

Chronotherapeutics and Science

A Selection of Abstracts

These abstracts are but a very minute glimpse of what has been published on the subject. For an extensive list of relevant reading, please consult www.cet.org.

Wirz-Justice A, Benedetti F, Berger M, Lam RW, Martiny K, Terman M, Wu JC: Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med* 2005;35:939–944.

The Committee on Chronotherapeutics, delegated by the International Society for Affective Disorders (ISAD), makes the following recommendations after reviewing the evidence as of November 2004. (1) Wake therapy is the most rapid antidepressant available today: approximately 60% of patients, independent of diagnostic subtype, respond with marked improvement within hours. Treatment can be a single or repeated sleep deprivation, total (all night) or partial (second half of the night). Relapse can be prevented by daily light therapy, concomitant administration of SSRIs, lithium (for bipolar patients), or a short phase advance of sleep over 3 days following a single night of wake therapy. Combinations of these interventions show great promise. (2) Light therapy is effective for major depression--not only for the seasonal subtype. As an adjuvant to conventional antidepressants in unipolar patients, or 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, outperforming their weak response to drugs. This method provides a viable alternative for patients who refuse, resist or cannot tolerate medication, or for whom drugs may be contraindicated, as in antepartum depression. (3) Given the urgent need for new strategies to treat patients with residual depressive symptoms, clinical trials of wake therapy and/or adjuvant light therapy, coupled with follow-up studies of long-term recurrence, are a high priority.

Wirz-Justice A, Bromundt V, Cajochen C: Circadian disruption and psychiatric disorders: the importance of entrainment. *Sleep Med Clin* 2009, in press.

Strong evidence for an involvement of the circadian clock in psychiatric disorders has emerged. Indeed some of the major hallmarks of diseases such as major depressive disorder, bipolar disorder, Alzheimer's disease and schizophrenia are abnormal sleep/wake, appetite, and social rhythms. In addition, many of the successful treatments in psychiatry affect circadian rhythms, and it appears that the phase shifts, resetting and stabilisation of rhythms produced by these treatments are important for therapeutic efficacy. Psychiatric disorders account for more than 25% of inpatient beds worldwide, and disturbed sleep-wake cycles in patients are a top-cited reason for the choice of inpatient care. For this reason, the relationship between circadian disruption and psychiatric disorders is a topic of great medical relevance.

Bunney JN, Potkin SG: Circadian abnormalities, molecular clock genes and chronobiological treatments in depression. *Br Med Bull* 2008;86:23-32.

BACKGROUND: A long-standing challenge in the treatment of depression is the development of a rapidly acting antidepressant. Conventional antidepressants typically require 2-8 weeks for clinical remission. In contrast, chronobiological interventions such as sleep deprivation treatment dramatically reduce depressive symptoms within 24-48 h in 40-60% of depressed subjects. It is hypothesized that fast-acting treatments for depression may alter circadian rhythms through chronobiological mechanisms relevant to clock gene function. SOURCES OF DATA: A bibliographic review using Entrez PubMed with Boolean search terms 'circadian' and 'depressive' identified more than 1000 clinical papers published over a 40-year period (1966-present). AREAS OF AGREEMENT: A large body of clinical data reports that sleep, temperature, hormone and mood changes in depression are consistent with disturbances in circadian-related processes. AREAS OF CONTROVERSY: Consensus has not been achieved in terms of defining underlying chronobiological mechanisms for optimal methods to produce rapid and sustained antidepressant responses to circadian interventions. GROWING POINTS: Chronobiological augmentation using combinations of sleep deprivation with light therapy and/or sleep phase advance in medicated patients supports a clinical strategy for accelerating and sustaining antidepressant responses. AREAS TIMELY FOR DEVELOPING RESEARCH: Advances in technology including improved assays for clock gene expression will facilitate exploring the role of clock genes and may lead to new rapidly acting antidepressant strategies and potential novel drug targets.

Terman M, Terman JS: Light therapy; in Krieger M, Roth T, Dement W (eds): *Principles and Practice of Sleep Medicine, ed 5. Philadelphia, Elsevier, 2009, in press.*

The susceptibility of the circadian system to selective phase shifting by timed light exposure has broad implications for the treatment of sleep-phase and depressive disorders. Light therapies have been developed to normalize the patterns of delayed sleep phase disorder (through circadian phase advances) and advanced sleep phase disorder (through circadian phase delays). Doctors and patients need to be cognizant of the daily intervals when light exposure—and darkness—can facilitate or hamper adjustment to the desired circadian phase. The critical intervals lie at the edges of the “subjective night,” which coincide with the tails of the nocturnal melatonin cycle, but can be inferred clinically through a morningness-eveningness questionnaire or habitual sleep timing. The schedule of light exposure may have to be continually adjusted during treatment as the subjective night shifts gradually in the desired direction.

The treatment strategy for seasonal and nonseasonal depression is similar. In winter depression, the size of circadian rhythm phase advances correlates with the degree of mood improvement, and the optimum timing of light therapy must be specified relative to the individual's circadian clock rather than solar time. Apart from its use as a monotherapy, light therapy in both outpatient and inpatient trials indicates that it accelerates remission of nonseasonal depression in conjunction with antidepressant and mood-stabilizing medication.

This chapter provides the clinician with guidelines for selecting lighting apparatus based on safety, efficacy, and comfort factors; summarizes adverse effects of light overdose; and offers a protocol to guide the selection of treatment time.

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

Psychiatric chronotherapeutics is the controlled exposure to environmental stimuli that act on biological rhythms in order to achieve therapeutic effects in the treatment of psychiatric conditions. In recent years some techniques (mainly light therapy and sleep deprivation) have passed the experimental developmental phase and reached the status of powerful and affordable clinical interventions for everyday clinical treatment of depressed patients. These techniques target the same brain neurotransmitter systems and the same brain areas as do antidepressant drugs, and should be administered under careful medical supervision. Their effects are rapid and transient, but can be stabilised by combining techniques among themselves or together with common drug treatments. Antidepressant chronotherapeutics target the broadly defined depressive syndrome, with response and relapse rates similar to those obtained with antidepressant drugs, and good results are obtained even in difficult-to-treat conditions such as bipolar depression. Chronotherapeutics offer a benign alternative to more radical treatments of depression for the treatment of severe depression in psychiatric wards, but with the advantage of rapidity of onset.

Benedetti F, Smeraldi E: Neuroimaging and genetics of antidepressant response to sleep deprivation: implications for drug development. Current Pharmaceutical Design 2009, in press

Despite confirmed evidences about some neurochemical effects of antidepressant treatments, there is still an high level of uncertainty about which biological changes are needed to recover from a major depressive episode. Changes of monoaminergic neurotransmission are paralleled by profound changes in brain metabolism, neural responses to stimuli, sleep architecture, biological rhythms, and, at the intracellular level, neuronal signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms.

Sleep deprivation targets the biological mechanisms which are responsible of the possibility, unique to mood disorders, of rapid switching between depression, euthymia, and mania. The rapidity of action of sleep deprivation enables the study of the correlates of antidepressant response at close time points, providing a good model to study the biological basis of the antidepressant response and of the pathophysiology of affective illness.

Current knowledge suggests that multiple neurobiological effects of sleep deprivation are responsible for the clinical mood amelioration, suggesting a multi-target mechanism of action. An impressive group of brain imaging studies using different brain imaging techniques (positron emission tomography, single photon emission tomography, functional magnetic resonance imaging, proton spectroscopy, arterial spin labeling) showed that clinical response is associated

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with changes in the functioning of specific brain areas. The combination of these new methodological acquisitions with the classical neurobiological and pharmacogenetic perspective provides an evolving knowledge about brain changes associated with antidepressant response, and will then help to identify the real targets of antidepressant treatment.