Biological Rhythms and Depression: Treatment Opportunities

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Introduction

In all cultures, altered biological rhythms have been recognized as an essential characteristic of major depression. Diurnal variation of mood, early morning awakening, and sleep disturbances belong to the core symptoms, and depressive phases often follow a regular periodicity. Bipolar patients, in particular rapid cyclers, undergo remarkably precise switches between clinical states. In temperate latitudes, seasonal affective disorder (SAD) is linked to decreasing light availability in autumn and winter. Circadian (24-hour) rhythms not only underlie mood disorders, but, importantly, manipulations of rhythms or sleep can treat them. Sleep deprivation has long been established as the most rapid antidepressant known—about 60% of patients improve on the next day. Light is the treatment of choice for SAD. A much broader range of applications for light is developing, in particular, in nonseasonal major depression. These biologically based, nonpharmaceutic treatments, which are fast-acting, inexpensive, and with few side effects, fulfill the requirements to become—alone or combined—part of standard antidepressant treatment in both industrialized and developing countries.

Circadian rhythms and sleep regulation

Life on this rotating planet is subject to a predictable 24-hour rhythm of day alternating with night, and daylength changing with the seasons. All species have evolved to adapt to the solar light-dark cycle with appropriate timing of behavior and physiology. This timing has become internalized: a complex genetic clockwork located in the suprachiasmatic nuclei (SCN) generates all circadian rhythms. The genetic program is slightly different from 24 hours (in humans usually longer) and thus the internal clock requires regular synchronization to the external 24-hour day by so-called "zeitgebers" or entraining agents. The major zeitgeber for the SCN is light. The SCN contain the highest serotonin concentrations in the brain, through input from the raphe nuclei. The SCN drive the rhythm of nighttime melatonin synthesis in the pineal gland as well as receiving feedback about the amount of circulating melatonin via melatonin receptors in the SCN.

This concept of light and melatonin as major zeitgebers synchronizing the biological clock is important when we consider how they can be used as therapeutic agents. Other known zeitgebers are social signals (see E Frank, this issue), meals, and exercise—which provide the daily structure well known to psychiatrists as important, but now conceptualized in terms of their ability to synchronize and stabilize rhythmic behavior.

Sleep is regulated by interactions between the circadian pacemaker in the SCN and a homeostatic process (described by sleep pressure rising during wakefulness and being dissipated during sleep). This "two-process model" explains many aspects of sleep-wake cycle physiology. It has also been used to help understand possible abnormalities in mood disorders. Depressive patients might have a poor buildup of sleep pressure. Perhaps the short-term improvement after a night's sleep deprivation is related to sleep pressure rising to normal levels only after 40 hours of wakefulness (but then inducing relapse by dropping to former low values following a recovery night's sleep). If light can improve mood—this effect could occur through its zeitgeber ability to synchronize rhythms (shifting phase), or to increase the amplitude of the circadian signal leading to higher day-to-day stability. Another direct effect of light is on brain serotonin turnover—the more light received, the higher the levels of this neurotransmitter known to be involved in the affective state. Without going into the serious body of clinical research that has investigated mechanisms and efficacy of sleep deprivation in its various forms or light therapy in many different psychiatric and sleep disorders (see 'Further reading' for reviews), this paper will focus on practical applications.

Wake therapy

Although many thousands of patients all over the world have improved with sleep deprivation, it has not really caught on as a first-line treatment for major—particularly melancholic—depression. It may be the paradox of recommending the opposite of what is expected—to take sleep away from someone who has sleep problems is not very convincing. That is why in recent years we have changed the name to wake therapy—instead of robbing a depressed patient of her wished-for sleep, we give her more wakefulness as a cure! Over the years, modifications of total sleep deprivation have been developed—partial sleep deprivation in the second half of the night appears to work just as well. Thus, the patient can go to bed early, have a few hours of deep sleep, and wake up at 01:00 or 02:00 and stay up for the rest of the night. In the "phase advance" treatment, sleep is not deprived but shifted to 5-6 hours earlier than usual for a few days until improvement occurs. The important factor for improvement in this procedure is not the loss of sleep itself but being awake in the second half of the night (the circadian minimum where mood is at its lowest).

The main reason, however, why sleep deprivation has remained a curious phenomenon

and not a mainline treatment, is that the majority of patients relapse after recovery sleep. Why invest staff and patient effort in wake therapy if the improvement is only transient? On the one hand, the rapid improvement and rapid relapse has made sleep deprivation an ideal research tool to better understand factors underlying mood switches. But for everyday practice, the focus has been to find techniques to maintain the improvement obtained so rapidly. One of the most cited unmet needs in the psychopharmacology of depression is the slow latency of response to current medications. The idea that wake therapy can meet this need by switching patients out of depression within hours, not weeks, makes it attractive to look for combinations with other methods to prevent relapse. In Milan, a group of psychiatrists have been using (repeated) wake therapy for more than a decade to treat hospitalized bipolar and unipolar depressed patients. Successful maintenance of response has been found in patients when treated with lithium, with selective serotonin reuptake inhibitors, and light therapy. They find no enhanced switch rate into (hypo)mania. An example is presented in Case #1.

Case #1:
Bipolar depression and wake therapy

A 51-year-old woman with difficult-to-treat bipolar disorder type I was hospitalized in the San Raffaele Clinic in Milan during a depressive episode that had lasted eight months. All medication was stopped, except lithium, which was increased. After five mood episodes and three forced hospitalizations in two years, with so many disappointing therapeutic failures, the patient and her relatives had very low expectations psychiatry in general and the chronotherapeutic approach in particular. She underwent three consecutive cycles of total sleep deprivation, each followed by a recovery night sleep. However, after the first wake therapy she experienced rapid and complete amelioration of the depressive syndrome leading to perceived euthymia in the early morning. The first recovery sleep was followed by a partial but definite depressive syndromal relapse. The second wake therapy led again to perceived euthymia, without relapse after recovery sleep; the benefit was sustained after the third wake therapy. Euthymia persisted during the following days, and the patient was discharged. Plasma lithium levels were kept high for six months, and then reduced to a target level of 0.75 mEq/L. Nine years later, the patient is still euthymic. She still takes lithium, which also prevents the moderate seasonal mood fluctuations which recurred over her lifetime. Her brother, who suffered from severe bipolar disorder, also showed a good response to wake therapy for depression and dark therapy for mania. (F. Benedetti, personal communication)

Light therapy

Light therapy was specifically developed as a zeitgeber treatment for SAD patients, who become depressed as the days shorten and spontaneously remit during the longer days in spring and summer. The efficacy of light is greatest in the early morning, but patients also improve at other times of day, suggesting that light acts both to shift rhythms earlier in the morning (zeitgeber action) and as an antidepressant "drug" (without a time dependency). The most effective time of day for beginning morning light treatment for SAD patients can be individually prescribed according to their circadian rhythm type, by means of an online morningness-eveningness questionnaire (see Auto-MEQ on www.cet.org). This nonprofit site has been established to provide practical information for doctors and patients on all aspects of light therapy, and is being expanded through translation into a number of languages.

Light is now clearly established as the treatment of choice for SAD, and many psychiatrists understand this application but are not aware of further developments over the last decade. In particular, light therapy has been applied in many other psychiatric disorders, from bulimia to the sleep-wake cycle disturbances of Alzheimer's dementia and antepartum depression. Double-blind placebo-controlled studies have shown that light therapy combined with a selective serotonin reuptake inhibitor leads to more rapid (within a week) and more profound (by ca. 30%) improvement in patients with nonseasonal major depression, suggesting an advantage of using combined light and drug.

Although environmental light supplementation seems an obvious approach for treating winter depression, it has not yet been widely used for nonseasonal depression. If one considers the social withdrawal in major depression, then a secondary consequence might be less exposure to outdoor light (indoor light is not bright enough to have any clinical effect). Many doctors from tropical countries have asked—somewhat skeptically—why should we use light treatment in our country which has so much sunshine? Yet it would be interesting to measure how much bright light depressed patients in such climates actually get. Since sunny countries are often also hot, people escape the heat and remain inside, away from the sunshine. When outdoors, they wear sunglasses. I would predict that all over the world, independent of climate and latitude, depressed patients probably hide from the light. Odd as it may seem (especially for tropical countries), we recommend that the doctor order a 30-minute walk outside every day in the early morning for depressed patients. This could be considered a "natural" and, moreover, free therapeutic option, but requires regularity to be efficacious.

In contrast, "dark therapy" (keeping patients in longer-than-usual nights) may treat mania as fast as neuroleptics, and even stop rapid cycling.

Two examples from Siberia (Case #2) and New York (Case #3) illustrate the new applications. The best timing of light in bipolar patients appears to be different from the early morning light recommended for SAD. The case study #2 here corroborates find-

ings in a recently published series of bipolar patients who showed mixed states with morning light and improvement with afternoon light.

Case #2:
Bipolar depression and light therapy

A bipolar patient in Novosibirsk had experienced her first depressed / hypomania phases at age 22. Depression episodes significantly outnumbered and were longer than hypomania episodes. There was a rapid (within a day) switch from depression to hypomania (which lasted less than 1 month). Depression was characterized by atypical features, but anxiety often prevailed in affect. Although not reaching the criteria for SAD, she entered a light treatment trial at age 29 out of interest. After morning light (08:00-10:00, 2500 lux for 2 hours for a week), she experienced clear activation, better mood, but anxiety, irritability, and a feeling of dissatisfaction appeared to increase. The negative effect was brief, but with repeated daily light exposures it became more prominent. When switched to afternoon light (16:00-18:00), she felt better than after morning light, with no mixed states. From 1991 the patient has had her own light box at home and regularly uses light therapy on her own for 15-20 minutes in the afternoon. (K. Danilenko and A. Putilov, personal communication)

An even more striking application of light therapy for nonseasonal depression is in adjunctive treatment for chronic or treatment-resistant depression, as exemplified in Case #3. More trials of these combinations are required to establish a solid evidence base, but given the lack of side effects, the ease of application, and the often rapid improvement that had not been attained with antidepressant drugs alone, adding light therapy seems to be widely indicated.

Case #3
Treatment-resistant chronic depression and light therapy

A 24-year-old single woman in New York with a lifetime history of dysthymia and a history of anorexia and social phobia, suffered from chronic major depression for the last 6 years. She had been unresponsive to multiple drug trials. Treatment with the monoamine oxidase inhibitor tranylcypromine 100 mg induced a full complement of early, middle, and late insomnia. Light therapy at 07:15 for 30 min promptly coalesced sleep (23:30-07:00) and within 3 weeks the patient showed complete remission and was discharged. She continued with light + tranylcypromine at home, but was not compliant with light treatment. Whenever she stopped using the light she would experience relapse within 2 days. On resumption of the light, she would feel improvement within 2 days and complete remission in 4 days. Although light alone might have maintained her improvement, with such a serious chronic depression it is difficult for psychiatrists to withdraw the drug and rely on light monotherapy. (M Terman, with permission)

Melatonin

Melatonin, exogenously administered, also acts as a zeitgeber to synchronize circadian rhythms and sleep (for example, in blind persons). It induces sleepiness by causing vasodilatation of hands and feet and hence heat loss, with a consequent decline in core body temperature, which facilitates a rapid sleep onset. Melatonin has few minor effects on sleep itself (as measured in the EEG), and thus is a sleep-promoting agent rather than a direct hypnotic in the classical sense. Very low doses suffice (~ 1 mg) and rarely have any side effects been documented. We hope that well-researched pharmaceutical quality-controlled preparations of melatonin will soon be recognized by regulatory agencies. Melatonin itself is not an antidepressant, but improving and stabilizing sleep is an important part of antidepressant therapies.

Chronotherapeutics for major depression

Chronotherapeutic options are summarized in the Table below and can be added on to antidepressant "treatment as usual".

Implication for clinical practice

(SAD and nonseasonal depression, unipolar and bipolar disorder, chronic and therapy-resistant, adjuvant to medication)

Wake therapy (a whole night's sleep deprivation, or partial sleep deprivation in the second half of the night) is the most rapid antidepressant known
Repeated wake therapy (followed by recovery sleep) to promote maintained response
Phase advance of the sleep-wake cycle to maintain the sleep deprivation response
Morning timed light therapy to maintain the sleep deprivation response
Dark therapy (to stop rapid cycling, mania)
Melatonin (for sleep disturbances in depression)
Melatonin (in the evening) to enhance phase advances with light (in the morning)
Light therapy is the treatment of choice for winter depression (SAD), which is most prevalent at temperate latitudes
Light therapy for nonseasonal depression with or without medication

Implementation of this strategy in clinical practice will be provided by a new manual in preparation (Benedetti F, Terman M, Wirz-Justice A. Psychiatric Chronotherapeutics: A Treatment Manual). Treatments can be combined in a flexible manner step by step according to the patient's response, as exemplified below:

1. all patients can use light therapy. Treatment of 10 000 lux for 30 min is begun at the time allocated by the patient's MEQ chronotype. This timing of light remains fixed throughout a trial of at least two weeks. Depending on response, dosage can be increased by lengthening the duration of light therapy by 15 min every few days.
2. for patients who are willing to try wake therapy, a single night's sleep deprivation is carried out, with light treatment in the morning at the calculated optimum, continuing as in 1.
3. for the "complete chronotherapeutic package", a single night's sleep deprivation is accompanied by light therapy as in 2. On the recovery night after sleep deprivation, the patient goes to bed five hours earlier than usual and wakes up five hours earlier than usual ("phase advance" therapy). On night two, sleep is shifted to three hours earlier than usual, and, on night three and thereafter, sleep is maintained one hour earlier than usual.

Close monitoring of the patient's state can help decide which chronotherapeutic should be tried next. The full combination of repeated sleep deprivation and/or phase advance may be required only for treatment-resistant patients.

Both wake and light therapy can be considered to fulfill the World Psychiatric Association's requirements for globally applicable, low-cost, rapidly effective antidepressants.

FURTHER READING

Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev.* 2007;11:509-522. **Lam RW.** *Seasonal Affective Disorder and Beyond. Light Treatment for SAD and Non-SAD Conditions.* Washington DC: American Psychiatric Press; 1998. **Sit D, Wisner KL, Hanusa BH, Stull S, Terman M.** Light therapy for bipolar disorder: a case series in women. *Bipolar Disord.* 2007;9:918-927. **Terman M, Terman JS.** Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS Spectr.* 2005;10:647-663.
Terman M. Evolving applications of light therapy. *Sleep Med Rev.* 2007;11:497-507. **Wirz-Justice A, Van den Hoofdakker RH.** Sleep deprivation in depression: what do we know, where do we go? *Biol Psychiatry.* 1999;46:445-453.