



Light therapy and other interventions that target the body's biological clock could help treat depression and other mood disorders

Is Internal Timing Key to Mental Health?

EVERY YEAR, AFTER THE COLORS OF autumn faded from the trees and left barren branches to herald the winter, Herbert Kern would feel his mental skies darken. As the days shortened, the middle-aged materials researcher would retreat from almost all social interaction. The routine was so familiar to Kern's colleagues at Bell Labs in Murray Hill, New Jersey, that they would not expect much work from him during those winter months in the 1970s. The seasonality of Kern's depression was reflected in the pocket notebooks in which he kept a log of his life. "During the rest of the year, I could fill a notebook every 2 weeks; in the winter, it would take months," recalls Kern. Neither the few approved antidepressants of the time nor lithium injections did anything to help.

Then, in the late '70s, Kern learned about research in animals showing that melatonin, a hormone regulated by the light-dark cycle of day and night, plays a role in controlling seasonal behaviors such as mating. Wondering if the hormone had something to do with his condition, he got in touch with psychiatrist and melatonin specialist Alfred Lewy at the National Institute of Mental Health (NIMH) in Bethesda, Maryland, who was wrapping up a study demonstrating that exposure to bright light during the night suppressed nighttime secretion of the hormone in normal humans. When Kern sank into

depression the following winter—in December 1980—Lewy's team exposed him to a few hours of light in the dark mornings and evenings, trying to match the amount of natural light of a spring day. After a few days of the treatment, "I began to be bubbly again," says Kern, who later continued the regimen at home. "It worked like magic."

Kern's case, and 3 years of follow-up work, led researchers to identify winter depression as a psychiatric illness that subsequently came to be known as seasonal affective disorder. SAD has since been shown to afflict millions of people, primarily in the northern latitudes, and a recent analysis by the American Psychiatric Association (APA) in Arlington, Virginia, provided a strong endorsement for light therapy as a treatment. And yet it's not settled how light, or other interventions that target the circadian clock, helps people with SAD.

SAD provides the strongest evidence to date of a link between the biological clock—the body's 24-hour timekeeper—and mental health, a proof of principle that circadian rhythms that are out of sync could underlie some mood disorders. But there is increasing evidence that circadian disturbances are involved in other common mental ailments such as bipolar disorder and more obscure ones such as a syndrome in which people compulsively eat at night. In

recent years, psychiatrists working with small groups of patients have shown that correcting abnormal circadian rhythms—through exposure to light, melatonin pills, or even sleep deprivation—can help treat some of these disorders and can also benefit patients with neurodegenerative illnesses such as Alzheimer's. Some drug companies are even taking heed. "The circadian model is clearly beginning to bear fruit," says David Avery, a psychiatrist at the University of Washington School of Medicine in Seattle. "It is logically getting extended beyond SAD and should lead to better treatments for a number of psychiatric disorders."

The fog about light

When Kern contacted Lewy at NIMH, scientists already knew that all mammals have a master clock in the brain's suprachiasmatic nucleus, which regulates the waxing and waning concentration of numerous hormones and proteins in the body over an approximately 24-hour cycle. They also knew that the rhythms of many of these body chemicals—including melatonin, secreted by the pineal gland during darkness—were synchronized to the light-dark cycle of the environment. In treating Kern with light, the NIMH researchers—led by Lewy and his senior colleague, Thomas Wehr—simply simulated the earlier dawn and later dusk of

spring, hoping that by shortening the duration of melatonin secretion, they'd lift Kern out of his depression.

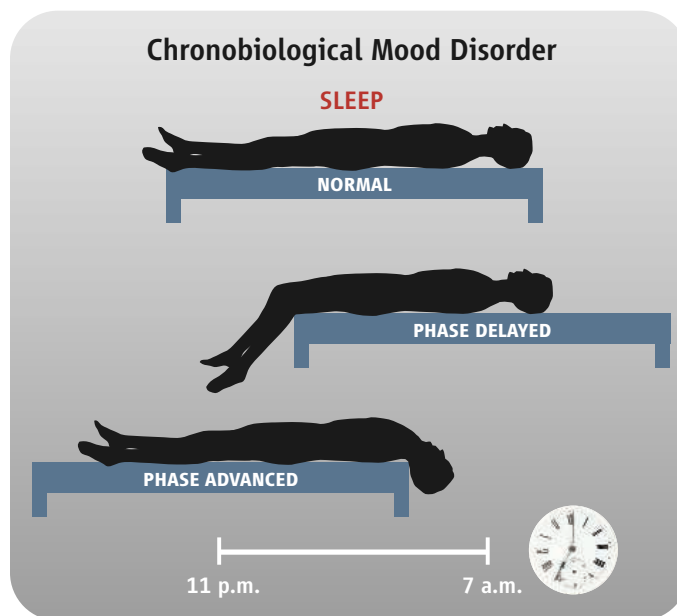
Although it worked—and has since proven effective in treating many other cases of SAD—Wehr and Lewy formed different opinions about light therapy's mechanism. Wehr grew convinced that the antidepressant effect was a result of the artificially lengthened daytime, which led to less melatonin secretion and presumably had downstream effects leading to an improvement in the patient's mood. Lewy instead came to believe that the effect was due to the resetting of the patient's circadian clock, not the overall duration of melatonin production. In most SAD patients, he argued, the depression was the result of circadian clocks being out of sync with respect to the sleep-wake cycle, like a chronic form of jet lag. The theory has become known as the phase-shift hypothesis.

Last year, researchers led by Lewy—who has been at Oregon Health and Science University in Portland since 1981—presented the strongest evidence to date for this theory. Rather than using bright lights to reset the circadian clock, Lewy and his colleagues gave SAD patients melatonin pills. (The body's melatonin rhythm is tightly coupled to rhythms of other hormones such as cortisol and serotonin, and researchers have established that administering melatonin is a way to shift all of those rhythms en bloc.) People normally start secreting melatonin a couple of hours before bedtime to prime the body for sleep, so administering the hormone in the afternoon should advance a patient's circadian clock relative to his sleep-wake cycle. If given in the morning, it should have the opposite effect.

By making patients stick to their regular sleep times, the researchers ensured that their sleep-wake cycle remained constant throughout the study. After 3 weeks, they found that SAD patients whose circadian clocks normally lagged behind their sleep-wake cycle did better when they received afternoon melatonin and worse when they were given the hormone in the morning. The treatments had the opposite effects on those whose cycles were shifted the other way. Lewy points out that the treatments increased the duration of melatonin production, yet patients improved when their cycles were brought into sync. "If Tom [Wehr] was right,

these people should have gotten worse," he says. Lewy notes that the melatonin results are consistent with previous studies showing that morning light is significantly better at treating SAD than evening light (which corresponds to there being a higher proportion of phase-delayed rather than phase-advanced individuals among SAD patients).

Wehr, who retired from NIMH in 2003 and is now a practicing psychiatrist in Bethesda, Maryland, remains unconvinced. He points to animal studies showing that morning light brings about a quicker end to melatonin secretion without really affecting the hormone's onset time in the evening. It's possible, he argues, that afternoon melatonin led Lewy's patients to stop secreting the hormone a lot earlier than normal the following morning, in effect shortening the length of their melatonin production. To settle the question, Wehr says, researchers would need to keep a continuous track of the patients' 24-hour melatonin profile.



Out of sync. Some researchers believe that misalignments between certain circadian rhythms and the sleep-wake cycle may be a driver of mental illnesses.

Lewy's hypothesis does not rule out the possibility that additional mechanisms are involved in light's antidepressant action. Some studies have shown, for example, that exposure to sunlight can increase brain levels of serotonin—a neurotransmitter associated with well-being—and Lewy says it's possible that serotonin is related to circadian alignment. To get a full mechanistic account of the clock's role in mental health, researchers still need to understand what cellular events are triggered when out-of-sync rhythms are snapped back into phase with each other, and

by the same token, what happens in the brain when rhythms go awry—as they do even in healthy individuals who are jet-lagged.

Beyond SAD

A better understanding of these mechanisms could shed light on disorders beyond SAD, for abnormal circadian rhythms are turning out to be a factor in a number of other mental illnesses. Two years ago, in *Chronobiology International*, Vishwajit Nimgaonkar and his colleagues at the University of Pittsburgh Medical Center in Pennsylvania reported that among 75 patients with bipolar disorder, internal biological clocks—as measured by a questionnaire probing activity and sleep patterns—tended to be disturbed in comparison to those of a set of normal individuals.

And in two ongoing studies, researchers led by Anna Wirz-Justice of the Centre for Chronobiology at the Psychiatric University Clinic in Basel, Switzerland, are finding abnormal circadian rhythms in schizophrenic patients and in patients with borderline personality disorder. (The preliminary results from the studies were presented at the annual meeting of the Society for Light Treatment and Biological Rhythms in Copenhagen, Denmark, in June.) Also this summer, at a meeting on biological clocks and rhythms at Cold Spring Harbor Laboratory in New York state, psychiatrist Namni Goel of the University of Pennsylvania reported that many 24-hour hormonal rhythms in patients with night eating syndrome were either advanced or delayed with respect to the sleep-wake cycle.

Some researchers suspect that defects in the gears of the body's biological clock, caused by genetic mutations, will be shown to play a role in mental health problems. They point to studies such as one reported last year by

Colleen McClung and her colleagues at the University of Texas Southwestern Medical Center in Dallas. The researchers created mice missing the *Clock* gene—which encodes a key protein in the machinery of the circadian system—and found that the animals showed manic behaviors, becoming hyperactive and keener to take risks. Expressing the *CLOCK* protein in the animals' midbrains restored behavior of the mutant mice to normal, McClung and her colleagues further reported in the 10 April issue of the *Proceedings of the National Academy of Sciences* this year.

If disrupted circadian rhythms contribute to mental illnesses other than SAD, those conditions could also benefit from light therapy. Indeed, researchers have begun testing this idea in small groups of patients, and they say the results look promising.

Nearly 200 people with Alzheimer's disease, spread across 10 homes for the elderly, are now helping researchers test whether light therapy can alleviate some symptoms of the fatal neurodegenerative disease—one of which is disturbed sleep-wake rhythms. Psychiatrist Eus J. W. van Someren of the Netherlands Institute for Neuroscience in Amsterdam and his colleagues have installed bright light fixtures in the lounges of six of the homes; at the remaining sites, they installed similar but fewer lights to set up the lighting equivalent of a placebo. Van Someren says that the unpublished preliminary results, based on more than 4 years of data, show that bright light improved

biking. Although how the technique works is poorly understood, psychiatrists routinely use sleep deprivation to produce a rapid emotional lift in deeply depressed patients, including those hospitalized after a failed suicide attempt.

Benedetti and others have shown that this dramatic effect, which invariably vanishes after a day, can be sustained for several weeks by using light therapy to shift the patient's sleep-wake cycle in the days that follow. The idea again is to bring the circadian rhythms back in alignment. The researchers have reported, in a study published in *The Journal of Clinical Psychiatry* in 2005, that combining light therapy with initial sleep deprivation can effectively treat bipolar patients. In a more recent study involving 55 bipolar patients, presented at the Cold Spring Harbor meeting by University of California, Irvine, psychiatrist Joseph Wu, those who received a treatment package including antidepressant

Wisconsin School of Medicine and Public Health in Madison, declared in April 2005 in *The American Journal of Psychiatry* that “the effects of light therapy are comparable to those found in many antidepressant pharmacotherapy trials.” However, the authors lamented the relatively small number of studies that met their criteria for the analysis—only 20 out of a total of 173 that were initially identified—and they noted that “additional randomized, controlled trials with appropriate numbers of subjects are needed.”

Until even a few years ago, “people looked at us as if we were some kind of strange witch healers,” says Benedetti, who began combining light therapy with sleep deprivation in the 1980s. Still, with recent data showing that drugs do not significantly help up to 40% of patients with mood disorders, he says, “there is a growing interest in chronobiological methods of treatment.”

Unfortunately, proponents of such methods say, funding has been hard to come by, in part because of the perception that effective antidepressants are available. Michael Terman, a psychiatrist at Columbia University, recalls that one grant application turned down by the National Institutes of Health contained this comment: “Why do we need a new antidepressant modality when we already know that drugs work?” The proposed work, a randomized trial testing light therapy in pregnant women with depression, is now being funded by the Swiss National Science Foundation.

“The pharma-driven model is so strong that it is difficult to win support for studying anything that does not involve drugs,” says Wirz-Justice.

Nonetheless, the French pharma company Servier has patented a melatonin agonist called agomelatine that is now undergoing clinical trials in Europe and in the United States as a treatment for depression. Merck has also set up a research group to look into the circadian basis of mood and sleep disorders in hopes of developing more effective drugs. “As therapies go, it would be far easier to pop a pill than carry around a fluorescent bulb,” says Anthony Gotter, a member of the group.

Kern, who is now practically blind from macular degeneration, would welcome a pill substitute. He says that light therapy became less and less effective for him over the years as his eyesight faded. “Now I can hardly see, and all hell has broken loose,” he says with surprising cheer in his voice. “I have had periods of depression lasting over a year, and highs lasting as long. I think my clock is just running freely, without any control by the environment. I don't know when I'm going to feel what.”

—YUDHIJIT BHATTACHARJEE



Dispelling gloom. Psychiatrist Alfred Lewy wants to understand why light therapy (being set up, *above*) works in patients with seasonal affective disorder.

the sleep-wake rhythms of patients. He claims the data also show that it slowed their cognitive decline, hinting that the disturbed circadian rhythms were a partial cause.

Light and melatonin are not the only interventions that researchers are using in their attempts to treat mental disorders by tinkering with the circadian clock. Francesco Benedetti, a psychiatrist at the San Raffaele Scientific Institute in Milan, Italy, has spent the last decade studying the antidepressant effects of total sleep deprivation—a strategy discovered by chance in the 1960s when German clinicians observed significant improvement in a depressed patient who had spent the night

medication, light therapy, and sleep-wake adjustment following total sleep deprivation did significantly better than those who only received medication.

Witch healers?

Such studies seem to be making an impression on the broader psychiatric community. In 2005, a group set up by APA to examine the efficacy of light therapy concluded from a meta-analysis of published literature that the treatment significantly reduced depression symptoms in SAD, as well as in other mood disorders. The group, led by psychiatrist Robert Golden, now at the University of