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Invited commentary

From the basic neuroscience of circadian clock function to light therapy for depression: On the emergence of chronotherapeutics

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Biological psychiatry seeks to establish the genetic, neurochemical, and physiological basis of mental disorders and their treatments. Chronobiology, or biological rhythm research, has made a set of discoveries in recent years across these same levels of functional organisation. And psychiatric chronotherapeutics is the fast-growing application of circadian principles in treating mood and sleep disorders.

The most provocative data come from understanding the interactions between the ever-growing number of “clock” genes discovered in all species from unicellular organisms to humans, that provide the molecular clockwork programming the “day within” (Maywood et al., 2007). This genetic programme anticipates the appropriate function or behaviour to occur at the right time of the 24-hour day, and separates incompatible functions from each other in time. Clock genes tick at their endogenous frequency in every cell and every organ of the body. It is obvious that this clock orchestra needs a conductor to keep all rhythms intact.

A circadian pacemaker in the brain, a group of approximately 10,000 neurons in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus, functions as this conductor, driving and synchronising all 24-hour rhythms in the body—whether the sleep–wake cycle, hormonal output, or even at

the psychologic level of performance and mood (Maywood et al., 2007).

The SCN, when isolated in a petri dish, also ticks at its endogenous frequency, which arises from coupling between individual neurons, each manifesting the frequency of their constitutive clock genes (Beersma et al., 2008). Both individual cells and the SCN have a circadian period somewhat different from—in humans usually longer than—24 h. Thus, in order to synchronise to the 24-hour day–night cycle, the SCN requires daily entrainment signals, so-called zeitgebers, of which light is the most important.

Light synchronises the SCN by means of a neuronal tract from a group of specialised ganglion cells in the retina containing the novel photopigment melanopsin, primarily sensitive to blue-wavelength light (Hankins et al., 2008). This non-visual photic input tells the SCN whether it is dawn or dusk, light or dark—it is separate from, but interacts with, the rods and cones of the retina, sending photic input to the normal visual system. Light in the morning advances the timing of the SCN clock; light in the evening delays it. Thus, the daily resetting to a strict 24-hour rhythm occurs by subtle shifts induced by light exposure at the twilight transitions.

The pineal hormone melatonin, synthesised only at night and suppressed by light, provides the body with a signal of darkness (Arendt, 2006). The length of the night (seasonal change) is mirrored in the length of nocturnal melatonin

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secretion. The hormone also feeds back on the SCN, which is rich with melatonin receptors. Exogenous melatonin thus can act as a zeitgeber when the pineal is inactive, shifting the biological clock earlier when administered in the evening, or later when administered in the morning.

Much is known of the circadian system wiring diagram: from retina to SCN and other brain regions, input pathways to the SCN (e.g. a serotonergic pathway from the raphe providing non-photic information), the links to sleep-regulating areas (e.g. the ventrolateral preoptic area), and the neurotransmitters involved in these pathways.

Such is the synopsis of biological clock function from the basic neuroscience perspective. The relevance to psychiatry—in particular affective disorders—lies in the broad evidence base documenting rhythm disturbances in these illnesses (Germain and Kupfer, 2008).

Periodicity in psychopathology is most evident in bipolar disorder. The illness is cyclic, often remarkably so. Physiological studies show that sleep–wake cycles, temperature rhythms, and many other measures shift their timing with clinical state—delayed during depression, advancing in mania. The switch out of depression is often accompanied by a spontaneous night of sleep loss; conversely, a prescribed sleep deprivation can be rapidly antidepressant. Furthermore, a phase advance of sleep timing can induce longer-lasting antidepressant effects. In unipolar depression the evidence is less homogeneous, but again, many rhythms show circadian phase abnormalities, lower (weaker) amplitude, and increased day-to-day variability.

So how do we jump from the lab to the clinic? Light therapy derives from basic research showing that seasonal rhythms of hibernation or reproduction in the hamster could be mimicked or reversed by manipulating daylength—more specifically, by changing the duration of melatonin secretion to simulate a winter or summer night. Patients with seasonal affective disorder (SAD) were hypothesised to have abnormal responses to diminishing daylength in autumn—and thus could be treated with morning light signalling a spring dawn. The treatment has been remarkably successful and is now used world wide (Terman and Terman, 2005; Terman, 2007).

Light is first of all a circadian intervention. It can shift phase, increase amplitude, and stabilise rhythms. It is not limited to treating SAD—many other psychiatric illnesses are accompanied by disrupted circadian sleep–wake cycles. Evidence is emerging that the worse the entrainment of the sleep–wake cycle, the worse the psychiatric symptoms, independent of diagnosis. Light also acts like a drug—it directly affects similar neurotransmitter substrates as the antidepressants. The wider application of psychiatric chronotherapeutics seeks to implement methods such as light, melatonin, and blue-blocking glasses (= circadian darkness), to improve entrainment and thereby clinical state, cognitive behaviour, and mood.

Manipulation of sleep timing has proved antidepressant in thousands of patients over the last thirty years, acting in a matter of hours (Benedetti et al., 2007; Wirz-Justice and Van den Hoofdakker, 1999). Sleep deprivation (total or confined to the second half of the night) and sleep phase advance have been used by many psychiatrists to achieve rapid response, but these methods are still far from standard on the inpatient unit. Newer studies have overcome the main disadvantage of

sleep deprivation—relapse after recovery sleep—using adjunct light therapy, SSRIs, and lithium and pindolol (in bipolar patients) (Benedetti et al., 2007).

ISAD convened a Committee on Chronotherapeutics in 2004 to advance the use of sleep deprivation (wake therapy) and light therapy in major depression, with the hope that a consensus statement would get colleagues interested (Wirz-Justice et al., 2005), since these non-pharmacologic treatments are not patentable, and thus are not marketed. Not much has happened, unfortunately.

Psychiatrists and pharmacologists alike are searching for new antidepressants that might fulfil the unmet needs of rapid onset with fewer residual symptoms. Why don't we use the methods we already have? Why isn't sleep deprivation and light therapy routine for inpatients and outpatients alike? They are exemplary for biological psychiatry research leading to new treatments (the buzz-word 'translational' really applies here). Their application will depend on learning a few simple techniques beyond drug administration. To explain how this effort is highly worthwhile, in particular for the patient in a depressive episode, we have written a treatment manual for step-by-step implementation of chronotherapeutic methods for treating depression (Wirz-Justice et al., 2009).

Chronotherapeutics works. A single week of treatment—which can be combined with medication as necessary—can get depressed patients out of hospital under remission, with lower relapse rate months later. The first chronotherapeutics combination studies are extremely promising (Benedetti et al., 2007; Wu et al., in press; Moscovici and Kotler, in press; Martiny et al., in press). We look forward to discussions in a new professional forum hosted by the nonprofit Center for Environmental Therapeutics (www.chronotherapeutics.org), where colleagues can debate, troubleshoot, and contribute to the transition of chronotherapeutics into general psychiatric practice.

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