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Chronotherapeutics for Affective Disorders

A Clinician's Manual for Light and Wake Therapy

33 figures, 21 in color, 10 tables, 2009

Chapter excerpts

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Case Study 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 had suffered from chronic major depression for 6 years. She was 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 7 a.m. for 30 min promptly coalesced sleep (11:30 p.m. to 7 a.m.), 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 [32].

3.3

Wake Therapy Added to Medication

The earliest observations in the 1970s of rapid clinical remission under wake therapy prompted the question whether wake therapy might potentiate the response to medication [20]. Rather than increasing antidepressant dosage for non-responders, adding wake therapy can trigger improvement.

Case Study 4 demonstrates that wake therapy can alleviate depression in lithium-treated bipolar patients.

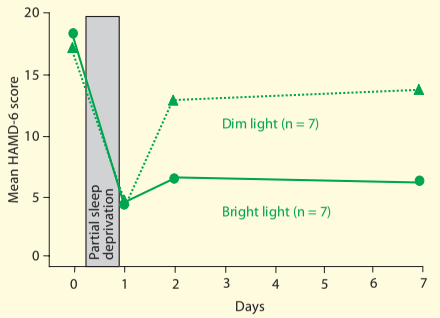
Case Study 4
Bipolar Depression and Wake Therapy
A 51-year-old woman with difficult-to-treat bipolar 1 disorder was hospitalised in the Ospedale San Raffaele in Milano during a depressive episode that had lasted 8 months. After five mood episodes and three forced hospitalisations in 2 years, with so many disappointing therapeutic failures, the patient and her family became very pessimistic about psychiatry in general, so it was no surprise that they were skeptical about trying the chronotherapeutic approach. Upon admission, all medication was stopped, except for lithium, which was increased. 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 relapse. The second wake therapy led again to perceived euthymia, without relapse after recovery sleep, a benefit sustained after the third wake therapy. Euthymia persisted over the following days and the patient was discharged. High plasma lithium levels were maintained for 6 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 had 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 [Benedetti].

Table 5. Medications that have been used with wake therapy

Lithium	Amitriptyline	Desipramine
Clomipramine	Nortriptyline	Amineptine
Fluoxetine	Sertraline	Paroxetine
Fluvoxamine	Duloxetine	Maprotiline
Pindolol		

Wake therapy appears to be synergistic with antidepressant drugs that potentiate monoaminergic neurotransmission, and lithium salts. Many trials have used both TCAs and newer antidepressants: sleep deprivation hastens and potentiates the response to antidepressants acting on all neurotransmitter target systems (serotonin, noradrenaline, dopamine), and mixed drugs (table 5). The only negative finding comes from a single study combining wake therapy with the antidopaminergic, sedative substance, trimipramine [73]. Indeed, patients do not respond well to sleep deprivation when on neuroleptics (dopamine antagonists).

Research Precedent 7
Responders to partial sleep deprivation in the second half of the night were given dim light (placebo) or bright light for a week. Patients on bright light did not relapse (redrawn from [74], with permisson).



Ideally, wake therapy is administered when beginning medication, so rapid mood improvement occurs during the latency of action of antidepressants. From a practical point of view, both the patient and physician can expect substantial improvement during the most painful days when adequate medication has been prescribed, but has not taken effect. Moreover, the short-term response to wake therapy predicts long-term response to drug [20]. Even during the latency of action, medication can sustain the antidepressant effect of wake therapy, and prevent the usual relapse after recovery sleep.

3.4

Wake and Light Therapy Added to Antidepressant Drugs or Mood Stabilisers

In an expanded protocol, medicated patients with non-seasonal unipolar depression received light therapy and a single session of late-night wake therapy at the start of treatment [74]. There was marked improvement in one day and benefit over a dim light control within one week (Research Precedent 7). In Milano, this model has been extended to general inpatient use, guided by successful treatment studies of non-seasonal major depression (in conjunction with citalopram) and bipolar disorder (in conjunction with lithium), both of which showed large benefits attributable to morning light therapy.

Case Study 5 demonstrates how a colleague who had never administered sleep deprivation became convinced of its efficacy.

Case Study 5
Very First Experience of Combined Wake and Light Therapy in a Copenhagen Hospital
Mrs. K was 65 years old and had a 30-year-long history of bipolar illness. Her depressive episodes often lasted more than 3/4 of a year and did not much improve on antidepressant treatment, whereas her manic periods responded well to low doses of neuroleptics. In her previous depressive episode, which had lasted for 2 months without any sign of improvement, she had heard from her doctor of the possibility of carrying out wake therapy. She was admitted to an open unit, diagnosed with Major Depression with a score of 18 on the Hamilton Depression rating scale. Her medication was left unchanged. She did not have any problem staying up all night. In the morning, her Hamilton score was reduced to 2. After a normal night of sleep she performed two more total sleep deprivations interspersed with a normal night's sleep. During the early morning of the sleep deprivations she received 30 min of light therapy (10,000 lx), which was repeated later that morning. Her Hamilton score remained below 3 and she was discharged after 5 days. At home, she continued daily light treatment and was able to avoid sleep-

15 Chronobiology in Everyday Life

15.1 Know Your Chronotype

The concept of chronotype was introduced in order to emphasise individual differences in internal clock phase relative to the day-night cycle. Chronotype reflects preferred sleep timing as well as the optimum distribution of daytime physical and mental performance. This is not a minor matter, despite light-hearted teasing of morning 'larks' and night 'owls'. In early agrarian society, 'the early bird catches the worm' had validity. Dawn and dusk delineated the work day – there was little choice but to carry out most activities in daylight. Now, in a 24/7 society that demands continuous services, we do not have to get up at dawn, yet the conventions of the past age remain, with the moral virtue of the early bird shining over the turpitude of the night owl.

It is important to recognise that we do not choose our chronotype: the largest part is genetically determined. Furthermore, chronotype changes with age [108]. The most remarkable shifts occur during adolescence, where average sleep timing drifts forward by about 15 min per year from age 12 to 20. The delay is greater for boys than girls. In girls, we have even been able to link the onset of delay shifts to menarche. After age 20, the average chronotype slowly shifts back earlier over the decades. Late chronotypes suffer varying degrees of 'social jet lag', manifested in delayed bedtimes and wake-up times as well as oversleeping on weekends in an attempt to catch up on alarm-clock-shortened sleep duration during the week [110]. Obviously, given the usual timing of school and work, the late chronotype suffers the most.

If we stratify the population for chronotype, we find significantly more depression in owls, who have the greatest difficulty in synchronising day-night rhythms with the day-night cycle. Clinicians should probe for chronotype whenever they meet a new patient. Chronotherapeutics can reduce this mismatch and the burden it creates.

15.2 Timing of School and Work Schedules versus Sleep

School times in every country have their regularity, as do normal work schedules. The range is quite small compared to the variability of chronotypes who have to fit their circadian clocks into the procrustean bed of the real world's demands.

The biologically determined delay in sleep timing with adolescence provides a serious argument for delaying the start of the school day. The additional peer pressure to stay up late may in fact reflect the delayed chronotype of this age group. The longer sleep need of younger children (9–10 h) would also be better accommodated by a later start to the school day. Current research on the role of sleep for learning and memory consolidation of the prior day's input emphasises the importance of sufficient sleep duration. By implementing delays in the school schedule, the educational establishment has an opportunity to promote daily cognitive and behavioural functioning and mental health, and perhaps even forestall the onset of mood and sleep disorders in adulthood.

Flexible work schedules (with block times for attendance) are one way to provide individuals with a time range – albeit usually small – to schedule their day to best fit their chronotype. Extreme owls usually self-select occupations that allow night work, since they are the ones that suffer most from enforced early morning job arrival. Even with a later schedule, however, owls tend toward depression and should consider bright light therapy on awakening. One psychiatrist with delayed sleep phase disorder, who could not awaken before noon and was mildly depressed, focused office hours in the evening, which appealed to many of her patients. Her goal was not to normalise her sleep schedule, and light therapy at noon served to relieve her depression. By contrast, one neuroscientist who had slept from 7 a.m. to 3 p.m. for a decade, threatened with job loss for showing up at the lab at 5 p.m., was able to normalise sleep onset to 11:30 p.m. within two weeks using an advancing schedule of low-dose, controlled release melatonin (plus blue-blockers) 4 h before sleep onset and light therapy upon awakening on a schedule of daily advances. His reaction to the change was incredulous: 'I was positive my SCN was permanently damaged!' Motivation matters.

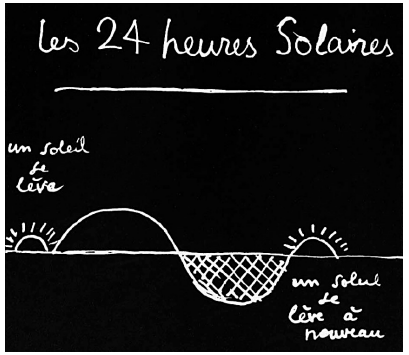


Fig. 33. The 24 solar hours, the fundamental rhythm in human life. From a lecture given in Milano, 1954. From Le Courbusier [159], p. 205, with permission. © FLC / 2009, ProLitteris, Zurich.

15.3 Light and the Built Environment: Implications for Architecture

'L'architecture est le jeu savant, correct et magnifique des volumes assemblés sous la lumière.' (Architecture is the masterly, correct and magnificent play of volumes brought together in light).

Le Corbusier: Vers une architecture, 1923

While the social clock dictates our sleep-wake schedule on work days, the built environment interacts by setting our access to daily light exposure. The intensity of room light usually lies in the range of 50–300 lx, adequate for visual perception and performance, but inadequate for maximising rhythmic stability on the desired schedule. How can we incorporate our knowledge of zeitgeber function into architectural practice? Can we implement rational light timing and intensity parameters that will work effectively depending on individual characteristics (e.g. chronotype, retinal sensitivity), or will circadian lighting installations require a compromise for the average needs of the group (workers, students, hospitalised patients)?

The principles of the circadian system and its response to light, as applied in chronotherapeutics, also directly apply to lighting design, with the aim of recapturing the biological benefits of exposure to the solar cycle. Dawn and dusk are the key signals for advancing and delaying the circadian clock, respectively; the regularity of this signal embeds sleep within the biological night and stabilises the rhythm. Light during the day is important for maintaining the amplitude of the rhythm, and a higher amplitude means better synchronisation. Thus, both appropriate timing and sufficient daytime exposure levels are necessary for healthy rhythms.

The increased incidence of sleep and depressive disorders over the last decades has of course a multitude of origins, including adverse societal