medical and affective symptoms in patients with sleep problems. In turn, treatment focused on realigning biologic rhythms may provide benefits for wide-ranging symptomatology (Crowley et al, 2004; Rahman et al, 2010; Smith et al, 2009).

- The central circadian clock in the SCN is directly synchronized by the light/dark cycle, whereas peripheral clocks in other areas of the brain and surrounding tissues are synchronized by neuroendocrine and autonomic signals originating in the SCN
- Patients with CRDs experience ES because of a low circadian drive during wake and insomnia due to a high circadian drive at desired sleep times
- Patients with chronic sleep disorders, such as SWD, often underreport the severity of their sleepiness
- Morning ES and nighttime insomnia characterize DSPD, whereas morning insomnia and late afternoon/evening ES characterize ASPD

Recognizing Circadian Misalignment in Primary Care Populations

Sleep disturbances are underrecognized in primary care, at least in part because problems with sleep are often seen as secondary to a primary medical condition. Providers may therefore treat the apparent primary disorder assuming that the sleep disturbance will improve as
a result. Circadian misalignment may go undetected if clinicians fail to directly question their patients about the presence of sleep-related symptoms or work schedules. In fact, a survey by the National Sleep Foundation found that only 30% of physicians inquire about their patients’ sleep habits (NSF, 2005). Patients themselves present barriers to diagnosis; some have experienced sleep/wake problems for so long that they eventually accept their symptoms as normal and feel no need to report them. Assessment is further complicated by patients’ ambiguity about their symptoms. They may, for example, say they are “tired,” a term that could describe sleepiness or fatigue, which are 2 distinct physiologic conditions. Sleepiness is a neurophysiologic state characterized by a tendency to fall asleep or inability to stay awake, which is improved by sleep (Shen et al, 2006). Fatigue, in contrast, is a psychoneuromuscular condition characterized by weariness, exhaustion, and loss of energy that is alleviated by rest (Shen et al, 2006). Patients reporting tiredness should be prompted to be more specific in describing their symptom with the goal of ascertaining its source.

As previously discussed, CRDs result from an alteration of the external sleep/wake environment relative to the timing of a person’s internal circadian clock or from changes in a person’s endogenous circadian timing that are not consistent with societal or personal demands. Recognizing CRDs is thus predicated on knowing how a person’s internal timing mechanism relates to his or her external environment. Both behavioral screening tools (eg, Morningness-Eveningness Questionnaire) and objective assessments of circadian rhythms (eg, dim light melatonin onset [DLMO]) exist; however, according to the American Academy of Sleep Medicine (AASM) Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders, a CRD diagnosis can often be made based only on a patient’s sleep history and sleep log (Morgenthaler et al, 2007a). These tools provide details that inform a diagnosis, helping the clinician determine the difference between actual and desired sleep times. Useful information in a sleep history or log includes, among other important details, days when the patient’s sleep/wake schedule is not dictated by personal or social obligations (eg, holidays, weekends), circumstances at the onset and duration of sleep problems, and conditions that exacerbate or alleviate symptoms. Additional assessments, although not always practical in primary care, may facilitate evaluations of circadian timing and can help PCPs characterize a patient’s endogenous rhythms when necessary. One such measure, actigraphy, involves a portable device worn on the wrist to record movement over time (Morgenthaler et al, 2007b). The resulting documentation provides a longitudinal estimate of sleep and wakefulness and can be compared with a patient’s desired sleep and wake times (Morgenthaler et al, 2007b; Sack et al, 2007a). The device has been recognized by the AASM Standards of Practice Committee as useful for evaluating patients with CRDs (Morgenthaler et al, 2007b). Other objective circadian phase markers include core body temperature measurements and melatonin level assessments using DLMO (Sack et al, 2007a, 2007b).

CRD-related symptoms may also be used to uncover circadian misalignment. Certainly, when the cardinal CRD symptoms ES and insomnia are identified during the course of a patient’s evaluation, circadian misalignment must be considered for differential diagnosis. Various patient-administered questionnaires may also prove practical for symptom recognition and evaluation. The self-report Insomnia Severity Index, for example, quantifies the severity of insomnia (Bastien et al, 2001). One of the more widely used questionnaires, the Epworth Sleepiness Scale (ESS; Figure 2), provides an efficient, quantifiable measure of sleepiness (Johns, 1991). The ESS evaluates a patient’s reported level of sleepiness and/or monitors the effects of treatment once a therapeutic protocol is in place. Clinicians should be aware, however, that although subjective sleepiness often correlates with objective measures, the correlation is not robust, especially in patients with chronic ES, who may consider the state “normal” (Benbadis et al, 1999; Chervin et al, 1997).

KEY INSIGHTS

» Patients who report feeling tired should be prompted to be more specific about their symptoms to allow for a precise differential diagnosis

» Recognizing CRDs is predicated on knowing how patients’ internal biologic clock relates to external cues from their environment

» Obtaining a thorough sleep history and sleep log is usually sufficient to diagnose a CRD

Circadian Dyssynchrony: Realignment and Symptomatic Control

Initial and ongoing treatment plans for patients with CRDs should be multimodal, ideally addressing both circadian realignment and symptom control. To meet these treatment goals, appropriately timed light exposure is often employed as part of the therapeutic plan. When administered before or after the core body temperature reaches its
This and additional activities are available at SLEEPClinician.com

nadir, bright light exposure can induce a phase delay or advancement, respectively (Figure 3) (Khalsa et al, 2003; Lewy et al, 1998; Zee and Manthena, 2007). Accordingly, light should be administered for DSPD in the morning to advance circadian rhythms and promote earlier sleep onset and wake time, whereas, in patients with ASPD, evening light can be used to delay the circadian clock. Other CRDs, such as SWD, can also be managed with appropriately timed light (Zee and Manthena, 2007). While complete re-entrainment greatly improves alertness and performance during night shift work, often workers find it difficult to adapt to a night shift if the schedule renders them misaligned during days off. Complete circadian realignment to a night work shift and day sleep schedule, however, may not be necessary to improve night shift alertness and lengthen daytime sleep in this patient population. Combining bright light during night shifts, the use of dark sunglasses outside, and scheduled sleep episodes in darkness has been shown to partially entrain rhythms, significantly improve mood and performance, and reduce fatigue in shift workers (Smith et al, 2009).

Administration of melatonin at appropriate times—opposite to the times used for light exposure—can also shift the circadian phase in patients with CRDs. In contrast to light therapy, melatonin administered before or after the nadir of the core body temperature can induce a phase advancement or delay, respectively (Figure 3) (Skene and Arendt, 2006; Zee and Manthena, 2007). Although available data support the use of melatonin to advance the circadian phase in patients with CRDs, the agent’s efficacy in promoting phase delays in ASPD has not been firmly established (Sack et al, 2007b). Often, clinicians combine light with melatonin to optimize phase shifting.

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**Figure 2. Epworth Sleepiness Scale Questionnaire**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
<tr>
<td>Watching TV</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
<tr>
<td>Sitting inactive in a public place (eg, in a theater or at a meeting)</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
<tr>
<td>In a car while stopped for a few minutes in traffic</td>
<td>0 = None, 1 = Slight, 2 = Moderate, 3 = High</td>
</tr>
</tbody>
</table>

**Total ESS score**

| Scoring: | 
| <10 = normal | 10-12 = mild sleepiness |
| 13-15 = moderate sleepiness | ≥16 = severe sleepiness |


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**Figure 3. Light and Melatonin Phase Response Curves**
Patients with CRDs may also require symptomatic management. To alleviate the hallmark CRD symptoms ES and insomnia, behavioral and pharmacologic approaches can be implemented to optimize sleep (Roth et al, 2010a). Maximizing sleep is a cornerstone of most therapies for patients with sleep/wake disorders. ES and insomnia may be reduced in part by promoting good sleep/wake practices and thereby establishing conditions that promote sleep during the major sleep episode and alertness during wake times (Table 1) (Stepanski and Wyatt, 2003; Thorpy, 2003).

Scheduled napping before or during work improves alertness and performance in night shift workers without affecting post-shift daytime sleep (Ficca et al, 2010). Further, caffeine taken at appropriate times and doses can augment a planned sleep schedule to enhance alertness in shift workers (Morgenthaler et al, 2007a; Walsh et al, 1990). One study found that a 2-hour nap at home before shift work, combined with 300 mg of caffeine at the beginning of the shift, resulted in less sleepiness and improved work performance at the end of the shift (Schweitzer et al, 2006). PCPs need to inform patients, however, that the long half-life of caffeine and the side effects (eg, insomnia, anxiety) associated with high caffeine doses can be problematic, particularly if intake occurs too close to the desired sleep time.

Whereas caffeine may address symptoms of ES by promoting alertness, melatonin may induce the opposite effect to ameliorate CRD-related insomnia. Melatonin has hypnotic effects in addition to the phase-shifting properties discussed above. Administration prior to daytime sleep after a night shift has been shown to reduce latency to sleep onset (Sadeghniiat-Haghighi et al, 2008). Similar effects may be beneficial in patients with JLD after travel across multiple time zones; appropriately timed exogenous melatonin may reduce symptoms and improve sleep in these patients (Hershheimer and Petrie, 2002). Melatonin is available as an over-the-counter nutritional supplement; it should be noted, however, that the agent is not approved by the US Food and Drug Administration (FDA). Concerns have been raised regarding the purity of various commercially available products, and, like all drugs, side effects must be considered.

Prescription medications should also be considered for management of CRD-related symptoms. Indeed, the AASM supports the use of pharmacologic agents for the treatment of CRD symptoms (Table 2) (Morgenthaler et al, 2007a). ES and insomnia may be especially responsive to pharmacotherapy. For instance, the circadian alerting signal may cause sleep onset and maintenance difficulties during night shift workers’ desired sleep time. Hypnotics have proven effective for these symptoms in some patients with SWD or JLD. The hypnotics triazolam and temazepam have been shown to reduce sleep onset latency and improve sleep maintenance in simulated night shift work studies, and similar findings, although with somewhat mixed results, have been reported for the management of JLD symptoms (Morgenthaler et al, 2007a; Porcu et al, 1997; Walsh et al, 1991; Walsh et al, 1988). Of note, hypnotics may reduce insomnia symptoms, but ongoing patient monitoring is necessary to minimize or eliminate adverse effects, including carryover sedation. Also important to note, patients with comorbid sleep disorders, such as obstructive sleep apnea (OSA), may worsen with hypnotic treatment, highlighting the need for individualized patient management (Morgenthaler et al, 2007a).

<table>
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<tr>
<th>Goal</th>
<th>Practical Advice</th>
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| Establish a regular sleep/wake schedule | • Get up and go to bed at the same time every day including nonwork days and holidays  
• Sleep 7 to 8 hours  
• Avoid napping during the day; it can disturb the normal pattern of sleep and wakefulness |
| Minimize noise, light, and extreme temperatures during sleep | • Sleep in a room away from house/street noise (eg, rear of the house away from street noise)  
• Use ear plugs if ambient noise is intrusive  
• Avoid watching television, using the computer, listening to the radio, reading, or eating in bed  
• Reduce light exposure before bed  
• Ensure the room has sufficiently well-lined curtains, or install blackout blinds on all windows  
• Aim for a temperature of around 20°C (68°F)  
• Avoid too many bedclothes |
| Avoid large meals, stimulants, and alcohol before the scheduled sleep period | • Schedule meal times so that the main meal of the day is eaten 4 to 6 hours before sleep  
• Discontinue caffeine and nicotine use 4 to 6 hours before sleep |
| Relax each night before bed | • Take a warm bath  
• Read a book (outside of the bedroom)  
• Avoid exercise 4 to 6 hours before sleep  
• Listen to calming music |

Prescription medications that may prove helpful for treating ES include stimulants, such as amphetamines and methamphetamines. These agents may be prescribed off-label to enhance wakefulness during shift work. Caution, however, is required because stimulants are associated with adverse cardiovascular effects and significant abuse liability (Schedule II) (Thorpy, 2010). Studies demonstrate that the alerting agents modafinil and armodafinil—FDA-approved for the treatment of ES associated with SWD—improve vigilance, performance, and cognition in chronic shift workers (Erman et al, 2007; Schwartz et al, 2010). These therapies may be preferable over traditional stimulants, because they have fewer and less severe adverse effects, which include headache, nausea, dizziness, and insomnia (Kumar, 2008; Schwartz et al, 2010). In addition, their abuse liability is negligible (Schedule IV) (Kumar, 2008; Schwartz et al, 2010).

Most patients with CRDs can be effectively managed in the primary care setting. Collaboration with and referral to a sleep specialist may be necessary for chronic sleep/wake complaints that prove refractory to treatment. A sleep specialist referral may also be required to confirm a suspected comorbid sleep disorder, such as OSA or restless leg syndrome (RLS). To optimize patient outcomes, ongoing communication is required between the sleep specialist and referring PCP.

### Conclusions

Primarily known for their deleterious effects on sleep and alertness, CRDs impinge on numerous health domains (Drake et al, 2004; Roth et al, 2010b). Because PCPs are familiar with the sign and symptom profiles of each of their patients, primary care provides the ideal setting to recognize and treat patients with CRDs. ES and insomnia, however, are associated with multiple conditions, and an accurate differential diagnosis is required to inform the best approaches to patient care. Nevertheless, given the consequences of CRDs, prompt diagnosis and targeted management are important. Typically, multifaceted treatment strategies that target both circadian realignment and symptomatic control will reduce CRD-related morbidity and improve patient outcomes.

Visit SLEEPClinician.com/CRDReport to access this activity and earn credit.
References


Johns MW. Sleep. 1991;14:540-545.


McMenamin TM. Monthly Labor Rev. 2007;130:3-15.


Walker MP. Prog Brain Res. 2010;185:49-68.


CME Posttest

CIRCADIAN RHYTHM DISORDERS IN PRIMARY CARE: CAUSES, CONSEQUENCES, AND CLINICAL MANAGEMENT

Based on your participation in this CME activity, please rate your level of agreement with the following statements:

1. Morning excessive sleepiness and nighttime insomnia characterize advanced sleep phase disorder.
2. Diagnosis of circadian rhythm disorders is most accurately conducted using polysomnography.
3. Patients with chronic sleep disorders, such as shift work disorder, often underreport the severity of their sleepiness.
4. Central circadian entrainment is thought to help maintain normal cardiovascular function.
5. Obtaining a thorough sleep history and sleep log is usually sufficient to diagnose a circadian rhythm disorder.
6. The suprachiasmatic nucleus promotes synchrony of peripheral clocks via neuroendocrine and autonomic nervous signals.
7. Circadian misalignment with conventional sleep/wake time is often associated with cognitive impairment and performance deficiencies.
8. Circadian rhythms in various organs, excluding the brain, are directly synchronized by light.
9. Circadian rhythm disorders are often characterized by excessive sleepiness.
10. Patients with circadian rhythm disorders experience excessive sleepiness because of a low circadian drive during wake.

Practice Profile

How many patients do you see during a typical week?
- Less than 20
- 21-49
- 50-99
- 100-150
- Greater than 150

How many patients with CRDs do you see during a typical week?
- None
- 1-15
- 16-30
- 31-45
- Greater than 45

Before this activity, how often did you…
- Administer an Epworth Sleepiness Scale
- Obtain a sleep history
- Inquire about performance and/or cognitive deficits while awake
- Encourage good sleep hygiene

Following this activity, how often do you plan to…
- Administer an Epworth Sleepiness Scale
- Obtain a sleep history
- Inquire about performance and/or cognitive deficits while awake
- Encourage good sleep hygiene

Activity Evaluation

Online participation is also available at www.SLEEPClinician.com/CRDReport. Alternatively, to obtain 1.0 AMA PRA Category 1 Credit™, please complete the Activity Evaluation and Self-Report Credit Form, along with the CME Posttest and Practice Profile, and mail to CCME, 3301 Bainbridge Avenue, Bronx, NY 10467, or fax to (718) 798-2336. All requests for credit should be submitted no later than March 14, 2012.

Please answer the following questions by checking the box that best describes your evaluation rating.

1. What is your overall rating of the activity?
   - Poor
   - Satisfactory
   - Excellent

This and additional activities are available at SLEEPClinician.com™
2. To what extent did your participation in this activity enhance your ability to:

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3. Was this activity effective in teaching you something new?

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4. To what degree do you believe this course was objective, scientifically rigorous, and free of commercial bias?

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5. If you perceived commercial bias, what factors contributed to that perception?

6. Did the information from this course confirm how you treat and/or manage patients?

7. Did this activity provide evidence-based information that will be useful in your job or practice?

8. After participating in this course, I:

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9. Rate the course and faculty/authors:

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<th>Activity</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
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<td>• This course provided information relevant to my professional role or subspecialty.</td>
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<td>• The authors were knowledgeable and presented the information clearly.</td>
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<td>• The course method of delivery was an effective way to learn.</td>
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<td>• The course length was:</td>
<td>Too short</td>
<td>Appropriate</td>
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10. Should additional topics be covered in future reports?

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11. Additional comments:

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**First Name** _______________ **Last Name** _______________

**Degree(s)** _______________ **Clinical Specialty** _______________

**Mailing Address 1** ____________________________________________

**Mailing Address 2** ____________________________________________

**City** _______________ **State** _______________ **ZIP** _______________

**Phone** _______________ **Fax** _______________

**E-mail** ____________________________________________

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**Attestation**

I attest that I have spent __________ hour(s) __________ minutes completing this CME activity. Signature (required) __________________________ Date _______________

☐ Please check here if you would prefer not to participate in a future survey to assess outcomes for this activity.

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CE-SLP-110