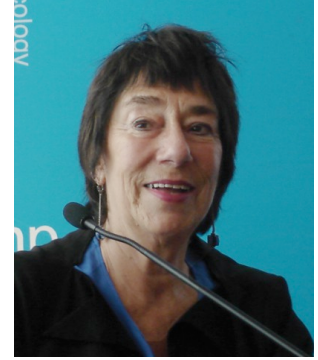


Chronotherapeutics Corrects Circadian Rhythm Abnormalities in Many Psychiatric Disorders

By Caroline Helwick
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Anna Wirz-Justice

AMSTERDAM (EGMN) –Circadian dysfunction can greatly affect brain function – impairing behavior, cognition, and affect – and can be improved with a “chronotherapeutic” approach, according to one of the leading researchers in the field. Anna Wirz-Justice, Ph.D., professor emeritus at the center for chronobiology at Psychiatric University Clinics in Basel, Switzerland, who is one of the leading researchers in this field. She coauthored the treatment manual, “Chronotherapeutics for Affective Disorders: A Clinician’s Manual for Light and Wake Therapy” (Basel: Karger, 2009).

“In the treatment of affective disorders, chronotherapeutics offers a new synthesis of nonpharmacologic interventions designed to accelerate remission. Combining it with concomitant or follow-up medications shows great promise,” said Dr. Wirz-Justice, who has led numerous investigative studies in the field and lectured on the role of circadian rhythms in affective disorders at the annual congress of the European College of Neuropsychopharmacology.

Circadian rhythms are directed by a master biological clock in the suprachiasmatic nucleus (SCN) as well as circadian oscillators in all brain regions and peripheral tissues. The SCN is synchronized daily by environmental signals, mainly light. Receiving information on lighting conditions directly from the retina, the SCN drives secretion of melatonin and regulates peripheral “clocks,” whose outputs modulate the SCN through feedback or feed-forward effects.

Specific circadian genes such as CLOCK, BMAL1, and PER are responsible for the main SCN “clock-working” machinery. New interest in the role of circadian dysregulation in psychiatric disorders has arisen from the finding that a mutation in a core circadian clock gene induces hyperactivity, decreased sleep, and manialike behavior in mice.

“Animal studies were the key development that brought the field to its present exciting position, by suggesting that ‘clock genes’ are directing the circadian rhythms in all physiological processes,” she said.

Clinical Impact on Affective Disorders

In healthy individuals, physiological and biochemical variables such as

body temperature, cortisol and melatonin, thyroid stimulating hormone, norepinephrine and serotonin exhibit circadian rhythms. However, in patients with affective disorders, many of these rhythms are disturbed in phase and amplitude.

For instance, in major depressive disorder (MDD), most patients present with sleep disturbances and altered circadian rhythms, including hormonal secretion, cardiac function and body temperature. Sleep disruption is a major symptom in depression and is often the factor prompting depressed persons to seek medical help.

Synchronizing impaired circadian rhythms through “chronotherapeutics” – improving sleep or paradoxically staying awake most of the night – can be extremely helpful in treating patients with MDD and bipolar disorder, but the approach is not limited to depression. In addition to major depression (seasonal and nonseasonal), chronotherapeutics indications include bipolar disorder, premenstrual dysphoric disorder and depression during pregnancy, bulimia nervosa, attention-deficit/hyperactivity disorder, dementia, Parkinson’s disease and shift work and jet-lag disturbances, according to Dr. Wirz-Justice.

“Light therapy has been used to resynchronize disturbed sleep schedules back to a more normal pattern. Light is also an effective antidepressant, acting on many of the same neurotransmitter systems and brain structures as antidepressant drugs,” she said.

“The new message is that light therapy is not just for seasonal affective disorder but for all forms of depression and for many other disorders,” she added. “As an adjuvant to antidepressants in unipolar depressive patients or to lithium in bipolar patients, morning light hastens and potentiates the antidepressant response. Light therapy shows benefit even for patients with chronic depression of 2 years or more and provides a viable alternative for patients who refuse, resist, or cannot tolerate medication.”

Elements of chronotherapy include light therapy, dark therapy or blue-blocking sunglasses, wake therapy (total or partial sleep deprivation in the second half of the night), phase advance of the sleep-wake cycle, and exogenously administered melatonin.

Sleep Deprivation and Dark Therapy

A 1-night sleep deprivation, or “wake therapy,” is the most rapid antidepressant known, according to Dr. Wirz-Justice. A single night’s sleep deprivation induces similar brain changes as many weeks of antidepressant drugs (Curr. Pharm. Des. 2009;15:2637-49).

“Approximately 60% of patients, independent of diagnostic subtypes, respond with marked improvement within hours,” she said. “Mostly, however, they relapse after recovery sleep, which indicates how important wakefulness must be. We have found you can prevent relapse by

combining daily light therapy with antidepressants or lithium or a short phase advance of sleep over 3 days.”

Dark therapy (defined as keeping patients in a dark setting and extending rest-sleep for periods of 10-14 hours) has yielded positive results in controlling symptoms in acute mania and calming rapid-cycling bipolar patients in the manic phase, she said. Because this approach is impractical, an alternative being investigated is the use of blue-blocking sunglasses. Blue is the wavelength to which the circadian system is particularly sensitive, thus by blocking this range in the light spectrum one can induce “circadian darkness” while not impairing vision, she explained.

Dr. Wirz-Justice is advocating wider use of these techniques in psychiatry and their incorporation into residency programs. “In clinical practice, there is still rather widespread ignorance about circadian sleep disturbances and chronotherapeutics in spite of the significant evidence base,” she said. “Enterprising doctors should try this out, and the techniques should be taught in residency programs.”

Disclosures: Dr. Wirz-Justice reported no potential conflicts of interest.

For more information on chronotherapeutics, check out the Center for Environmental Therapeutics’ [Web site](#).

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