The Implications of Chronobiology for Psychiatry

by Anna Wirz-Justice, PhD

Chronobiology—the science of daily (circadian), monthly, tidal, and seasonal rhythms—has undergone exponential growth in the past decade, with major discoveries at the molecular and neuroanatomic level. The most ubiquitous rhythms are those linked to the 24-hour day-night cycle. These circadian rhythms manifest themselves at every hierarchical level: from the general population (eg, more traffic accidents late at night) to the individual (eg, the sleep-wake cycle), in each organ, cell, and molecule. Rhythmic change provides the temporal organization necessary for optimum behavior—the right function at the right time.

The field of chronobiology is exemplary in its bench-to-bedside translational approach. Groundbreaking research into the genetic clockwork covers all phyla, from cyanobacteria to the weed *Arabidopsis,* utilizing the rich mutant possibilities in fruit flies and mice and scanning for polymorphisms of clock genes in clinical disorders. On the basis of this research, novel, nonpharmacological treatments for chronobiological disorders have been developed. Chronotherapeutics is defined as controlled exposure to stimuli that act on biological rhythms (eg, light) or direct manipulations of sleep to treat psychiatric disorders.

Biological rhythms are not new to psychiatry. The 19th century German psychiatrists, in particular, collected enormous numbers of case studies that demonstrated periodicity in psychopathology. In 1960, Menninger-Lerchenthal[1] proposed a hypothalamic neuroendocrine mechanism to underlie the astonishing precision of daily and seasonal rhythms in clinical symptoms and behavior—a very prescient prediction that has been characterized in detail by modern research.

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DISCLOSURES

Dr Wirz-Justice has no relationships to disclose relating to the subject matter of this article. Applicable CME LLC staff have no relationships to disclose relating to the subject matter of this activity.

This activity has been independently reviewed for balance.

TARGET AUDIENCE

This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

GOAL STATEMENT

This activity provides information that will enable participants to treat depressive patients with novel nonpharmacological chronotherapeutic measures.

ESTIMATED TIME TO COMPLETE

The activity in its entirety should take approximately 90 minutes to complete.

LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Better appreciate what constitutes chronobiology
- Understand how the circadian system works, including the related neurobiology (eg, suprachiasmatic nuclei, zeitgeber, circadian oscillators) and its involvement in sleep regulation
- Recognize the importance of the relationship between biological rhythms, sleep, and affective disorders
- Implement treatment options and strategies for affective disorders, in particular light therapy and wake therapy

COMPLIANCE STATEMENT

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The circadian system

A master pacemaker, or biological clock, resides in the hypothalamic suprachiasmatic nuclei (SCN) and generates circadian rhythms in the entire organism (**Figure 1**).[2] One of the most obvious outputs of the biological clock is the sleep-wake cycle. The timing and architecture of sleep is regulated by interactions between the circadian clock and a homeostatic process of rising sleep pressure that depends on the duration of prior wakefulness and dissipates during sleep.[3]

A clock gene network in the SCN encodes for endogenous periodicity, usually slightly longer than 24 hours, and requires daily synchronization to the external day-night cycle.[2] Circadian regulation interacts with, and is determined by, neurotransmitter function; for example, the SCN receives serotonergic input from the raphe nuclei that may modulate the response of the SCN to light and nonphotic stimuli. CNS serotonin turnover undergoes marked circadian and seasonal rhythmicity and is rapidly stimulated by light exposure.[4] Direct serotonergic manipulation by an SSRI can reset the clock in vitro.[5]

The major synchronizing agent, or "zeitgeber," for the SCN is light, transmitted directly from the retina via the retinohypothalamic tract.[6] The photic input to the SCN is nonvisual. Thus, classic cone and rod photoreceptors, important for vision—color, movement, shape, edges—play a secondary role to novel circadian photoreceptors located in retinal ganglion cells. These contain the photopigment melanopsin that is sensitive to blue light.[7] One important pathway from the SCN leads to the pineal gland, where the hormone melatonin is synthesized at night. Melatonin secretion is suppressed by light and feeds back onto melatonin receptors in the SCN.[6]

The primary characteristic of a zeitgeber is that it can shift the phase of circadian rhythms in different directions, depending on time of day. Both light and melatonin are zeitgebers. Morning light and evening melatonin administration advance the clock to earlier; evening light and morning melatonin administration delay the clock to later (thus their use for combating jet lag).

Wake therapy is the most rapid antidepressant known: approximately 60% of patients respond with marked improvement within hours, a finding that has been replicated in thousands of cases.

Even though the SCN is the so-called master clock, circadian oscillators are found in every organ and in every cell (**Figure 1**).[2] Moreover, each organ has its own appropriate zeitgeber. Light is the major zeitgeber for the SCN, but it does not affect the clock in the liver—the zeitgeber for the liver is food. Adequate temporal organization is important for coordinating functions that need to occur together and for separating those that are antagonistic (eg, we want to have low cortisol levels in the evening before sleep and high cortisol levels on awakening). Therefore, the brain and body clocks, which tick at their own frequencies in every cell, are dependent on regular daily zeitgeber exposure for good coordination.

It is easy to imagine how desynchronization might occur between different body clocks and between the timing of body rhythms and the day-night cycle (such as occurs with shift work or when crossing time zones). With insufficient zeitgebers, even correctly functioning biological clocks can become desynchronized.[6] Anyone who has experienced jet lag and shift work sleep disturbances can understand that good entrainment is a prerequisite not only for consolidated nighttime sleep and daytime alertness but also for adequate mood state, cognition, and neurobehavioral function. Circadian dysentrainment does not necessarily cause psychopathology, but it may perpetuate or exacerbate clinical symptoms.[8]

For example, Bromundt and colleagues[9] looked at the repercussions of circadian rhythm characteristics on cognitive performance and psychopathology in 14 patients with schizophrenia. **Figure 2** shows circadian rest-activity cycles in 3 of these patients: one very well entrained, one with irregular sleep times, and the third with extremely disrupted day-night rhythms. When the Trail Making Test was applied to assess attention, psychomotor speed, cognitive flexibility, and executive function (**Figure 3**), there was a high correlation between the degree of consolidated circadian rhythms (as measured by relative amplitude of the day/night difference), and cognitive functioning in these patients with schizophrenia.

Nonphotic zeitgebers, such as physical exercise, sleep, and food, also contribute to entrainment of peripheral clocks. Social zeitgebers, such as jobs and social demands, act indirectly on the SCN, since they determine the timing of meals, sleep, physical activity, and outdoor and indoor light exposure, and they have been construed as a therapeutic option.[10]

Biological rhythms and affective disorders

Periodicity is most striking in affective disorders: illness recurrence ranges from seasonal depression to rapid-cycling manic-depressive episodes. The symptoms of diurnal variation of mood and early morning awakening suggest rhythmic dysfunction. Circadian rhythms, including hormonal secretion, neurotransmitter function, and body temperature, are altered in timing (phase), amplitude, and day-to-day stability.[11,12]

Dysregulation of circadian rhythms and sleep disturbances are also core elements of bipolar disorder and might be involved in its pathogenesis.[13] Insomnia often appears before and predicts the onset of mood disorder symptoms[14]; sleep disturbances are a frequent residual symptom of depression, and insomnia marks an increased risk of relapse or recurrence. Any misalignment of sleep and rhythms brings with it the propensity for mood fluctuation, particularly in vulnerable individuals.[8] A dramatic example is the greater incidence of depressive episodes after a westward flight or manic episodes after flying east.[15]

Light therapy

The first studies of seasonal affective disorder (SAD) were initiated 30 years ago.[16] If SAD arose from the environmental trigger of shortened days, then light simulating a summer day was the logical treatment—and it worked. Light therapy emerged as the first successful treatment in psychiatry based on neurobiological principles and is now established as the treatment of choice for SAD.[17] Significantly, light is also an effective antidepressant in nonseasonal depression.[18-20]

As an adjuvant to antidepressants in unipolar depressive patients or to lithium in bipolar patients, morning light hastens and potentiates the

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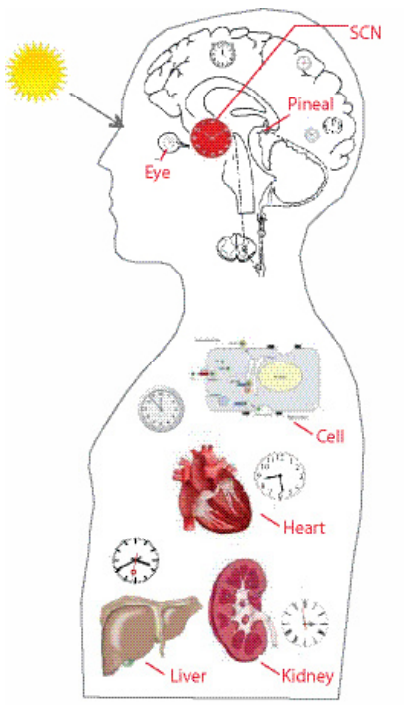
Figure 1 The human circadian system



The major pacemaker resides in the suprachiasmatic nuclei (SCN), with direct input from the light-dark cycle via melanopsin photoreceptors in retinal ganglion cells. A mutisynaptic pathway leads from the SCN to the pineal gland, site of melatonin synthesis. Circadian clocks are found in all neurons of the brain and all cells of the body. Examples of organ clocks are the eye, heart, liver, and kidneys.

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antidepressant response.[18-20] Light therapy confers benefit even for patients with chronic depression of 2 years or more[21] and for geriatric patients with depression.[22] Light therapy is also a viable alternative for patients who refuse, resist, or cannot tolerate medication or for whom drugs may be contraindicated, as in those with antepartum depression.[23] In addition, light therapy has been used successfully in other psychiatric or neurological illnesses, including bulimia nervosa, childhood and adult ADHD, borderline personality disorder, Alzheimer dementia, and Parkinson disease.[24-26] In sleep medicine, light is used as a zeitgeber to resynchronize disturbed sleep schedules (eg, in delayed or advanced sleep phase syndrome, shift work, and jet lag disturbances).[17]

Light boxes are the standard, most tested devices used in light therapy (see Terman M, Terman JS,[17] and Center for Environmental Therapeutics [CET][27] for details). The optimal antiglare design requires a downward-tilted diffusion screen with a UV filter; 10,000 lux at a distance of approximately 12 inches (30 to 33 cm) is recommended.

Long-term exposure to wavelengths between 400 and 500 nm may induce photochemical retinal injury, called the blue light hazard; this has been implicated in age-related macular degeneration. Thus, recommended light boxes provide broad-spectrum white illumination and filter wavelengths lower than 450 nm to minimal levels.[28] Even though the circadian photoreceptor system is most sensitive in this short wavelength range,[7] there are no long-term safety or efficacy studies to allow narrow-band blue light devices to be recommended at present.

The timing of light therapy is important for optimum outcome in SAD patients.[17] Optimum timing needs to be individually defined, since not everyone has similar body clocks and sleep-wake cycle timing ("owls" and "larks"). The patient's sleeping habits provide an indirect estimate of internal body clock time, and feedback from a chronotype questionnaire (eg, the Horne-Ostberg Morningness-Eveningness Questionnaire), available on www.cet.org, can be used to gauge the best time to begin light therapy.[27]

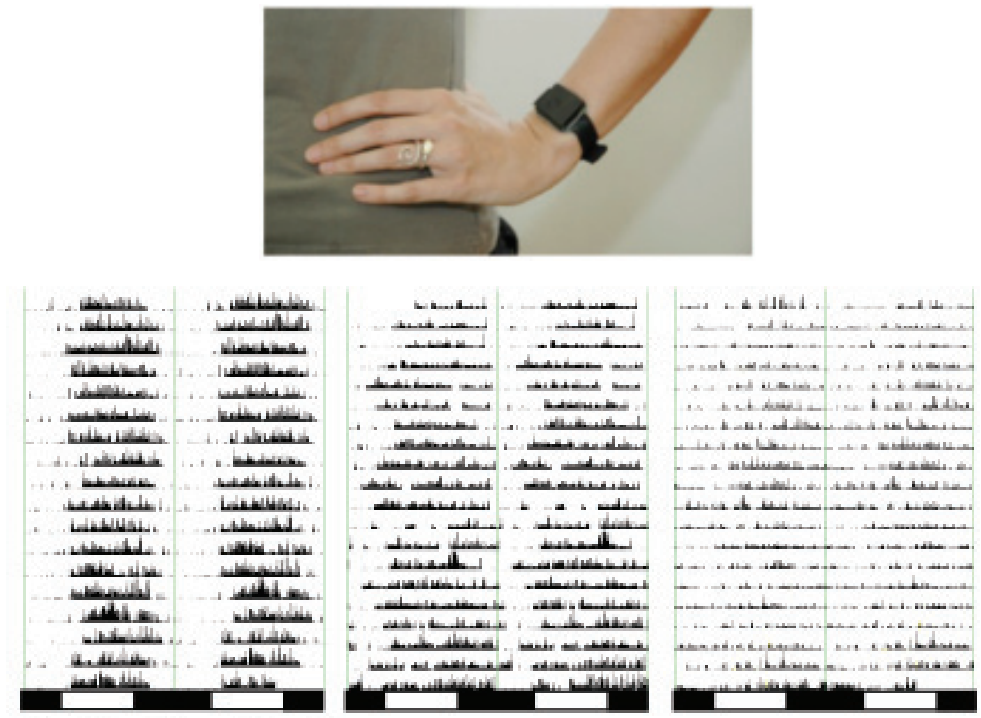
Adverse effects are rare. Infrequent adverse effects include hypomania in bipolar patients, mild visual complaints, irritability, headache, and nausea, which usually subside within a few days of treatment or with dose decreases.[17] If sleep disturbances emerge, they are usually related to timing and can be rapidly adjusted (late evening light can lead to difficulties in falling asleep and early morning light, to premature awakening).

No obvious light-induced ophthalmological pathology has been documented following years of white light therapy.[29] There are no definite contraindications other than retinopathies and awareness of putative interactions with photosensitizing medications.[17,27]

Dawn simulation is a novel alternative to the light box. Simulation of a naturalistic dawn produces a relatively dim signal that gradually rises over 45 minutes or longer from about 0.001 lux (starlight) to approximately 300 lux (sunrise), which is presented during the last period of the patient's sleep episode. This technique obviates time spent in front of a light box and is similarly effective.[17] However, the effectiveness of dawn simulation may depend on the presentation of diffuse, broad-field illumination that reaches the sleeper in varying postures. This is not the case for bedside commercial alarm clock lamps, which have small, directional fields and a ramp rise in light intensity over a short period.

There are no FDA-approved devices for the treatment of SAD. However, partial or full insurance reimbursement for light box purchases is now common, following the example of Empire

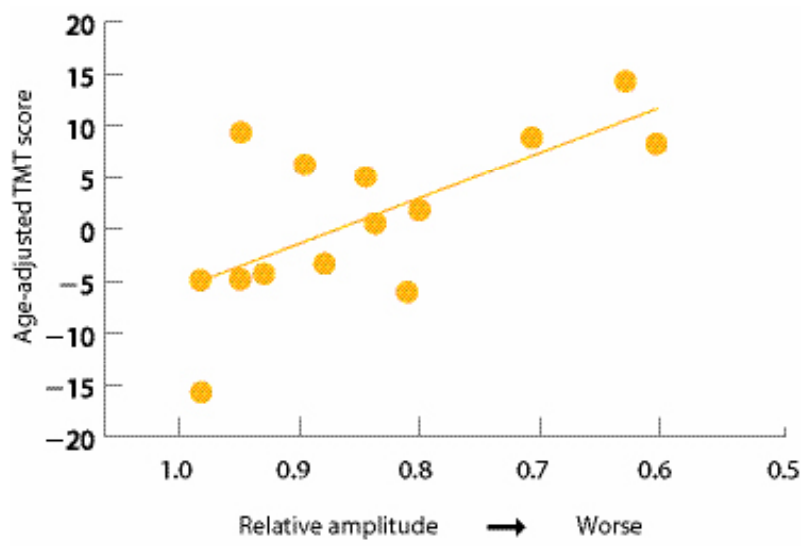
Figure 2 Circadian rest-activity cycles



Circadian rest-activity cycles in 3 patients with schizophrenia measured with an actimeter worn on the nondominant arm: data double-plotted over 48 hours, sequential days below each other. The range from highly synchronized to low-amplitude, poorly entrained rhythms can be seen.

Adapted from Bromundt V et al. *Br J Psychiatry.* 2011.[9]

Figure 3 Correlation of the day/night difference (relative amplitude) with the Trail Making Test (TMT) scores in all schizophrenic patients (N = 14; R^2 = 0.45; *P* = .009)



The Trail Making Test assesses attention, psychomotor speed, cognitive flexibility, and executive functions. Findings indicate that the lower the circadian rhythm amplitude, the worse the patient performs on this test.

Adapted from Bromundt V et al. *Br J Psychiatry.* 2011.[9]

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BlueCross BlueShield in 2004. A prescription is required for the light box; patients can submit a claim to their insurance company for reimbursement. The appropriate diagnostic code for mood or circadian rhythm disorder should be listed with the physician's letter of endorsement.

Wake therapy

The slow response to most antidepressants is a big problem for psychiatrists and their depressed patients. In remarkable contrast is the improvement within hours afforded by staying awake all night. This apparently paradoxical behavioral treatment of major depression—a night of total sleep deprivation—was first scientifically studied 40 years ago. It is the most rapid antidepressant we know: approximately 60% of patients respond with marked improvement within hours, a finding that has been replicated in thousands of cases.[24] Timing the sleep deprivation to the second half of the night, with equivalent effects, suggests a circadian component in the response—and not just that of being awake. A third sleep manipulation that supports this interpretation is that when sleep is shifted a few hours earlier—without deprivation—a slower, but longer-lasting antidepressant effect is induced.

Several combination strategies have been used to maintain the rapid response after wake therapy. The most studied protocol has added daily morning light therapy to concomitant administration of antidepressants or lithium.[30-32] In patients with bipolar I disorder, 70% with no history of drug resistance improved rapidly with the brief intervention and 57% remained euthymic at 9-month follow-up. The rate was lower in drug-resistant patients; however, the 44% response in these patients is still remarkable when compared with standard antidepressant drug response rates.[33] Thus, a short-term chronotherapeutic protocol can induce long-term remission. Adding sleep phase advance for 3 days after sleep deprivation to regular light therapy also results in long-term maintenance of response.[34,35] For patients who relapse, further sessions can be used.

Wake and light therapy may also reduce duration of hospitalization. In a general psychiatric hospital setting, the combination of wake therapy (3 sessions over a week) with antidepressants resulted in discharge 3 days sooner than drug treatment alone.[33] Furthermore, retrospective analyses have revealed a 3-day advantage for patients exposed to more natural light in sunny hospital rooms than those staying in dimmer rooms.[36,37]

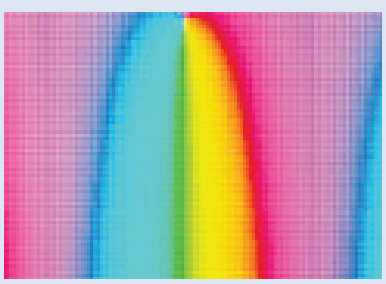
Table

Chronotherapeutic applications for major depression

- Light therapy for SAD, nonseasonal depression
- Light therapy as adjuvant to SSRIs (nonseasonal depression, chronic depression, therapy-resistant depression) or lithium (bipolar disorder)
- Total sleep deprivation (wake therapy)
- Partial sleep deprivation in the second half of the night
- Phase advance of the sleep-wake cycle
- Combinations of sleep manipulations with antidepressants, lithium, light therapy
- Dark or rest therapy to stop rapid cycling
- Dark therapy for mania
- Evening melatonin to enhance circadian phase advances with light
- Melatonin for sleep disturbances in those who are blind or visually impaired

SAD, seasonal affective disorder.

Biological Rhythms and Psychiatric Illness



Most patients with psychiatric diagnoses present with sleep disturbances that can have as great an impact on health-related quality of life as the mental illness itself.[48] Sleep disturbances are usually treated with sleep-promoting psychopharmacological agents—benzodiazepines or newer hypnotics. Although these sleep-wake rhythm disturbances are not as closely linked to causation as in bipolar disorder, there is accumulating evidence that the worse the entrainment to the 24-hour day, the worse the clinical symptoms.

Disturbed sleep-wake cycles in patients with schizophrenia were correlated with poor cognitive function.[9] In patients with borderline personality disorder, they were correlated with atypical depressive symptoms and daytime sleepiness.[49] The primary chronobiological postulate is that integrity of the circadian sleep-wake cycle, as the most obvious output of the biological clock, promotes healthy functioning in all psychiatric disorders.[8]

This reformulates the classic strategy of establishing stable daily structures to support the process of clinical improvement in neurobiological terms and extends its purview to pragmatic techniques to promote re-entrainment. Light therapy may be a helpful additional therapeutic option.[49] ■

Image © iStockphoto.com

Dark therapy

Another chronotherapeutic element, dark therapy, focuses on darkness, particularly in bipolar patients. Keeping acutely manic patients in dark rooms during the night has been shown to improve symptoms and immediately stop rapid cycling.[38-40] Dark therapy is interesting because the response to it is so rapid, but it is not very practical. One alternative being investigated is the use of blue-blocking sunglasses to induce "circadian darkness" while not impairing the patient's vision.[41]

Melatonin

The hormone melatonin, secreted by the pineal gland, is a signal of darkness as well as of night length (and its concomitant in seasonal change).[42] The evening rise in serum melatonin level sets a thermophysiological cascade in motion (warm hands and feet and heat loss, followed by cooling of core body temperature) that prepares the organism for sleep.[43] If rhythms are out of sync, as in depression, melatonin is secreted at the wrong time and the sleep disturbance is accentuated. Not a sedative per se, exogenously administered melatonin acts as a zeitgeber to synchronize circadian rhythms and promote sleep onset.[42]

Melatonin has not been shown to have major effects on mood in trials with healthy persons and those with insomnia, and depressive symptoms may worsen with melatonin.[44] There is a great deal of research in treating sleep disturbances with melatonin in persons who are blind or visually impaired, since it provides the zeitgeber signal that they lack.

The broad availability of melatonin as an over-the-counter supplement promotes its indiscriminate use. Even more worrying are melatonin-containing beverages. Lack of quality control or patent protection means that there are limited safety data and lack of controlled trials for specific indications. An exception is the slow-release prescription formulation of melatonin, Circadin (Lundbeck), approved in the European Union for sleep disturbances in the elderly. In the United States, 2 melatonin agonists have FDA approval:

- Rozerem (Takeda) for insomnia
- Tasimelteon (Vanda), which has completed phase 3 clinical trials and has been granted orphan drug status, for circadian rhythm distur-

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bances in the blind

The melatonin agonist agomelatine (Valdoxan, Servier), approved in the European Union, should not be put in the same category. Like melatonin, it acts as a zeitgeber to establish regular sleep but has additional antidepressant properties related to the serotonergic antagonist component, which make it an interesting novel drug to treat depression.[45]

Pragmatic guidelines for chronotherapeutic combinations

A treatment manual has been written under the auspices of the nonprofit CET to provide practical chronotherapy guidelines for clinicians.[24] Chronotherapeutic combinations are flexible and should be implemented step-by-step according to the patient's response. Concomitant antidepressants as required are included to provide treatment as usual. Chronotherapeutic options usually begin with light therapy for patients who cannot sustain wake therapy. A second step is light therapy combined with a single night's sleep deprivation. A third step includes a 3-day phase advance. The full combination of light therapy, 3 times wake therapy, and 3-day sleep phase advance will not be necessary or feasible in all cases, but it can be the trigger for complete symptom remission in major depression.

CASE VIGNETTE

Ms F, aged 21, had experienced a manic episode followed by an anergic depression that lasted nearly 8 months despite treatment with sodium valproate, lithium, and quetiapine at adequate therapeutic levels. The following year, when she lapsed back into the same anergic, hypersomnic, emotionally flat depression, she was attracted to the ultra-rapid response potential of chronotherapeutics in addition to her ongoing lithium treatment.

Using an outpatient facility and full-time staff coverage during her waking hours, Ms F was treated with an initial night of total sleep deprivation, followed by 3 days of sleep phase advance (ie, sleep period from 6 PM to 1 AM the first night, 8 PM to 3 AM the second night, and 10 PM to 5 AM the third night). In addition, 10,000 lux light therapy was administered for 30 minutes in the morning, timed according to her chronotype.

Ms F's score on the SIGH-SAD-SR (self-rating Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders) was 29 before the procedure. As is typical for this protocol, she experienced an improvement within the first 18 hours of treatment. Her posttreatment SIGH-SAD-SR score on day 5 was 2. This improvement has persisted for several months without further treatment except ongoing lithium and daily bright light therapy.

While chronotherapy case studies lack blinded treatments and control groups, the case for the use of chronotherapy to treat Ms F is strengthened by her nonresponse to multiple mood-stabilizing and antidepressant medications during her first episode of depression compared with a rapid and sustained response during her second episode (J. Gottlieb, personal communication, 2011).

A list of chronotherapeutic applications is found in the **Table**. More details are found in the consensus report of a committee convened by the International Society for Affective Disorders and in the chronotherapy manual.[24,46]

Despite good evidence for efficacy of these chronotherapeutic methods, the limited use of these treatments is surprising and a true cause for concern. Obviously, treatments that are not patentable do not make profits, thus denying the commercial marketing model used for drugs. Nonetheless, the advantages for the patient of rapidity of action, minimal adverse effects, combination with ongoing medication, and long-term maintenance of improvement would be considered a convincing sales pitch were the treatments wrapped up in pill form.

In Europe, a number of inpatient units use these methods routinely.[30,31] The first US clinic to use chronotherapy, founded 7 years ago (www.columbia-chronotherapy.org), has had some success with light therapy for treatment-resistant patients on an inpatient unit.[47] It has been encouraging to see the opening of a first outpatient program in psychiatric chronotherapy (www.chicagochronotherapy.org).

Conclusion

Chronotherapeutic measures provide an untapped potential for the unmet needs in the treatment of depression. Wake and light therapy are safe, with minimal adverse effects. The accumulated data on light therapy support its broader application in psychiatric clinical practice to improve sleep-wake cycles and not just mood.

References

1. Menninger-Lerchenthal E. *Periodizität in der Psychopathologie*. Vienna: Wilhelm Maudrich Verlag; 1960.

2. Hastings MH, Maywood ES, Reddy AB. Two decades of circadian time. *J Neuroendocrinol.* 2008;20:812-819.

3. Daan S, Beersma DGM, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol Regul Integr Comp Physiol.* 1984;246:R161-R178.

4. Lambert GW, Reid C, Kaye DM, et al. Effect of sunlight and season on serotonin turnover in the brain. *Lancet.* 2002;360:1840-1842.

5. Sprouse J, Braselton J, Reynolds L. Fluoxetine modulates the circadian biological clock via phase advances of suprachiasmatic nucleus neuronal firing. *Biol Psychiatry.* 2006;60:896-899.

6. Cajochen C, Chellappa S, Schmidt C. What keeps us awake? The role of clocks and hourglasses, light, and melatonin. *Int Rev Neurobiol.* 2010;93:57-90.

7. Hankins MW, Peirson SN, Foster RG. Melanopsin: an exciting photopigment. *Trends Neurosci.* 2008;31:27-36.

8. Wirz-Justice A, Bromundt V, Cajochen C. Circadian disruption and psychiatric disorders: the importance of entrainment. *Sleep Med Clin.* 2009;4:273-284.

9. Bromundt V, Köster M, Georgiev-Kill A, et al. Sleep-wake cycles and cognitive functioning in schizophrenia. *Br J Psychiatry.* 2011 Jan 24; [Epub ahead of print].

10. Grandin LD, Alloy LB, Abramson LY. The social zeitgeber theory, circadian rhythms, and mood disorders: review and evaluation *Clin Psychol Rev.* 2006;26:679-694.

11. Wirz-Justice A. Biological rhythm disturbances in mood disorders. *Int Clin Psychopharmacol.* 2006;21(suppl 1):S11-S15.

12. Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol.* 2008;23:571-585.

13. Dallaspezia S, Benedetti F. Melatonin, circadian rhythms, and the clock genes in bipolar disorder. *Curr Psychiatry Rep.* 2009;11:488-493.

14. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord.* 2011 Feb 5; [Epub ahead of print].

15. Jauhar P, Weller MP. Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. *Br J Psychiatry.* 1982;140:231-235.

16. Rosenthal NE, Sack DA, Gillin JC, et al. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry.* 1984;41:72-80.

17. Terman M, Terman JS. Light therapy. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medecine*. 5th ed. St Louis: Elsevier/Saunders; 2010:1682-1692.

18. Even C, Schröder CM, Friedman S, Rouillon F. Efficacy of light therapy in nonseasonal depression: a systematic review. *J Affect Disord.* 2008;108:11-23.

19. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry.* 2005;162:656-662.

20. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database Syst Rev.* 2004;(2):CD004050.

21. Goel N, Terman M, Terman JS, et al. Controlled trial of bright light and negative air ions for chronic depression. *Psychol Med.* 2005;35:945-955.

22. Lieverse R, Van Someren EJ, Nielen MM, et al. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. *Arch Gen Psychiatry.* 2011;68:61-70.

23. Wirz-Justice A, Bader A, Frisch U, et al. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *J Clin Psychiatry.* 2011;72:986-993.

24. Wirz-Justice A, Benedetti F, Terman M. *Chronotherapeutics for Affective Disorders: A Clinician's Manual for Light and Wake Therapy*. Basel, Switzerland: S Karger AG; 2009.

25. Riemersma-van der Lek RF, Swaab DF, Twisk J, et al. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA.* 2008;299:2642-2655.

26. Willis GL, Turner EJ. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. *Chronobiol Int.* 2007;24:521-537.

27. Center for Environmental Therapeutics. http://www.cet.org. Accessed August 18, 2011.

28. MD Support: The Eyes of the Macular Degeneration Community. http://www.mdsupport.org. Accessed August 18, 2011.

29. Gallin PF, Terman M, Remé CE, et al. Ophthalmologic examination of patients with seasonal affective disorder, before and after bright light therapy. *Am J Ophthalmol.* 1995;119:202-210.

30. Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev.* 2007;11:509-522.

31. Martiny K, Refsgaard E, Lund V, et al. Wake therapy yields sustained response and remission. A rater-blind 9 weeks controlled study using a chronotherapeutic intervention compared to exercise. *Eur Psychiatry.* 2011;26(suppl 1):2031.

32. Martiny K. Adjunctive bright light in non-seasonal major depression. *Acta Psychiatr Scand Suppl.* 2004;(425):7-28.

33. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. *J Clin Psychiatry.* 2005;66:1535-1540.

34. Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry.* 2009;66:298-301.

35. Moscovici L, Kotler M. A multistage chronobiologic intervention for the treatment of depression: a pilot study. *J Affect Disord.* 2009;116:201-207.

36. Beauchemin KM, Hays P. Sunny hospital rooms expedite recovery from severe and refractory depressions. *J Affect Disord.* 1996;40:49-51.

37. Benedetti F, Colombo C, Barbini B, et al. Morning sunlight reduces length of hospitalization in bipolar depression. *J Affect Disord.* 2001;62:221-223.

38. Barbini B, Benedetti F, Colombo C, et al. Dark therapy for mania: a pilot study. *Bipolar Disord.* 2005;7:98-101.

39. Wehr TA, Turner EH, Shimada JM, et al. Treatment of rapidly cycling bipolar patient by using extended bed rest and darkness to stabilize the timing and duration of sleep. *Biol Psychiatry.* 1998;43:822-828.

40. Wirz-Justice A, Quinto C, Cajochen C, et al. A rapid-cycling bipolar patient treated with long nights, bedrest, and light. *Biol Psychiatry.* 1999;45:1075-1077.

41. Phelps J. Dark therapy for bipolar disorder using amber lenses for blue light blockade. *Med Hypotheses.* 2008;70:224-229.

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42. Cajochen C, Kräuchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol.* 2003;15:432-437.
43. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Warm feet promote the rapid onset of sleep. *Nature.* 1999;401:36-37.
44. Carman JS, Post RM, Buswell R, Goodwin FK. Negative effects of melatonin on depression. *Am J Psychiatry.* 1976;133:1181-1186.
45. Arendt J, Rajaratnam SM. Melatonin and its agonists: an update. *Br J Psychiatry.* 2008;193:267-269.
46. Wirz-Justice A, Benedetti F, Berger M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med.* 2005; 35:939-944.
47. Terman M. Evolving applications of light therapy. *Sleep Med Rev.* 2007;11:497-507.
48. Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. *J Fam Pract.* 2002;51:229-235.
49. Bromundt V, Wirz-Justice A, Kyburz S, et al. Circadian sleep-wake cycles, well-being and light therapy in borderline personality disorder. *J Personality Disord.* In press.

Additional Information

Center for Environmental Therapeutics (www.cet.org; www.chronotherapeutics.org; accessed August 19, 2011) is a non-profit Web site for patients and clinicians, with access to self-rating scales for chronotype (morningness-eveningness questionnaire), depression status, seasonality, and information about light therapy. The site also provides downloads of relevant clinical assessment instruments and a privacy-protected forum for clinicians to exchange experiences with the new methods. ❐

CATEGORY 1 POSTTEST

In order to receive *AMA PRA Category 1 Credits™*, posttests and activity evaluations must be completed online at <www.PsychiatricTimes.com/cme>.

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The activity can be accessed online the 15th of the month at www.PsychiatricTimes.com/cme.

To speak to a customer service representative, call (800) 447-4474 or (201) 984-6278 (M - F, 9 AM to 6 PM Eastern Time).

1. Chronobiology is
   A. The study of the functional circuits of the brain that mediate behavior
   B. The study of environmental and societal influences on psychopathology
   C. The study of circadian, monthly, tidal, and seasonal rhythms
   D. The study of temperature fluctuations in humans

2. The process of clinical improvement in patients with mental health disorders should combine stable daily structure and pragmatic techniques to promote re-entrainment.
   A. True
   B. False

3. A zeitgeber is
   A. An agent synchronizing circadian rhythms to the 24-hour day
   B. The standard, most tested treatment device used to treat sleep disorders
   C. A psychotherapeutic technique used to reset a person's biological clock
   D. None of the above

4. The first treatment with chronotherapy usually begins with light therapy.
   A. True
   B. False

5. Dysregulation of circadian rhythms and sleep disturbances may play a role in
   A. Rapid-cycling manic-depressive episodes
   B. Seasonal affective disorder
   C. Depression
   D. All of the above
   E. None of the above

6. The optimum intensity of a light box used in light therapy should be
   A. 500 lux
   B. 1000 lux
   C. 5000 lux
   D. 10,000 lux
   E. None of the above

7. Wake therapy—a night of total sleep deprivation—has been successfully used to alleviate symptoms of
   A. Bipolar mania
   B. Major depressive disorder
   C. Anxiety disorder
   D. PTSD

8. Melatonin secretion by the pineal gland generally occurs at
   A. Midday
   B. Dawn
   C. Twilight
   D. Nightfall

9. In patients with borderline personality disorder, disturbed sleep-wake cycles were correlated with
   A. Episodes of psychosis
   B. Reduced cognitive function
   C. Atypical depressive symptoms
   D. None of the above

10. The master biological clock that generates circadian rhythms in the entire organism is found in the
    A. Nucleus accumbens
    B. Hypothalamic suprachiasmatic nuclei
    C. Dorsal raphe nuclei
    D. Basal ganglia

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Erratum

The Goal Statement for the Category 1 CME activity that appeared in the September 2011 issue of Psychiatric Times *was incorrect. The statement should have read: This activity will provide participants with a better understanding of the efficacy and safety issues associated with antidepressant treatment of patients with alcohol and substance use disorders that are comorbid with depression and anxiety.*