Curr Psychiatry Rep (2015) 17: 95
DOI 10.1007/s11920-015-0633-6

SLEEP DISORDERS (P GEHRMAN, SECTION EDITOR)

Chronobiological Therapy for Mood Disorders

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Published online: 19 October 2015

Abstract Chronobiological therapies for mood disorders include manipulations of the sleep–wake cycle such as sleep deprivation and sleep phase advance and the controlled exposure to light and darkness. Their antidepressant efficacy can overcome drug resistance and targets the core depressive symptoms including suicide, thus making them treatment options to be tried either alone or as adjunctive treatments combined with common psychopharmacological interventions. The specific pattern of mood change observed with chronobiological therapies is characterized by rapid and sustained effects, when used among themselves or combined with drugs. Effects sizes are the same reported for the most effective psychiatric treatments, but side effects are usually marginal or absent. New treatment protocols are developed to adapt them in different clinical settings. This review deals with the general principles of clinical chronobiology and the latest findings in this rapidly developing field.

Keywords Mood disorder · Bipolar disorder · Chronotherapeutics · Sleep deprivation · Light therapy · Sleep phase advance · Dark therapy · Depression

This article is part of the Topical Collection on *Sleep Disorders*

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Introduction

Depression is expected to become a leading burden of disease by 2020, due to its high lifetime prevalence (10 to 25 % for women; 5 to 12 % for men) and to its effects on daily function and mortality [1]. Despite an array of empirically validated pharmacological interventions, only 50 to 70 % of patients respond to their first antidepressant treatment and less than 40 % achieve remission [1]. Most antidepressant drugs show a delayed therapeutic effect, which is linked with early dropout [2] and increased suicidal risk [3], and pharmacotherapeutic agents are associated with side effects and drug–drug interactions [4]. Moreover, the use of antidepressant drugs is rather unwieldy, both in specific medical conditions, and during pregnancy, in the light of safety concerns for the developing fetus [5] and of possible anxiety-like behaviors in adulthood after prenatal antidepressant exposure [6].

Indeed, new effective and safe antidepressant therapies are still needed. Despite recent findings in pharmacology, new classes of drugs [7] are not yet ready for clinical use in the treatment of depression. On the contrary, the usefulness of chronotherapeutics has been proven by different clinical studies. These non-pharmacological clinical interventions achieve the antidepressant effect through the manipulation of the sleep–wake rhythm (such as in sleep deprivation and sleep phase advance) and of the light–dark cycle (such as in light therapy, dark therapy) [8, 9]. Clinical trials now confirm the sustained antidepressant efficacy of chronobiological interventions when used by themselves or in combination with psychiatric drugs [10], together with their safety and rapidity of action.

Sleep Deprivation

Although vague clinical impressions and thoughts about the antidepressant efficacy of sleep deprivation may be dated back

to the early nineteenth century [11], the first clinical report about antidepressant sleep deprivation (SD) was published in 1959 [12] and it was followed in the 1970s by the first experimental trials [13, 14].

SD shows a rapid antidepressant effect in every depressive syndrome, with a better efficacy having been found when treating endogenous major depression [15] and bipolar depression [16]. Neither gender, age, number of hospitalizations, earlier treatments, duration of the episode, or severity of depression appears to predict response [17]. The core depressive symptoms are the first targets of SD, and the rapid improvement immediately includes suicidal thinking and planning: an effect closely similar to that of ketamine infusion and possibly due to a similar immediate dampening of glutamatergic NMDA neurotransmission [18].

Safety concerns are minimal, but given that SD can trigger seizures, it should be carefully monitored in patients affected by epilepsy [19]. Moreover, since when treating delusional depression with SD, in some cases, a worsening of psychotic symptoms [20, 21] paralleled an "increased intensity of drives" after treatment, SD should be used with caution in these conditions, notwithstanding reports affirming its efficacy [20, 22, 23].

Acute Response Rates

The response rates to SD range from 50 to 80 % of treated patients, similar to those reported with antidepressant drugs, and are influenced by the same genetic functional polymorphisms which condition the efficacy of pharmacological treatment [24]. Contrary to antidepressant drugs which show long response latencies, SD shows a rapid (within 24–48 h) reversal of depressive symptoms [25] and the clinical benefit of SD was shown even in drug-resistant depression [26, 27].

When treating bipolar depressed patients with repeated total SD (three cycles in a week), a 4.85 % switch rate into easily controlled mania was observed. This rate is similar to that observed when using placebo [28] and much lower than that linked with use of antidepressant drugs (15 to 25 %) [1, 29].

How Many Hours of Sleep Deprivation Are Needed to Have an Antidepressant Effect?

It is still unclear how many hours of SD are needed to achieve its full antidepressant effect. Usually, the wake period starts in the morning after regular awakening and lasts about 36 h until the evening of the day after (total SD), but it can also start with an awakening within the second half of the night and include the following day (partial SD) [30], with marginal reductions in efficacy in respect to total SD [31]. This approach was reported as better tolerated in some studies, and protocols with repeated partial SD, once or twice a week, have been proposed for the continued treatment of patients [32] or even as a prophylactic treatment, to sustain response and prevent relapses [33, 34].

Focusing on the possibility that a short nap can block the antidepressant effects of SD, controversial results have been found. Indeed, while some studies reported a mood worsening, both after napping [35] and even after subjectively unrecognized microsleeps [36], others reported that napping did not change mood in responders and it even ameliorated mood in non-responders [37]. Interestingly, responders to SD seem to adapt to sleep loss without the need of the huge homeostatic sleep rebound which is observed in non-responders and which precedes the early relapse [38, 39].

The Early Relapse Problem

The clinical usefulness of SD in the treatment of mood disorders has been questioned by the short duration of its antidepressant effects, with up to 80 % of SD responder patients relapsing (though mostly not completely) after the recovery sleep night [40]. In the following days, a trend of progressive worsening is shown by patients who often reach a clinical severity similar to that seen at baseline [41]. If other combined treatments are not added to SD, only the 5 % of early responders will maintain a stable euthymia after restoration of normal sleep [42, 43]. A minority of patients (10–15 %) shows an atypical trend of response with a clinical improvement after the night of recovery sleep and not after the night of wake [22]. Unfortunately, a deterioration of mood is expected in the following days also in this condition.

Strategies for Relapse Prevention

To prevent relapse, repetition of SD alone was proven useless, because after eventual discontinuation, patients relapsed in the same proportion [44], and a tolerance to the therapeutic effects was reported [45]. The concomitant use of other chronotherapeutic interventions such light therapy (LT) or sleep phase advance (SPA) (see below) has been proven to be effective at preventing the early relapse after SD. Bright LT was used during and after SD. It was found not only to maintain the clinical improvement generated by both partial [46] and repeated total SD [47] but also to increase the antidepressant effect. The efficacy of SPA in preventing SD early relapses has been proven using two different schedules: 1 week and 3 days. A one-week schedule was employed during early studies: one night of total sleep deprivation (RSD) was administered to patients; the day after, the first recovery night, bedtime started at 5 p.m. and was delayed daily by 1 h until reaching a bedtime of 11 p.m. [48–51]. The 3-day schedule, which was proven to be effective in preventing relapses as well as the 1-week one, has been proposed during more recent studies: after one night of TSD, bedtime started as well at 5

p.m. during the first recovery night, but then, it was delayed daily by 2 h until the conventional bedtime [52, 53].

In recent years, a triple chronotherapy protocol (combined TSD, SPA, bright LT) has been introduced. A single TSD night followed by a 3-day scheduled SPA and 3 [54] or 5 days [55] of bright LT was found to have sustained antidepressant effects, including in drug-resistant depressed patients [55]. Remarkably, these protocols showed similar efficacy and effect sizes irrespective of ethnic differences and associated treatments. Antidepressant SD has also been associated with both selective serotonin reuptake inhibitors [56–59] and tricyclic antidepressants, [60–62] with a synergistic effect which resulted in long-term benefits.

While the concomitant use of antidepressant drugs was shown to not change response rates to combined TSD and LT in bipolar depressed patients [26], the administration of lithium salts was proven to influence the clinical response to chronobiological treatment. Indeed, lithium salts were found not only to enhance the acute antidepressant efficacy of SD [63], but also to prevent both acute [47, 64] and delayed relapses [26, 43]. The use of combined repeated SD and LT together with a concomitant administration of lithium salts could then maintain clinical remission, with the most severe symptoms rapidly disappearing and euthymic conditions maintained for months [26, 65, 66]. The most recent study on bipolar depression resistant to drug treatments, using a triple SD associated and followed for 2 weeks by LT, showed a 70 % acute response rate, followed by a 21 % relapse rate in the following weeks, thus bringing the success rate to 55.3 % of treated patients [66].

Proposed Mechanisms of Action

Hypotheses about the mechanisms behind the rapid antidepressant effect of SD also have implications about the nature of depression and the function of sleep, which are both unsolved questions. Since depression is a multifactorial illness, antidepressant treatments show their efficacy influencing different systems [67]. Chronotherapeutics could act through the same mechanisms that are targets for antidepressant drugs [24] and probably some more.

SD was proven to target serotonin, norepinephrine, and dopamine systems [24, 68], which are influenced also by antidepressant drugs. Indeed, the antidepressant effect of the treatment is conditioned by biological factors affecting the activity of these pathways, such as genotypic variants [69–71], basal neurotransmitter levels [72], or the extent of receptor occupancy [73]. Glutamate neurotransmission and its interaction with monoamines could have a role in the rapid antidepressant effects of SD, with a reduction in cortical glutamate concentrations paralleling clinical response to the treatment [74]. These effects were detected in anterior cingulate cortex, which has been suggested to be linked to mood-congruent cognitive biases in depression [75]. Moreover, in this area, changes in 5-HT function were found to influence neural responses to depressive cognitive stimuli [76] and where chronotherapeutics were shown to profoundly change metabolism [77].

Changes in sleep homeostasis have been hypothesized to play a major role in the mechanism of action of antidepressants, including TSD [78], which recently was also found to influence the expression of some genes of the biological clock which are known to contribute to the homeostatic aspect of sleep regulation [79]. The hypothesis of an impaired sleep homeostasis in bipolar disorder [80] has been recently supported by findings of an altered pattern of cortical excitability during wake in bipolar depressed subjects. Indeed, patients did not show the progressive increase of cortical excitability during wake characterizing healthy subjects [81•]. When considering TSD in bipolar patients, responders to the chronobiological treatment, who sleep less after TSD than non-responders [82], showed also a lower increase of EEG theta power [81•]. Moreover, since, during the sleep/wake cycle, synaptic strength changes, it could be suggested that SD is linked to synaptic potentiation [83, 84]. If the progressive enhancement in cortical excitability after SD in bipolar depression may capture changes of synaptic efficiency and neuroplasticity, the antidepressant action of SD could then be related to the changes in neuronal connectivity paralleled by changes in brain function.

Since patients with severe depression who experience circadian rhythm abnormalities, including mood, sleep, hormonal, and/or temperature regulation, could have a state-related defect in clock gene machinery, SD has been proposed to stabilize clock gene machinery [85], but studies are still lacking.

Sleep Phase Advance Therapy

SPA therapy consists of advancing the timing of the sleep–wake cycle. Antidepressant effects of this intervention have been suggested by the theory linking depression to a misalignment among sleep–wake rhythms, the biological clock, and biological rhythms [86].

While SPA was shown to ameliorate depression, in non-depressed subjects, mood was found to worsen after an acute phase delay in sleep [87]. This mood worsening even generated a depressive syndrome in a minority of predisposed subjects [88]. These studies are in agreement with demonstrated relationships between rhythm phase shifts generated by transcontinental flights and mood episodes. Indeed, when passengers flew from east to west (having a consequent phase delay in circadian rhythms), they were shown to have an increased risk of depression incidence while the opposite was true for hypomania [89].

SPA was found to improve the antidepressant effects of drug treatments [90], and it was extensively used to improve and sustain response after SD [52, 53, 91, 92•]. Even if SPA therapy administered for 2–3 weeks was found to produce a clinical improvement in about 75 % of treated patients [86], SPA alone has never caught on in clinical settings, probably because a phase advanced sleep schedule does not match of with social and environmental cues and expectations.

Mechanisms of Action

According to the phase advance hypothesis, depression could be generated and maintained by a misalignment between the circadian system and sleep [93] and could then be corrected by SPA. Indeed, heterogeneous abnormalities in internal timing were supposed to characterized patients affected by mood disorders. Individualized manipulations of the sleep wake rhythms may be needed to achieve the optimal synchrony between different rhythms [94], and inducing a phase advance of the sleep–wake cycle could lead sleep to coordinate with other already advanced biological rhythms. The synchronization could have then an antidepressant effect by promoting a better "internal timing" [95]. There is, however, a lack of studies on the profile of the different biological rhythms in patients with mood disorders, and some studies in small samples suggest not only a delayed sleep phase in young people with unipolar or bipolar affective disorders [96], to be corrected with SPA, but also an extreme individual variability and desynchrony in the relationship between biological rhythms of melatonin and sleep [97]. Studies in the general population confirmed, however, that earlier parental set bedtimes are a protective factor against depression and suicidal ideation during adolescence [98], thus supporting the general usefulness of SPA.

Light Therapy

The therapeutic use of light therapy (LT) started in the 1980s, and for decades, it remained mainly confined to the treatment of seasonal affective disorder (SAD) despite early studies specifically addressing the treatment of non-seasonal depression [99–101]. LT is now acknowledged as a powerful antidepressant which can be used with the same efficacy and indications of antidepressant drugs [102–104].

Light Therapy for Seasonal Affective Disorder

LT for SAD was developed to extend daytime photoperiod and counteract winter darkness [105]. SAD is a form of depression that has a seasonal pattern, which typically occurs in the autumn and winter with remission in the spring or summer. The prevalence of SAD is 2–5 % in the general population in temperate climates [106]. In addition to general symptoms of depression such as depressed mood and diminished interest or pleasure, patients with SAD often show atypical vegetative symptoms including hyperphagia (particularly carbohydrate-rich foods), weight gain, and hypersomnia. Since the lack of sunlight during wintertime is related to SAD, LT is used in order to mimic a summer photoperiod.

LT is now considered to be the first-line treatment for SAD because of its low side effect profile [107] and high response rate [108, 109]. The meta-analysis of Terman et al. [110] found remission rates of up to 67 % in patients with milder SAD and up to 40 % in severe SAD patients. The conventional LT system consists of a set of white fluorescent bulbs installed in a box with a diffusing screen that filters out UV light. During LT sessions, patients sit in front of a light box mounted on a table with their eyes open. The recommended initial dose is 10,000 lux for 30 min/day in the early morning [111]. Lower intensities can also be effective, but they need substantially longer exposure durations [112, 113], e.g., 2500 lux for 2 h/day [106]. The effects of LT do not persist after discontinuation; therefore, treatment is usually continued until the time of usual spontaneous remission in the spring or summer. LT is generally well tolerated and well accepted by patients. Adverse effects may include headache, eyestrain, nausea, and agitation [107, 114], but these are usually transient and mild.

Light Therapy—Beyond Seasonal Affective Disorder

The APA Committee on Research on Psychiatric Treatments assessed the evidence base for the efficacy of LT in treating mood disorders and concluded that LT is an efficacious treatment not only for SAD but also for non-seasonal major depression with effect sizes equivalent to those in most antidepressant pharmacotherapy trials [103]. Antidepressants, first-line treatment for major depression, take 2–4 weeks to build up its effect and work fully, and this delayed action is one of the major issues of the current psychiatry. The double-blind, placebo-controlled studies found that LT combined with an SSRI leads to more rapid (within a week) and more profound (by approximately 30 %) improvement in patients with non-seasonal depression than drugs alone [115, 116]. The finding of these studies is consistent with the earliest reports [117] and suggests the usefulness of LT as an adjunct therapy in treating non-seasonal depression, especially in initial treatment phase.

Other than those above, therapeutic effects of LT have been reported in various psychiatric conditions: late luteal phase dysphoric disorder [118], bulimia nervosa [119, 120], antepartum depression [121, 122], adult ADHD [123], dementia [124], and elderly depression [125], even dangerous and difficult-to-treat depressive conditions, at risk of unpredictable mood swings and behavioral worsening, such as comorbid resistant depression and borderline personality

disorder [126] and bipolar adolescents with breakthrough depressive symptoms [127]. In some reports, LT, given at midday and not in the morning, could also be tailored to counteract the depressive swings, without exacerbating mania, in course of rapid cycling bipolar disorder [128]. Benefits can be obtained in the most severe, chronic, and refractory cases of depression [129].

A report on four treated cases [130] raised concerns about the possibility of triggering manic switches in bipolar disorder, but studies on hundreds of treated bipolar depressed patients over 30 years ruled it out and confirmed efficacy [18, 131–135].

Time of Administration

The therapeutic response to LT critically depends on time of delivery relative to personal circadian phase, which is determined by the onset of melatonin secretion. Terman et al. found that bright light administered 7.5–9.5 h after evening melatonin onset produces twice the remission rate (80 vs. 40 %) of light presented 9.5–11 h after melatonin onset and proposed to administer bright light about 8.5 h after melatonin onset for obtaining maximum therapeutic effect [108]. However, it is not always practicable to directly measure melatonin onset in daily clinical practice. A practical solution is found in the Horne–Ostberg Morningness–Eveningness Questionnaire (MEQ) [136] score, which strongly correlates with melatonin onset. Using this questionnaire, optimal administration time of LT can be determined without direct measurement of melatonin.

Although the exact mechanism of action of LT in treating SAD has remained unclear, it is assumed that LT exerts its therapeutic effect by restoring circadian rhythm to a normal phase position. The circadian rhythm of core body temperature, cortisol, and melatonin secretion is known to be phase-delayed in most SAD patients [137, 138]. Bright light in the morning, which causes phase advance of endogenous circadian rhythms, could correct misalignment between endogenous rhythms and sleep–wake cycle, resulting in clinical improvement. The treatment response usually begins 2–4 days after the start of LT, and it is completed within 2 weeks. If there is still no response, evening light (7–9 p.m.), which causes a phase delay of endogenous rhythms, should be tried since a small subgroup of SAD patients may be phase-advanced [139].

Low-Intensity Blue Light Treatment

In the last two decades, there was the seminal discovery of a new class of photoreceptors in the mammalian retina, expressing a photopigment named melanopsin [140, 141]. These new photoreceptors, melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs), play a major role in regulating the biological clock [140, 142]. These cells transmit the environmental light level to the "master clock" in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus and are the most sensitive to light with a wavelength of about 460 nm (blue light) [143]. The discovery of ipRGCs led to the recent development of a new concept of LT devices using blue or blue-enriched light. Although there is still insufficient evidence of their effectiveness, recent studies have suggested that therapeutic effects of low-intensity blue or blue-enriched light are comparable to those of the standard bright LT [144, 145].

Dawn Simulation Therapy

As mentioned above, administration of light at the optimal time is quite important for better response in the treatment of SAD. However, patients with SAD often delay or skip treatment because of excessive sleepiness in the morning. In order to bypass this problem, the application of a dawn simulator to the treatment of SAD has been considered. In dawn simulation, light gradually increases over 90 min or longer from about 0.001 lux (starlight) to 300 lux (sunrise under shade) in the early morning, to mimic a natural sunrise (CET manual). As bright LT, dawn simulation has an antidepressant effect and normalizes hypersomnic, phase-delayed and fractionated sleep patterns [146].

The advantage of this treatment technique is that the light signal is presented while the patient is asleep, and it can be applicable for patients with hypersomnolence. In addition, dawn simulation seems to be effective in ameliorating the difficulty awakening [147]. Early parallel-group studies comparing the efficacy of dawn simulation to conventional bright LT for the treatment of SAD have yielded conflicting results [148–150]. However, a recent crossover study showed that the therapeutic effect of these two therapies in treating SAD is comparable [151]. Further clinical trials are still needed to confirm the efficiency of dawn simulation, but this "automatic" therapy seems promising as a new treatment choice for SAD.

Mechanisms of Action of Light Therapy

Human circadian rhythms are endogenously driven by the SCN in the anterior hypothalamus. The SCN is synchronized to the external 24-h light/dark cycle by retinal light input. Bright light is thought to be the major time cue (zeitgeber) for human circadian rhythms and can shift biological clock earlier or later, depending on when it was given. Namely, morning light causes phase advance (a shift to an earlier time), and evening light causes phase delay (a shift to a later time).

As already touched upon, misalignment between endogenous rhythms and the sleep–wake cycle is assumed to play a role in pathogenesis of SAD (phase shift hypothesis (PSH)) [152]. According to the PSH, circadian rhythms are phase delayed relative to the sleep–wake cycle in most SAD patients during winter, and morning light could improve their

depressive symptoms by realigning endogenous rhythms with the sleep–wake cycle. The PSH further postulates that there is a smaller subgroup of SAD patients whose circadian rhythms are phase advanced [152]. The patients of this atypical group are considered to favorably respond to evening light, which causes phase delay of endogenous rhythms.

Monoamine is also speculated to be involved in the mechanisms of action of LT. Tryptophan (precursor of serotonin) depletion reversed the beneficial effect of LT in SAD patients [153, 154]. Similarly, catecholamine depletion caused relapse in SAD patents who responded to LT [155]. Recently, a PET study found that LT reduced 5-HT transporter binding in the anterior cingulate cortex (ACC) of healthy individuals during winter [156], suggesting that antidepressant effect of LT may exert by changing 5-HT transporter function in the ACC, a region involved in mood regulation.

Dark Therapy

A single pilot trial showed that while exposure to light is antidepressant, exposure to dark can reduce manic symptoms as rapidly as antipsychotic drugs, when administered during the first weeks of the manic episode [157], when patients might be more sensitive to chronobiological interventions [158]. Also, the continuous mood swings of rapid cyclers appear to stabilize when maintaining a regular light–dark rhythm with an enlarged darkness period [159, 160].

This promising approach, which could reduce the need for antipsychotic drugs and lead to shorter hospitalizations, is however still waiting for evaluation in randomized trials. Given the specific effects of blue light on the master clock, a "virtual darkness" approach has also been recently proposed, by suggesting the use of amber lenses which can block light in the blue spectrum, and a pilot trial confirmed that wearing amber lenses in the evening can improve sleep quality in healthy volunteers [161]. Considering the extreme sensitivity of bipolar patients to the biological effects of light [162] and that sleep loss is a common final factor in the triggering of mania [163], useful virtual darkness to optimize sleep and prevent mood swings may also include the filtering of blue light coming from computer screens, which can influence melatonin levels even when using normal tablet screens [164]. These approaches, which are diffusing in the general population thanks to the easy availability of amber glasses and of free dedicated software like f.lux (https://justgetflux.com) and redshift (http://jonls.dk/redshift), have never been tested in clinical conditions.

A controlled dawn–dusk simulation to keep stable the photoperiod despite seasonal changes has been proposed as a therapeutic intervention [165] and proven useful in ameliorating extreme desynchrony of rhythms, such as in Alzheimer dementia [166]. Future research will clarify if the darkness and virtual darkness approaches might be clinically useful alone or combined with LT and SD to improve clinical efficacy. These considerations extend to melatonin, which can effectively entrain rhythms in response to darkness, but which is still waiting for a proof of efficacy as an antidepressant [167].

Conclusions

Major depression was recently reported to be the most important contributor to the burden of mental and neurological disorders in Europe [168], and it was considered the leading cause of global burden of mental and neurological disorders in terms of disability adjusted life years (DALYs) [169]. In everyday clinical practice, antidepressant drugs are the mainstay for the treatment of depression, but treatment efficacy is lower than desired [170]. Chronobiological therapies in treating mood disorders are characterized by rapid and sustained effects, when combining them among themselves or with drugs. Effects sizes are the same reported for the most effective psychiatric treatments, but the latency of action is smaller and side effects are usually marginal or absent. Moreover, chronotherapeutics should be considered a treatment option in those patients for whom drug therapy may be contraindicated, such as pregnant women, elderly people, and people under drug treatment for other medical diseases.

In conclusion, chronobiological therapies could fill the gap left by traditional antidepressant drugs in the treatment of mood disorders and the manipulation of biological and circadian rhythms should be the starting point of the developing of more and more efficacious therapeutic interventions.

Compliance with Ethical Standards

Conflict of Interest Sara Dallaspezia, Masahiro Suzuki, and Francesco Benedetti declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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