

Chronotherapeutics Corrects Circadian Rhythms

BY CAROLINE HELWICK

EXPERT ANALYSIS FROM THE ANNUAL CONGRESS OF THE EUROPEAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AMSTERDAM – Circadian dysfunction can greatly affect brain function – impairing behavior, cognition, and affect – and can be improved with a “chronotherapeutic” approach, according to Anna Wirz-Justice, Ph.D., one of the leading researchers in the field.

Dr. Wirz-Justice, professor emerita at the center for chronobiology at Psychiatric University Clinics in Basel, Switzerland, 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 congress.

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 respon-

sible 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 mania-like 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,” Dr. Wirz-Justice said.

Clinical Impact on 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 who have 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, Dr. Wirz-Justice said, but the approach is not limited to depression.

In addition to major depression (seasonal and nonseasonal), chronotherapeutics indications include bipolar dis-

order, 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,” Dr. Wirz-Justice said.

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 brain changes similar to those that result from many weeks of antidepressant drugs (Curr. Pharm. Des. 2009;15:2637-49).

“Approximately 60% of patients, in-

dependent 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.

Since this approach is impractical, an alternative that is 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 at www.chronotherapeutics.org.

Psoriasis Tied to Increased Risk of Psychiatric Disorders in Kids

BY SHARON WORCESTER

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF DERMATOLOGY

MIAMI – Children with psoriasis have a significantly greater risk of developing a psychiatric disorder than do those without psoriasis, according to findings from a large, retrospective, case-control study.

Nationally representative health plan data for 7,404 children with psoriasis aged younger than 18 years found that 5.1% were diagnosed with or treated for a psychiatric disorder after health plan enrollment, compared with 4.1% of 37,020 controls. Psoriasis patients were particularly more likely to be diagnosed with depression (3%) or anxiety (1.8%), compared with controls (2.4% and 1.4%, respectively), Carol Bao, Ph.D., reported during a poster discussion session at the meeting.

For children with psoriasis, the estimated hazard ratio for developing any psychiatric disorder was 1.25, for developing depression was 1.23, and for developing anxiety was 1.32, said Dr. Bao, a senior manager at Abbott Laboratories, Chicago.

The investigators also looked at prescriptions for psychotropic medications in assessing risk for development

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Data Source: A large, retrospective, case-control study of 7,404 children with psoriasis under age 18 years and 37,020 controls.

Disclosures: Abbott Laboratories sponsored the study.

of psychiatric disorders. Prescriptions can be a marker for a diagnosis in cases where the prescribing physician may be hesitant to refer the patient or make a diagnosis, Dr. Bao explained, noting that this helped correct for possible underestimation of the development of psychiatric disorders and provided a risk estimate range.

When both diagnoses and prescriptions were considered, psoriasis patients had 25%-47% greater risk of developing a psychiatric disorder, 23%-62% greater risk of developing depression, and 32%-250% greater risk of developing anxiety, compared with controls, she said.

Patients included in the study had a mean age of 11.4

years. They were selected from a database of health plan participants who were enrolled in a plan at least 6 months before and after the first psoriasis diagnosis date (the index date), and who were followed from the index date until they were first diagnosed with any psychiatric disorder or were prescribed a drug used for the treatment of a psychiatric disorder. Any plan participant with a preenrollment psychiatric diagnosis or prescription was excluded.

Controls were matched to patients based on age, sex, and index date.

The findings of an increased risk of developing psychiatric disorders in case patients remained significant after controlling for age, sex, health plan, region of residence, and comorbidities, Dr. Bao noted.

The study is limited by the potential for coding and reporting errors in the data used and by lack of information on the severity of the psychiatric disorders. However, the findings do suggest that the psychiatric impact of psoriasis on children must be addressed because of the potential for both short- and long-term adverse effects.

“If we put these data in perspective, the development of psychiatric disorders at a young age can have a great impact in future adult life,” she said. ■