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Chronobiological strategies for unmet needs in the treatment of depression

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Chronobiological strategies may provide an effective means of addressing some of the unmet needs in the treatment of depression, such as shortening the latency of onset of antidepressant action, combating residual symptoms, and preventing relapse in the long term. Light is the treatment of choice for winter depression (or seasonal affective disorder, SAD). Light therapy given as an adjuvant to medication in major nonseasonal depression, as well as in chronic and therapy-resistant depression, speeds up and potentiates clinical response. Light is also efficacious in bipolar depression; in these patients "dark therapy" (long nights) can diminish manic symptoms and stop rapid cycling. Total or partial sleep deprivation in the second half of the night (better known as "wake therapy") induces marked improvement the following day. This amelioration can be maintained with concomitant treatment with antidepressants, lithium, light therapy, sleep phase advance, or combinations thereof. Careful control of the light-dark cycle and of the timing of mealtimes, activity, and sleep may appear to be old-fashioned methods ("daily structures") belonging to a long obsolete custodial psychiatry. However, these apparently simple methods gain new validation when reconsidered within the framework of modern chronobiology, since when appropriately timed, application of "zeitgebers" can aid treatment of affective disorders.

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The field of chronobiology studies 24-hour biological clocks (the circadian system) and their synchronizers ("zeitgebers") such as light, the pineal hormone melatonin, food, activity, as well as the factors regulating sleep.[1] Light therapy has arisen out of this basic research in circadian rhythms, whereas, in contrast, sleep deprivation ("wake therapy") was established by astutely following up clinical observations.[2] Chronotherapeutics can be defined as translating basic chronobiology research into valid treatments. The term is broad, and the treatments subsumed under this heading will grow as the field grows, and are of course not limited to affective disorders (there is an important body of evidence, for example, that the correct timing of cancer treatments augments survival and diminishes the often potent side effects).

The theme of meeting unmet needs in the treatment of depression is important and timely. The onset of action of antidepressants is still not rapid enough, a proportion of patients do not respond, others have residual symptoms that predict relapse. Although medication based on classic neurotransmitter systems is still a prime focus, drug targets other than monoamines are under intensive investigation.[3] Strategies promoting adjuvant therapy are on the increase, whether they encompass combination with other medications (eg, addition of pindolol, of thyroid hormone) or psychological interventions (eg, cognitive behavioral therapy). Mainstream psychiatry is becoming more and more eclectic, implementing a variety of approaches to help the individual patients. The question to be discussed here is focused on why not also combine the chronobiological strategies of light therapy and/or wake therapy with psychopharmacological medication? Light therapy has undergone widespread controlled randomized clinical trials, and wake therapy has been so widely studied over decades that the efficacy data are strong. These nonpharmaceutical, biologically based therapies are not only powerful adjuvants, but also antidepressants in their own right.[2,4]

Why are we interested in biological rhythms?

One of the most striking clinical phenomena in affective disorders is the periodicity of recurrence—ranging from seasonal, as in winter depression, to rapid cycling, which can be as short as 48 hours (reviewed in 5). Other periodic phenomena are found at the symptom level: diurnal variation of mood,

SELECTED ABBREVIATIONS AND ACRONYMS

5-HT	serotonin
5-HT_{2C}	serotonin receptor (subtype 2C)
MDD	major depressive disorder
PVN	paraventricular nucleus
SAD	seasonal affective disorder
SCN	suprachiasmatic nucleus
SSRI	selective serotonin reuptake inhibitor

early morning awakening, and sleep disturbances. Abundant research has documented abnormal circadian rhythms in biochemistry, neuroendocrine function, physiology, and behavior, often linked to changes in affective state. These have been reviewed in detail elsewhere; the findings are not homogeneous, even though a certain pattern appears characteristic of depression—there is increased variability in day-to-day rhythms, decreased circadian amplitude, and circadian phase that is either early (advanced) or late (delayed).[5-11] Bipolar disorder seems to be most clearly linked to abnormal or changing circadian rhythm phase.[6] In addition, alterations in the sleep EEG in depression, although neither pathognomonic nor specific, display recognizable patterns of disturbance.[12]

Principles of circadian timing and sleep regulation

The biological timing system is schematically described in *Figure 1.* Circadian oscillators are found in every organ and every cell—the so-called "peripheral clocks."[13] A master pacemaker or biological clock in the suprachiasmatic nuclei (SCN) coordinates these circadian rhythms in brain and body.[1] The SCN is synchronized to the external light-dark cycle primarily by retinal light input. A specialized ("nonvisual") retinohypothalamic tract provides direct neuronal connection to the SCN from novel photoreceptors in the retinal ganglion cells that measure illuminance.[14] Nocturnal synthesis of the pineal hormone melatonin is driven by the SCN; melatonin also feeds back on melatonin receptors in the SCN and thus melatonin belongs to the category of synchronizing agents or "zeitgebers" (light being the major one). A serotoninergic pathway from the raphe nucleus provides nonphotic input to the SCN. Nonphotic zeitgebers such as exercise, sleep, or darkness are probably much weaker zeitgebers than light on SCN function. Social zeitgebers (such as school or work schedules) may act directly or indirectly on the SCN, since they determine the timing of meals, sleep, physical exercise, and outdoor light exposure. The circadian pacemaker has inputs to sleep regulatory centers (eg, the raphe nucleus, the dorsolateral hypothalamus [orexin], ventrolateral preoptic area),[15] and sleep centers talk back to the clock.[16] The timing and architecture of sleep is considered to be a consequence of interactions between the circadian pacemaker and a homeostatic process of rising sleep pressure, dependent on the duration of prior wakefulness, that declines during sleep (the "two-process model").[17]

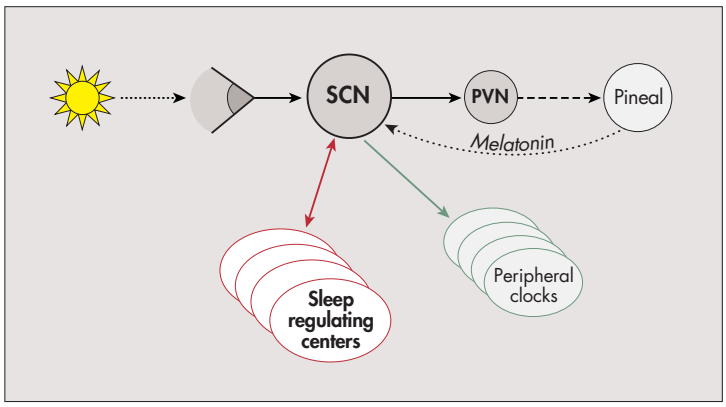

Figure 1. Schematic representation of the circadian timing system. Light (☀) is the major zeitgeber reaching the biological clock in the SCN via specialized "circadian photoreceptors" in the retina (◗). A multisynaptic pathway to the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on receptors in the SCN. The SCN also synchronizes the timing of peripheral clocks in other organs and cells, some of which have their own zeitgebers (eg, food for the liver clock). There are multiple connections from (and to) the SCN to areas of the brain involved in sleep regulation eg, the preoptic area, the dorsolateral and posterior hypothalamus, and the raphe nucleus.

Mood is dependent on both time of day and time awake

This parsimonious two-process model has been able to explain much of the physiology of sleep as well as of aberrant sleep-wake cycle behavior. Protocols developed to analyze the contributions of circadian phase vs the sleep homeostat have provided fascinating information not only about sleepiness—as might be expected—but also that mood is similarly regulated by the two processes. This is shown very clearly in the "forced desynchrony" protocol carried out in healthy subjects.[18] The circadian component of mood follows the circadian rhythm of core body temperature rather closely. We wake up in not too good a mood, but this improves throughout the day to reach a maximum in the evening, and then mood declines during the night. The wake-dependent component reveals that we are quite cheery after a good night's sleep when sleep pressure is low, but that thereafter mood declines monotonically with time awake. If the temporal alignment between the sleep-wake cycle and the circadian pacemaker affects self-assessment of mood in healthy subjects, it might be expected that this is even more important for patients with depression. The phenomenon of diurnal mood variation as a characteristic of depressive state may indeed arise from phase relationships gone awry.

Diurnal mood variation can be manipulated by shifting or depriving sleep. The improvement after a night's wake therapy usually begins in the second half of the night or the next day, suggesting that staying awake prevents the nocturnal plunge in mood.[10] Furthermore, a phase advance of sleep timing has been able to induce a day-by-day change in diurnal mood patterns over many weeks—evidence for the profound effect of shifting phase relationships on mood (a more severe form of jet lag).[19,20] Similar day-by-day changes in diurnal mood patterns have been found in a "forced desynchrony" experiment carried out in major seasonal depression.[21]

Shifting rhythms or sleep can be therapeutic

The above model helps to understand the change of clinical state with time of day and after manipulations of sleep. The clinical findings, however, are the important point to be made—extending wakefulness is antidepressant. Wake therapy has been well

established as a rapid treatment for depression for over 30 years, the response being particularly high in those patients who report daily mood swings.[10] Modified protocols have been developed, such as wake therapy in the second half of the night, or phase advance of the sleep-wake cycle.[10] These two modifications emphasize the circadian factor—it being important to remain awake at a particular time in order to prevent mood decline.

The main reason for the lack of enthusiasm for wake therapy as a treatment in everyday practice is the equally rapid relapse following recovery sleep. A number of groups have taken up the challenge of searching for methods to prevent this: do not give up wake therapy as a treatment just because its effects don't last long enough! In bipolar patients, the combination with lithium appears to maintain antidepressant response.[22-24] A number of different medications have been tried[25]; in particular, the use of SSRIs or light is recommended following one to three episodes of wake therapy.[26-29]

How are circadian rhythms related to depression?

The basic question of how circadian rhythms are related to depression has not yet been answered. Genetic vulnerability and stress influence circadian rhythms and sleep patterns, leading to many of the symptoms characteristic of affective disorders. Circadian and seasonal rhythms involve the same neurotransmitters postulated to be important for depression—so that changes in one system have repercussions on the other. For example, it is known that serotonin concentrations are highest in the SCN. The SCN also expresses high levels of melatonin receptors, and exogenous melatonin is known to be able to influence the phase and the period of the circadian clock. In humans, serotonin turnover changes markedly with time of day and year *(Figure 2),*[30-32] and light exposure rapidly simulates serotonergic function.[32] Serotonin is also important in sleep regulation, though its role appears complex. Prefrontal cortical serotonin has been linked with mood. These interrelationships have been conceptualized in a dual model of circadian rhythms and serotonin in depression *(Figure 3).*[33] The emphasis is on a system vulnerable to depression—whether genetic, hormonal, dependent on light availability and light exposure—and, in parallel, the circadian system and its phase relationships with sleep and with the outer world. Concurrent dysfunction can lead to major depression or its seasonal form. Circadian abnormalities alone lead to certain forms of sleep disorders (such as advanced or delayed sleep phase syndrome) without effects on mood. Serotonergic abnormalities alone lead to other serotonin-related illnesses (eg, obsessive compulsive disorder) again, without the mood disorder.

A digression on seasonality

Humans retain their capacity to undergo seasonal responses, even though their extent has declined in the last century since the invention of artificial light and the use of central heating and air conditioning to control environmental temperature. This is clearly seen in the seasonality of birth (conception) rates, that had a high spring peak in the 16th century, but declined to very low amplitude in the 20th century, with a shift to an autumn peak.[34] Psychiatrists have long remarked on seasonality in their patients' symptoms, for example Esquirol, who noted that the peak admission rates to the Salpêtrière hospital occurred in spring.[35] What is not usually recognized, is that not only depressive symptoms, but even response to placebo is seasonally modulated. The 10-day response rate to placebo in double-blind controlled trials of various antidepressants carried out at the New York State Psychiatric Institute was analyzed according to time of year *(Figure 4, page 226).*[36] Three times higher response rates occurred in summer than in winter. In conclusion, many aspects of behavior, physiology, and neuroen-

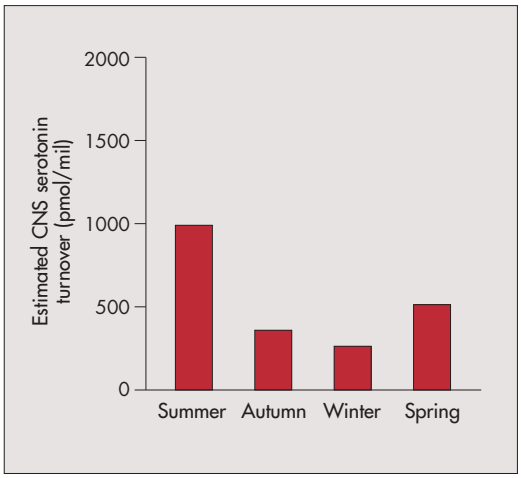

Figure 2. Average CNS serotonin turnover in vivo in healthy subjects according to season of measurement.
Redrawn from reference 32: Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD. Effect of sunlight and season on serotonin turnover in the brain. *Lancet.* 2002;360:1840-1842. Copyright © 2002, Elsevier Ltd.

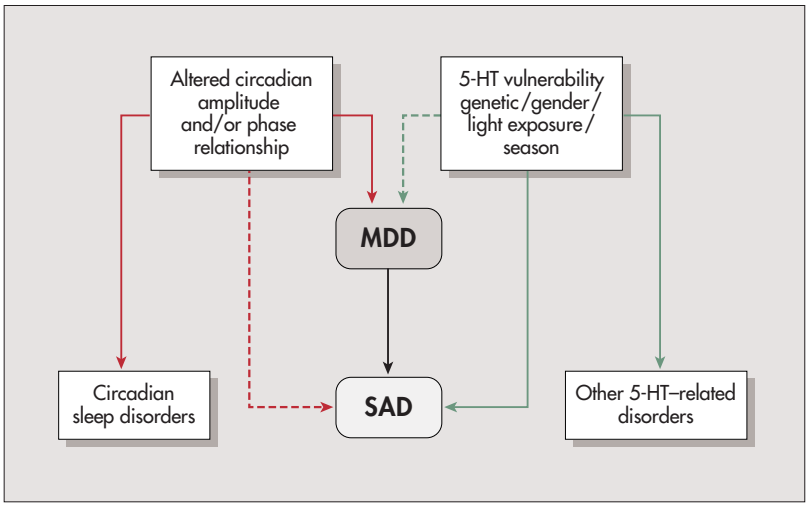

Figure 3. Dual model of depression. Both a disturbance in the circadian timing system and a neurobiological vulnerability (serotonergic [5-HT] hypofunction) are required for the manifestation of major depressive disorder (MDD) or seasonal affective disorder (SAD).
Redrawn from reference 33: Lam RW, Tam EM, Yatham LN, Shiah IS, Zis AP. Seasonal depression: the dual vulnerability hypothesis revisited. *J Affect Disord.* 2001;63:123-132. Copyright © 2001, Elsevier B.V.

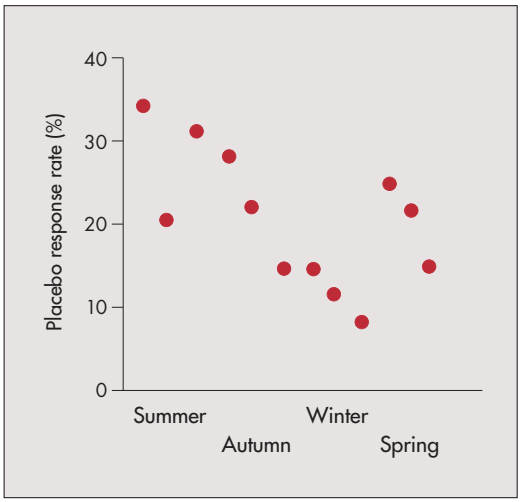

Figure 4. The 10-day response rate to placebo in double-blind controlled trials of various antidepressants. Each point is a single trial.

Redrawn from reference 36: Terman M. On the question of mechanism in phototherapy for seasonal affective disorder: considerations of clinical efficacy and epidemiology. In: Rosenthal NE, Blehar MC, eds. *Seasonal Affective Disorder and Phototherapy.* New York, NY: Guilford Press; 1989:357-376. Copyright © 1989, Guilford Press.

docrine function are sensitive to season. One example is presented, that of the in vivo turnover of central nervous system serotonin in healthy humans—much higher in summer than in winter *(Figure 2)*.[32]

More light!

As for the seasons, the annals of psychiatry abound with evidence that affective state can be modulated by exposure to environmental light or darkness.[37] The diagnosis of seasonal affective disorder (SAD) and the development of light therapy was based on neurobiological models of mammalian seasonality—the first treatment in psychiatry to be grounded in basic research. Although light therapy was initially propagated by Kripke for nonseasonal depression,[38] initial studies were too short in duration to provide the convincing results that a single week of light therapy can now achieve in SAD: it is only now, 20 years on, that controlled long-term studies of light at last have been and are being carried out in nonseasonal major depression, with extremely promising results. For example, the need for efficacious treatment of depression during pregnancy without side effects on the fetus has led to trials of monotherapy with light.[39] Double-blind placebo-controlled studies have now shown that light therapy combined with an SSRI leads to more rapid (within 1 week) and more profound (by ca 30%) improvement in patients with nonseasonal major depression.[27,40] Recently, a study of light treatment in chronic depression (of greater than 2 years duration) yielded impressive results in this often treatment-resistant group.[41] Thus, a new generation of clinical trials supports the therapeutic efficacy of light, alone or in combination with medication, for a variety of psychiatric disorders, and it is to be hoped that more will follow.

"More darkness" is a correlate of the above: pilot studies suggest that the simple measure of promoting long nights (more rest, more sleep, no light) can stop rapid cycling in bipolar patients,[42,43] or diminish manic symptoms[44]—intriguing findings that require replication.

Can chronotherapeutics provide new drugs as well?

Not only are the described chronotherapeutic approaches efficacious antidepressants in themselves, but they also offer new models for pharmaceutical research. Is part of the usefulness of light due to its zeitgeber function of stabilizing phase? Is part of its efficacy due to serotonergic mechanisms? Given that the antidepressant properties of selective serotonin (5-HT) reuptake–inhibiting drugs are considered to be related to the 5-HT_{2C} receptor subtype, it is interesting that 5-HT_{2C} receptor agonists in the rat SCN mimic the effects of light.[45] Serotonergic drugs and melatonin improve entrainment. In this respect, the pharmacological profile of agomelatine fits the above model, as it is a melatonin receptor type 1 and 2 (MT_1 and MT_2) agonist with 5-HT_{2C} properties.[46] Melatonin itself has no antidepressant characteristics.

In summary, circadian rhythm and sleep research have led to nonpharmacological therapies of depression (light therapy, wake therapy) that can be—and should be—used in everyday practice.[2,4] The rationale for attempting to resynchronize disturbed phase relationships between the clock and sleep is the concomitant improvement in mood. Chronobiological concepts emphasize the importance of zeitgebers and provide psychopharmacology with a novel approach for developing "chronobiotic" drugs. ❐

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STRATÉGIES CHRONOBIOLOGIQUES POUR LES BESOINS INSATISFAITS DANS LE TRAITEMENT DE LA DÉPRESSION

Les stratégies chronobiologiques peuvent représenter un moyen efficace pour faire face à certains besoins insatisfaits dans le traitement de la dépression. Ce sont : le raccourcissement du temps de latence qui précède l'apparition de l'effet antidépresseur, la lutte contre les symptômes résiduels et la prévention de la rechute à long terme. La lumière est le traitement de choix pour la dépression hivernale (ou trouble affectif saisonnier, TAS). La luminothérapie, comme adjuvant au traitement dans la dépression non saisonnière majeure comme dans la dépression chronique et résistante au traitement, accélère et potentialise la réponse au traitement. La lumière est aussi efficace dans la dépression bipolaire ; chez ces patients présentant ce trouble, le « traitement par l'obscurité » (nuits longues) peut diminuer les symptômes maniaques et arrêter les cycles rapides. La privation totale ou partielle de sommeil dans la seconde partie de la nuit (mieux connue sous le nom de « traitement par l'éveil ») induit une amélioration marquée le jour suivant. Cette amélioration peut être maintenue avec des traitements concomitants par les antidépresseurs, le lithium, la luminothérapie, l'avance de phase de sommeil ou l'association de plusieurs de ces mesures. Un contrôle soigneux du cycle jour-nuit et de l'heure des repas, de l'activité et du sommeil peut apparaître comme une méthode démodée (mise en place de « structures journalières ») appartenant à une obsolète psychiatrie d'institutionnalisation. Cependant, ces méthodes apparemment simples retrouvent une nouvelle légitimation quand on les reconsidère à l'intérieur du cadre de la chronobiologie moderne, puisque l'utilisation bien réglée de « synchroniseurs », ou « zeitgebers » peut améliorer le traitement des troubles affectifs.