The Human Circadian System in Normal and Disordered Sleep

Gary S. Richardson, M.D.

The human circadian system regulates rhythmicity in the human body and establishes normal sleep and wake phases. The suprachiasmatic nuclei (SCN), located in the hypothalamus above the optic chiasm, make up the human pacemaker known as the circadian or biological clock, but other essential parts of the circadian system include the pineal gland, retina, and retinohypothalamic tract. The importance of light in resetting the intrinsic human circadian cycle, the intrinsic period of which is slightly longer than 24 hours, ensures that the human cycle will stay entrained to the earth's 24-hour daily cycle. Within the SCN neurons, circadian rhythmicity is generated by the regular transcription of proteins. Since the circadian system is the foundation of the sleep-wake cycle, disorders and abnormalities in sleep are often connected with disorders or abnormalities in the circadian system. Circadian rhythm sleep disorders, such as jet lag syndrome and shift work sleep disorder, are those specifically attributed to dysfunctions or insufficiencies in the circadian system. Taking into consideration the preeminence of the circadian clock in timing sleep, it is likely that other sleep disorders, such as insomnia, are also linked to circadian system abnormalities.

(J Clin Psychiatry 2005;66[suppl 9]:3–9)

Over the last 20 years, the study of circadian rhythms and the system that controls them has evolved from a basic inquiry about the existence of a circadian clock into a comprehensive study of the functional anatomy, physiology, and neurophysiologic foundations of the circadian system. The circadian (from the Latin *circa,* meaning "about," and *dies*, meaning "day") system entrains rhythmicity in the human body and maintains normal sleep and wake phases. Consequently, abnormal or disordered sleep is often correlated with abnormal or dysfunctional circadian systems.

THE CIRCADIAN SYSTEM

The human circadian system comprises the retina, retinohypothalamic tract, pineal gland, and suprachiasmatic nuclei (SCN). Located in the hypothalamus above the optic chiasm, the SCN are primarily responsible for the endogenous generation of normal circadian rhythmicity and are commonly referred to as the circadian or biological clock.

From the Division of Sleep Medicine, Henry Ford Hospital, Detroit, Mich.

This article is derived from the planning roundtable "Sleep: New Frontiers in Psychiatry and Primary Care," which was held March 18, 2005, in Chicago, Ill., and supported by an unrestricted educational grant from Takeda Pharmaceuticals North America, Inc.

Corresponding author and reprints: Gary S. Richardson, M.D., Henry Ford Hospital, 2799 W. Grant Boulevard, CFP-3, Detroit, MI 48202 (e-mail: grichar1@hfhs.org).

Functional Physiology of the Circadian System

The SCN keep time for the body and engage in neuronal firing that instructs the various systems and organs of the body to perform or cease the activities appropriate to the time of the day, month, or year. A free-running human circadian clock exhibits a daily cycle of greater than 24 hours; however, the SCN rely on an outside *zeitgeber,* or "time giver" to provide an accurate measurement of environmental time and reset the human daily cycle appropriately each day.[1] As the most reliable measure of environmental time, the daily cycle of light and darkness acts as the *zeitgeber* for the circadian system of most species. The circadian rhythm is, therefore, a function of 2 cycles—the organism's internal circadian clock cycle and the earth's day/night cycle.

The Circadian Clock: The Suprachiasmatic Nuclei

The neuronal firing of the SCN is the mechanism that provides the basis for circadian rhythmicity. The SCN are 2 clusters of approximately 10,000 neurons located in the hypothalamus above the optic chiasm on either side of the third ventrical.[2] Explants of rodent SCN multiple units in vitro show persistence of rhythmic neuronal firing, evidencing that the SCN are the source of endogenous circadian rhythmicity.[3] When observed individually, each SCN neuron keeps its own time, although the precision of single neuron rhythmicity is not as great as the nucleus as a whole.[4] Thus, while the population of neurons within the SCN drive circadian rhythms in the intact organism, circadian rhythmicity is inherent in the bio-

© Copyright 2005 Physicians Postgraduate Press, Inc.

chemistry of the clock's most basic building blocks—the SCN's neurons.[5]

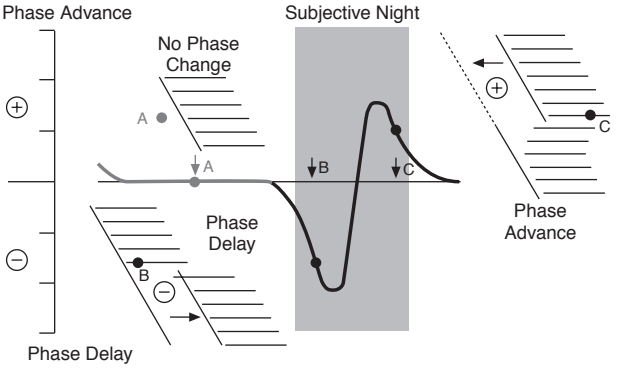
In the last few years, the functional origins of circadian rhythmicity within the SCN neurons have been attributed to the genetic transcription of proteins. The activity of 2 sets of proteins creates the circadian cycle. In mammals, the CLOCK protein binds with the BMAL1 protein to form a dimer (a pair of molecules) that acts as an "on" switch for the transcription process as the day begins.[6] The BMAL1/CLOCK dimer triggers the transcription of period (PER) and cryptochrome (CRY) proteins by binding to the *Per* and *Cry* gene promoters inside the nucleus. (The SCN neurons of mammals have 2 types of *Cry* genes, *Cry1* and *Cry2*, and 3 types of *Per* genes, *Per1*, *Per2*, and *Per*3; however, for the sake of simplicity in this text, all the genes are called either *Per* or *Cry*.) Throughout the day, these activated gene promoters send *Per* or *Cry* mRNA out to the ribosomes that translate the mRNA into PER and CRY proteins.

Unless PER protein binds with another PER or CRY protein to form a dimer, this protein is vulnerable to degradation because the casein kinase 1 epsilon (*CK1ε*) in the cytoplasm of the cell phosphorylates solitary PER protein, making it instable. The proteins that do bond into PER/PER or PER/CRY dimers translocate from the cytoplasm into the nucleus, assisted by the *CK1ε* in an unknown way. They then interact with BMAL1/CLOCK and prevent transcription of their own *Per* and *Cry* genes, creating a negative feedback loop. Throughout the night, no new PER or CRY proteins are created, while the dimers within the nucleus slowly degrade. As each dimer blocking the transcription process degrades, another dimer fills its space, continuing to obstruct transcription. Finally, when there are not enough dimers to prevent transcription, the *Per* and *Cry* promoters are activated once again, beginning the transcription of PER and CRY. This cycle of protein transcription, binding, and degradation is approximately 24 hours in duration and is the basis of mammalian circadian rhythmicity.

The circadian rhythm in gene transcription is translated into a rhythm in neuronal firing by tying the levels of ion channels, receptors, or transmitters to the rhythmically transcribed genes. The result is an endogenous rhythm in neuronal activity within the SCN. A study[7] of 2-deoxyglucose uptake in hamster brains showed SCN activity during circadian day and SCN inactivity during circadian night.

Having an understanding of the basic molecular functioning of the healthy circadian clock allows researchers more insight into the cause of sleep disorders. Since the *Per* and *Cry* genes play such an important role in maintaining the circadian clock, polymorphisms or variation in these genes can cause variations in the circadian clock mechanism, resulting in abnormally long or short circadian periods. These variations manifest clinically as kindreds in which affected members show abnormally early or late bedtimes (advanced sleep phase syndrome and delayed sleep phase syndrome, respectively).

Figure 1. Phase-Response Curve[a]



[a]Adapted with permission from Czeisler et al.[8]

Phase-Response Curve of the Circadian Clock

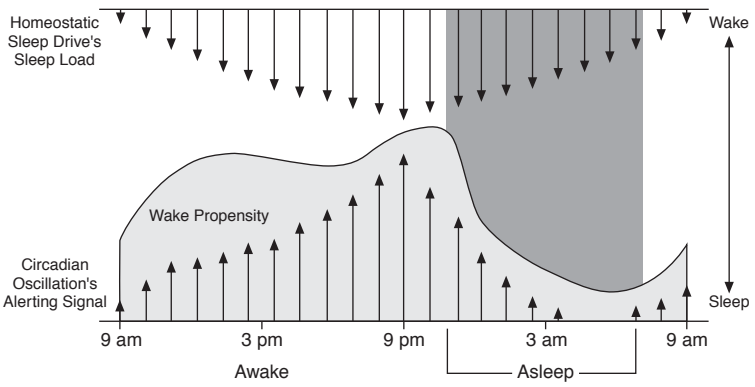
The phase-response curve is a mathematical expression of the relationship between the oscillation of the circadian clock and phase-altering stimuli, such as light. Specifically, the phase-response curve plots the phase of the circadian oscillation at which the phase-altering stimulus is applied (on the x-axis), and the direction and magnitude of the resultant change in phase (on the y-axis).

Phase-response curves are important in understanding how biological clocks may be manipulated and understanding treatment of circadian rhythm disorders. For example, a phase-response curve may show the phase-advancing and phase-delaying effects of light upon the normal circadian cycle (Figure 1).[8] Exposure to light during the middle of the day causes no phase change ("A" in Figure 1). Light exposure causes phase delay when it occurs early in the "dark period" or night ("B" in Figure 1) and causes phase advance when it occurs late in the night ("C" in Figure 1). This phase-response relationship between circadian phase and light is an inherent property of the circadian oscillation, and the same is true of the relationship between circadian phase and other potential manipulators such as melatonin.

CIRCADIAN CONTROL OF NORMAL SLEEP

The human circadian clock modulates the timing of sleep and wakefulness through direct effects on sleep tendency (sleepiness/alertness) and on the neurophysiologic processes governing sleep state expression. In a 1974 study of sleep-wake phases by Weitzman and colleagues,[9] 7 healthy adults were asked to adhere to a 3-hour sleep-wake cycle for 10 days. The subjects had 1 hour to sleep and 2 hours to be awake during the 3-hour period. Despite

Figure 2. Homeostatic Sleep Drive Versus Circadian Oscillation[a,b]



[a]Adapted with permission from Kilduff and Kushida[10] and Edgar et al.[11]
[b]Circadian oscillation and the homeostatic sleep drive both shape the sleep-wake cycle, but the oscillation of the circadian clock has a more powerful influence. For example, despite the great need for sleep around 9 p.m., sleep does not occur because of the high level of alertness caused by the circadian oscillation. Around 6 a.m., the trough of the circadian oscillation maintains sleep despite the very small need for sleep from the homeostatic sleep drive.

the accumulated sleep deprivation over the course of the study, subjects were not able to sleep well during the appointed sleep times that occurred during the peak of the body temperature rhythm, especially at 6 p.m. and 9 p.m. In contrast, when the appointed sleep time took place during the circadian phase conducive to sleep, in the trough of the body temperature rhythm (between 3 a.m. and 9 a.m.), subjects were able to use the 1 hour sleep allowance efficiently. These results reveal the strength of the circadian rhythm in dictating the timing of sleep. This relationship has serious implications for shift workers and other individuals who must live on a schedule that conflicts with the normal circadian cycle.

The Homeostatic Sleep Drive Versus Circadian Oscillation

The homeostatic sleep drive is the physiologic drive to get the amount of sleep required for normal, stable daytime functioning and alertness. The need for sleep accumulates during wakefulness and dissipates during sleep. Thus, sleep deprivation intensifies the homeostatic need for sleep, making sleep more likely at inappropriate or unusual times.

Under normal conditions, the circadian cycle and the homeostatic sleep drive interact to produce sleep and wakefulness of appropriate duration and timing. However, as shown in the study by Weitzman and colleagues,[9] under conditions of sleep deprivation (and markedly increased homeostatic sleep drive), the circadian clock prevents meaningful recovery sleep at certain circadian phases, indicating that the circadian clock is the more powerful influence on sleep-wake expression under these conditions (Figure 2).[10,11] A 2001 study by Cajochen and colleagues[12] examined sleep as a function of circadian rhythm and homeostatic sleep drive. Like Weitzman and colleagues, they found that circadian oscillation creates sleep "forbidden zones," when sleep rarely occurs, and other times when sleep is almost unavoidable.

MELATONIN

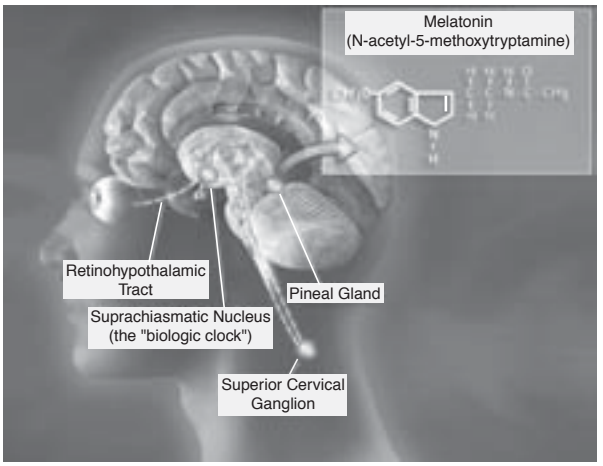
Melatonin (N-acetyl-5-methoxytryptamine) is the primary secretory product of the pineal gland; this hormone plays a fundamental role in circadian rhythmicity.[13] The pineal gland is a sympathetic efferent of the SCN that secretes melatonin into the general circulation in response to signals from the SCN (Figure 3).[14]

The pattern of melatonin secretion is dictated by the SCN, but the exact wave form is produced by the combination of the rhythmic influence of the SCN circadian oscillator and the photic inhibition of melatonin secretion caused by light. The signal from the SCN incorporates both circadian phase information and a direct signal about light and dark received from the retina. Melatonin secretion peaks during the night, when the SCN is in its trough and there is no light ("A" in Figure 4). The effect of light upon melatonin secretion can be shown by shining a light on the retina during the night; the light evokes an immediate decrease in melatonin secretion levels ("B" in Figure 4).

Melatonin Receptors

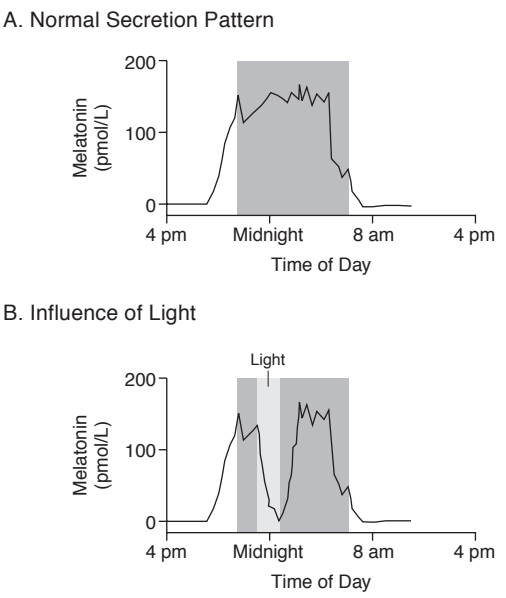
The human SCN contains specific, high-affinity melatonin receptors. Unlike other animals, humans appear to have very few melatonin receptors in the central nervous system (CNS) outside of the SCN.[15] There are 4 types of melatonin receptors, but only 3 of them exist in humans. MT1 and MT2 (also known as Mel_{1a} and Mel_{1b}) are CNS

Figure 3. Melatonin and the Circadian System[a]



[a]Adapted with permission from Brzezinski.[14]

Figure 4. Melatonin Secretion Pattern[a]



[a]G.S.R., unpublished data.

melatonin receptors, which are found in humans; MT3 (formerly called Mel_2) is the peripheral receptor. A receptor unique to frogs and birds, formerly called Mel_{1c}, has no name according to the new nomenclature.

Using knockout mice, Liu and colleagues[16] studied melatonin mediation of the inhibition of SCN neuronal activity. When bathed with melatonin, an explant from a normal (wild type) mouse SCN stopped firing, displaying dose-dependent melatonin inhibition of SCN neuronal activity. When an SCN explant from a mouse with no MT1 receptors was suffused with melatonin, there was no inhibition of neuronal activity, indicating that the MT1 receptors mediate this inhibition. Also, SCN explants with no MT1 receptors maintained their ability to move their peak activity earlier or later (phase shift); this implies that MT2 receptors mediate phase shifting. Some species do not even have MT2 receptors and are still able to inhibit SCN firing and shift phases, so this delineation of receptor function is not necessarily conserved across all phylogeny.

The Role of Melatonin in Circadian Rhythmicity

Melatonin is centrally involved in maintaining circadian rhythmicity. Like light, melatonin is able to cause a change in the phase of the circadian oscillator. Exogenous melatonin in oral form causes a phase advance when administered late in the day and phase delay when administered early in the morning. Since melatonin has the opposite phase-altering effect of light, melatonin may be an effective means for counteracting the effect of light on oscillation.

Melatonin and the SCN work together to control the sleep-wake cycle. The SCN control the timing of melatonin release, while melatonin feeds back on the SCN to inhibit its activity. The presumed function of this interaction is to "sharpen" the SCN waveform (Figure 5).[10,11,17] This interaction may be particularly important because, by sharpening the offset in SCN activity, melatonin may potentiate sleep onset over a relatively narrow phase range. If the SCN functioned entirely independently from melatonin, a more sinusoidal waveform of the circadian clock would allow sleep onset to occur anywhere across a broad range of circadian phases. Sleep onset might take much longer and be less predictable from night to night. However, with the release of melatonin, a sharp decrease in SCN activity occurs upon secretion, narrowing the transition into sleep to a much more limited phase length. This relationship may underlie some of the sleep-wake difficulties seen in those older individuals in whom melatonin secretion is attenuated.

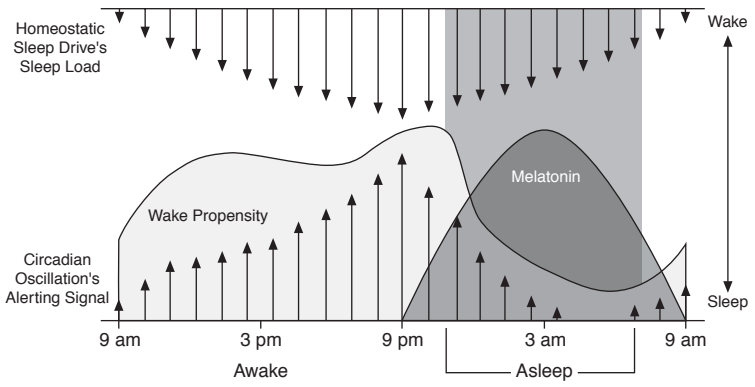
CIRCADIAN RHYTHM SLEEP DISORDERS

Since the circadian clock plays such a fundamental role in sleep, some sleep disorders are attributed directly to abnormalities in the circadian clock or system.

Delayed Sleep Phase Syndrome

In delayed sleep phase syndrome (DSPS), the circadian clock is oriented late relative to the desired sleep-wake time. An individual with DSPS has trouble going to sleep at a reasonable hour and has trouble arising at a reasonable hour in the morning. Patients with this syndrome are usually alert in the evenings and sleepy in the morning. They have long sleep onset latency when they try to go to bed at a socially appropriate time. As discussed

Figure 5. Melatonin and the Circadian Oscillator[a,b]



[a]Adapted with permission from Kilduff and Kushida,[10] Edgar et al.,[11] and Dijk et al.[17]
[b]Melatonin and the SCN circadian oscillator sharpen each other's wave form. The sudden drop in circadian alerting signal between 10 and 11 p.m. is caused in part by the increase in melatonin secretion that is taking place at that time, inhibiting SCN neuronal firing. Without the release of melatonin, the decrease in SCN activity at nighttime would happen more gradually, making the transition to sleep and sleep onset a much longer and less predictable process.

above, polymorphisms of the intrinsic clock genes may predispose an individual to DSPS by producing an unusually long circadian period. While cases of presumably genetic DSPS have been reported, it remains unclear what percentage of DSPS patients may have a genetic foundation.

Studies of individuals with DSPS show that sleep is normal at the biologically appropriate time and abnormal at the socially appropriate time.[18] If the schedules of DSPS patients allow them to fall asleep and wake up when they want, their sleep time and efficiency are normal. Also, constant routine body temperature recordings show the minimum body temperature of DSPS patients to occur several standard deviations late in the circadian cycle relative to age-matched norms.[19]

Advanced Sleep Phase Syndrome

In advanced sleep phase syndrome (ASPS), the circadian clock is oriented early relative to the desired sleep-wake time. Patients with ASPS are sleepy in the evening and alert in the morning, awakening very early in the morning. The typical patient with ASPS is older, but there are some young people with ASPS. As with DSPS, genetics may play a role in the syndrome. In families with genetic polymorphisms of *hPer2* genes, for example, even younger individuals experience ASPS symptoms.[20]

Jet Lag Syndrome

In jet lag or time zone syndrome, the circadian clock is attempting to function in the midst of a sudden change in light-dark orientation due to air travel across time zones. This disorder does not stem from a dysfunction of the circadian clock; rather, environmental cues and the light-dark cycle are in conflict with the circadian clock's internal timing. The symptoms of jet lag syndrome are generally mild and temporary.

Shift Work Sleep Disorder

In shift work sleep disorder (SWSD), symptoms arise because the individual is attempting to wake and sleep out of phase with the dictates of the endogenous circadian clock. As with jet lag disorder, the clock is functioning normally in shift work disorder; the requirements put upon the clock are abnormal. Even after several weeks of shift work, the circadian clock does not truly adapt to the abnormal schedule as long as the *zeitgeber*, light exposure, is providing information about the time of day.[21] SWSD affects performance both through the immediate impairment produced by attempting to function at an inappropriate circadian phase (night) and by the cumulative effects of sleep deprivation resulting from the foreshortened and disrupted sleep obtained at a nonconducive phase (day).

Non–24-Hour Sleep-Wake Syndrome

In non–24-hour sleep-wake syndrome, the circadian clock free-runs according to its endogenous circadian cycle of longer than 24 hours despite the presence of environmental cues. The clock is unable to entrain to the normal light-dark cycle. The majority of individuals with this syndrome are blind, but some sighted individuals also experience it.

Irregular Sleep-Wake Pattern

Individuals with irregular sleep-wake patterns complain of poorly consolidated or shortened sleep during the night and take frequent and irregularly timed naps during the day. Although some patients with this disorder have

functional lesions of the circadian clock, the majority of the cases of irregular sleep-wake pattern are attributable to poor sleep hygiene, in which irregular napping leads to difficulty sleeping at night.[22] For some patients, the disorder may be caused by a combination of both factors. The napping of individuals who experience this disorder as a result of poor sleep hygiene still respects the circadian clock's sleep forbidden zone, indicating that their circadian clocks are functioning and entrained properly.

INSOMNIA AND THE CIRCADIAN CLOCK

Is typical insomnia—that which is not diagnosed as a specific circadian rhythm sleep disorder—associated with alterations in the circadian oscillator as well? The importance of the circadian system in controlling sleep suggests that it might be. In a study[23] examining melatonin secretion in individuals with chronic primary insomnia, the amplitude of the melatonin rhythm was significantly reduced, particularly in those whose insomnia had lasted more than 5 years. Although the direction of the relationship in this study is not clear, these findings are nonetheless consistent with the hypothesis that a decrease in the functional contribution of melatonin by the pineal gland may contribute to chronic insomnia.

There is some debate about whether circadian phase is abnormal in insomnia, but a study[24] of individuals with early morning insomnia showed substantial circadian phase advance. Of course, as with the changes in melatonin amplitude, it is not clear whether the changes in phase are primary or secondary. The differential light exposure in the morning relative to the evening, as a result of rising early in the morning, may subsequently produce a phase shift. When insomnia patients are grouped according to complaint (sleep onset insomnia versus early morning insomnia), circadian phase abnormality is often correlated. People with sleep onset insomnia tend to be phase delayed, and people with early morning insomnia tend to be phase advanced.

If insomnia is related to circadian rhythm abnormality, chronobiotics (drugs capable of shifting the circadian phase) may be useful in treating insomnia. In a study by Garfinkel and colleagues,[25] controlled-release melatonin was efficacious in improving sleep efficiency, sleep latency, and wake after sleep onset for individuals with low melatonin levels. Since low melatonin levels may alter SCN-pineal gland feedback, chronobiotics may be able to treat insomnia by reversing the abnormal pineal effect, reestablishing the link between the SCN and the pineal gland, and reentraining the circadian rhythm.

CONCLUSION

The human circadian clock controls the timing of physiologic processes that are necessary for life. A functional and healthy circadian system is essential to the maintenance of optimal internal and external temporal organization. The importance of the circadian clock to normal function is particularly apparent in the expression of sleep and wakefulness.

Sleep disorders can often be traced to abnormalities in the circadian system. Insight into the nature of circadian rhythm disorders already allows clinicians to treat some of these syndromes. Research into the relationship between the circadian system and other sleep disorders will highlight the role of specific treatments that can manipulate the parameters of the circadian clock. As the scientific understanding of the circadian system grows, clinicians will have more opportunities to reentrain the circadian clock in order to correct disordered sleep.

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Moore-Ede MC, Czeisler CA, Richardson GS. Circadian timekeeping in health and disease, pt 1: basic properties of circadian pacemakers. N Engl J Med 1983;309:469–476
2. Hastings MH. Central clocking. Trends Neurosci 1997;20:459–464
3. Inouye ST, Kawamura H. Characteristics of a circadian pacemaker in the suprachiasmatic nucleus. J Comp Physiol 1982;146:153–160
4. Welsh DK, Logothetis DE, Meister M, et al. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythm. Neuron 1995;14:697–706
5. Hasting M. The brain, circadian rhythms, and clock genes. BMJ 1998; 317:1704–1707
6. Gekakis N, Staknis D, Nguyen HB, et al. Role of the CLOCK protein in the mammalian circadian mechanism. Science 1998;280:1564–1569
7. Schwartz WJ, Smith CB, Davidsen LC. In vivo glucose utilization of the suprachiasmatic nucleus. In: Suda M, Hayaishi O, Nakagawa H, eds. Biological Rhythms and Their Central Mechanism. New York, NY: Elsevier/North-Holland Biomedical Press; 1979
8. Czeisler CA, Richardson GS, Coleman RM, et al. Chronotherapy: resetting the circadian clocks of patients with delayed sleep phase insomnia. Sleep 1981;4:1–21
9. Weitzman ED, Nogeire C, Perlow M, et al. Effects of a prolonged 3-hour sleep-wake cycle on sleep stages, plasma cortisol, growth hormone and body temperature in man. J Clin Endocrinol Metab 1974;38:1018–1030
10. Kilduff TS, Kushida CA. Circadian regulation of sleep. In: Chokroverty S, ed. Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects. 2nd ed. Boston, Mass: Butterworth-Henieman; 1999:135–145
11. Edgar DM, Dement WC, Fuller CA. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. J Neurosci 1993;13:1065–1079
12. Cajochen C, Wyatt JK, Czeisler CA, et al. Separation of circadian and wake duration-dependent modulation of EEG activation during wakefulness. Neuroscience 2002;114:1047–1060
13. Cassone VM. Effects of melatonin on vertebrate circadian systems. Trends Neurosci 1990;13:457–464
14. Brzezinski A. Melatonin in humans. N Engl J Med 1997;336:186–195
15. Weaver DR, Stehle JH, Stopa EG, et al. Melatonin receptors in human hypothalamus and pituitary: implications for circadian and reproductive responses to melatonin. J Clin Endocrinol Metab 1993;76:295–301
16. Liu C, Weaver DR, Jin X, et al. Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. Neuron 1997; 19:91–102
17. Dijk DJ, Shanahan TL, Duffy JF, et al. Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement

sleep phase with phase of circadian melatonin rhythm in humans. J Physiol 1997;505:851–858
18. Weitzman ED, Czeisler CA, Coleman RM, et al. Delayed sleep phase syndrome: a chronobiological disorder with sleep-onset insomnia. Arch Gen Psychiatry 1981;38:737–746
19. Hayes B, Czeisler CA. Chronobiology of human sleep and sleep disorders. In: Touitou H, Haus E, eds. Biologic Rhythms in Clinical and Laboratory Medicine. New York, NY: Springer-Verlag; 1992:256–264
20. Toh KL, Jones CR, He Y, et al. An *hPer2* phosphorylation site mutation in familial advanced sleep phase syndrome. Science 2001;291:1040–1043
21. Knauth P, Rutenfranz J. Experimental shift work studies of permanent night and rapidly rotating shift systems. Int Arch Occup Environ Health 1976;37:125–137
22. Richardson GS, Malin HV. Circadian rhythm sleep disorders: pathophysiology and treatment. J Clin Neurophysiol 1996;13:17–31
23. Hajak G, Rodenbeck A, Staedt J, et al. Nocturnal plasma melatonin levels in patients suffering from chronic primary insomnia. J Pineal Res 1995; 19:116–122
24. Lack LC, Mercer JD, Wright H. Circadian rhythms of early morning awakening insomniacs. J Sleep Res 1996;5:211–219
25. Garfinkel D, Laudon M, Nof D, et al. Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet 1995;346:541–544