EXPERT REVIEWS

Chronobiological therapy for mood disorders

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Alteration of the sleep–wake cycle and of the sleep structure are core symptoms of a major depressive episode, and occur both in course of bipolar disorder and of major depressive disorder. Many other circadian rhythms, such as the daily profiles of body temperature, cortisol, thyrotropin, prolactin, growth hormone, melatonin and excretion of various metabolites in the urine, are disrupted in depressed patients, both unipolar and bipolar individuals. These disrupted rhythms seem to return to normality with patient recovery. Research on circadian rhythms and sleep have led to the definition of nonpharmacological therapies of mood disorder that can be used in everyday practice. These strategies, named chronotherapeutics, are based on controlled exposures to environmental stimuli that act on biological rhythms, and demonstrate good efficacy in the treatment of illness episodes. They include manipulations of the sleep–wake rhythm (such as partial and total sleep deprivation, and sleep phase advance) and of the exposure to the light–dark cycle (light therapy and dark therapy). In recent years, an increasing literature about the safety and efficacy of chronobiological treatments in everyday psychiatric settings has supported the inclusion of these techniques among the first-line antidepressant strategies for patients affected by mood disorders.

Keywords: bipolar disorder • chronotherapeutics • depression • light therapy • mood disorder • sleep deprivation

Alteration of the sleep–wake cycle and of the sleep structure are core symptoms of a major depressive episode, and occur in both of the courses of bipolar disorder and of major depressive disorder. Approximately 90% of depressed patients complain of poor quality of sleep, with sleep disturbances appearing weeks before the recurrence of mood episodes [1] and worsening in the days preceding the recurrence [2]. Sleep in major depression is characterized by disturbances of sleep continuity, a reduction of slow-wave sleep and a disinhibition of rapid eye movement (REM) sleep, involving a shortening of REM latency and an increase of REM density [3].

In bipolar disorder, the relationship between sleep disturbances has been documented for both depressive and manic episodes, with features that are peculiar to the episode polarity. Most factors known to precipitate a manic recurrence of illness could be related to the genesis of mania through a marked reduction in sleep. Moreover, a decreased need for sleep is a fundamental marker of the manic state [4].

Many other circadian rhythms have been found to be disrupted in depressed patients, both unipolar and bipolar individuals. These disrupted rhythms include the daily profiles of body temperature, cortisol, thyrotropin, prolactin, growth hormone, melatonin and excretion of various metabolites in urine [5,6], and most of them seem to normalize with patient recovery.

Polymorphisms in molecular clock genes, which play a pivotal role in maintaining circadian rhythms, show not only an association with affective disorder, but also seem to influence symptomatology characteristics and response to treatment [7]. Moreover, some drugs used to treat mood disorders interact with clock genes. Chronic treatment with fluoxetine increases expression of CLOCK and Bmal1 in the hippocampus [8], valproate alters the expression of several circadian genes in the amigdala [9], and lithium salts inhibit glycogen synthase kinase-3β expression [10] and lengthen the circadian period in several animals, including humans [11].

Circadian rhythm and sleep research have led to the definition of nonpharmacological therapies of mood disorder that can be used in everyday practice [12]. These clinical interventions, named chronotherapeutics, are based on controlled exposures to environmental stimuli that act on biological rhythms. The use of psychiatric chronotherapeutic techniques in everyday psychiatric work is a rather new achievement and is almost

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exclusive to the treatment of mood disorders, with antidepressant effects of different chronotherapeutic approaches described in all depressive conditions. Mainly developed in European countries over the last five decades [13], these techniques evolved from both the empirical observation of impressive clinical changes following random exposure to environmental stimuli (e.g., immediate mood improvement in sleep-deprived depressed patients), and from neurobiological models of behavior [14]. They include manipulations of the sleep–wake rhythm (e.g., partial and total sleep deprivation [SD] and sleep phase advance [SPA]) and of the exposure to the light–dark cycle (light therapy [LT] and dark therapy) [15].

Sleep deprivation

Clinical aspects

The clinical effects of SD in thousands of depressed patients worldwide have been reported in more than 60 studies. The common effect is a rapid (within 24–48-h) reversal of depressive symptoms.

Positive antidepressant effects of SD have been reported in different depressive conditions, but better effects have been shown in endogenous major depression compared with secondary depression [16], and in the treatment of bipolar disorder compared with unipolar disorder [17]. The reported response rates to SD are similar to those observed with antidepressant drugs, ranging from 50 to 80% of treated patients. The response to SD has been shown to be influenced by the same functional polymorphisms that influence the efficacy of antidepressant drugs, thus suggesting common mechanisms of action [18]. In particular, significant associations have been observed with gene variants affecting the promoter of the serotonin transporter [19], the serotonin receptor 2A [20], the catechol-*O*-methyltransferase [21] and the glycogen synthase kinase-3β promoter [22].

Clinical predictors of response to SD also include the presence of diurnal mood fluctuation and melancholic features. Moreover, brain imaging studies demonstrated that depressed patients who had a favorable clinical response to SD had higher relative metabolic rates in the ventral anterior cingulate, medial prefrontal cortex and posterior subcallosal cortex at baseline than either normal volunteers or depressed patients who did not respond to SD [23].

While antidepressant drugs show long response latencies, response to SD becomes clinically relevant in a matter of hours after the beginning of treatment (i.e., the day after) [24]. Clinical trials exploring the hypothesized superiority of antidepressant drugs on placebo have consistently affirmed that no difference can be expected between the active and placebo treatments during the first 2 weeks. Meta-analytical studies provide compelling evidence that treatment-emergent medication–placebo difference can be observed after some weeks [25]: a significant drug effect was first noted, on average, 2.40 (standard deviation: 1.48) weeks (range: 1–7 weeks) following randomization, and, in 92% of studies, by 4 weeks after randomization. In studies that provided data on the time course of response to tricyclic antidepressants, a medication–placebo difference was noted in 2.53 (standard deviation: 1.54) weeks (range: 1–6 weeks) and in studies with data on selective serotonin reuptake inhibitors (SSRIs), a medication–placebo difference was noted in 2.74 (standard deviation: 1.63) weeks (range: 1–7 weeks).

Chronotherapeutic interventions, such as manipulations of the sleep–wake rhythms and of the light–dark cycle, can certainly trigger mania when patients are in euthymic conditions. When repeated total SD (three cycles in a week) was administered to 206 patients affected by bipolar disorder type I as an antidepressant intervention during a major depressive episode, a 4.85% (4.54% if patients were receiving lithium salts) switch rate into mania was observed. This switch rate is similar to those observed with SSRIs and placebo, lower than those reported with tryciclic antidepressants [26], and much lower than those reported (10–29%) in bipolar patients receiving antidepressant drugs as maintenance treatment [27,28]. Moreover, the severity of mania was rather mild or moderate in the majority of patients, and less than half needed to combine antipsychotic medication with mood stabilizers to return to euthymia [29]. These low rates were confirmed when LT was combined with repeated total SD, thus confirming the favorable side-effect profile of chonotheraputic treatment in this respect [24]. Hence, the obvious benefit of overcoming the need for unwieldy treatment of bipolar depression with antidepressant drugs, which leads to the quandary of choosing between a high risk of relapse in the absence of maintenance treatment with antidepressants, and a risk of development of treatment-emergent mania in roughly a quarter of bipolar patients administered antidepressant drugs [28,30].

It is still unclear how many hours of SD are needed to achieve its full antidepressant effect. The typical antidepressant SD is called 'total' SD because wake is prolonged throughout the night of treatment. It begins with the extension of daytime wake into the night and lasts about 36 h until the evening of the day after.

Researchers still argue whether a short nap can stop the powerful effect of SD. Considering the available data, it could be supposed that the interaction between naps and lack of response may be linked with yet undefined individual characteristics, and that a full antidepressant response to SD can well occur independent of possible napping. Even if most of the studies showed a mood worsening, not only after napping [31], but also after subjectively unrecognized microsleeps [32], others did not, or even reported an improvement in mood after short naps [33]. Moreover, some researchers have suggested a circadian variation of propensity to relapse into depression as a function of nap timing, proposing early morning naps more related to a worse response [34]. This hypothesis is sustained by the observation that 'partial' late night SD, during which patients are awakened during the second part of the night, also shows a clear antidepressant effects in many subjects [35].

The amelioration in mood is usually followed by a high-rate symptomatological relapse in the morning after awakening from recovery sleep, even when a complete response had been achieved the evening before. In the following days, patients show a trend of progressive worsening and the severity of depression returns at the same levels observed at baseline [36]. It is also expected that approximately 10–15% of patients do not improve after the night of wake, but show an atypical improvement in the day after the recovery sleep [37]. Furthermore, in this case, the achieved improvement is expected to progressively deteriorate in the following days.

Many strategies have been developed in order to prevent this short-term relapse [38]. Repetition of treatment was proven unsuccessful, both because of reported tolerance to the therapeutic effects [39] and because, following eventual discontinuation, patients relapsed. The pattern that is typically observed shows repeated ameliorations after SD and repeated relapses after recovery sleep [40], with only 5–10% of treated patients maintaining a stable euthymia if no augmentation therapy is used [41].

The early relapse after SD can be prevented by combining it with other chronotherapeutic interventions, such as LT or SPA. Bright LT during and after SD was found to stabilize the antidepressant effect of both partial [42] and repeated total SD [43]. In a similar way, SPA has been shown to prevent the early relapse after SD [44]. It should be noted that one study reported that a phase advance of the activity–rest rhythms is a correlate of response to repeated SD combined with LT [45]; combining SD and SPA could then better achieve these changes in biological rhythms.

Antidepressant SD has been successfully associated with different antidepressant drugs, such as SSRIs [46–49], tricyclic antidepressants [50–52] and amineptine [53], with a synergistic effect.

Conversely, in bipolar patients, the long-term response rate to combined chronotherapeutics (e.g., repeated SD plus LT) was shown to be independent of concomitant antidepressant drugs in patients who were taking lithium salts as a long-term treatment for the disorder [54]. This finding is important for bipolar depression, where the use of antidepressant medications implies an increased risk of manic switch. The most efficacious mood stabilizer, lithium, seemed to be sufficient to prevent both acute relapse [43,55] and delayed relapse [41,54]. Moreover, lithium salts enhance the acute antidepressant response to SD, probably by overcoming the effect of the unfavorable genetic predispositions that may affect the functioning of the serotonergic system [56]. A treatment strategy based on the combination of repeated SD with LT and lithium seemed then to reach sustained remission rates, which were comparable to those obtained with long-term antidepressant drugs [30,54].

Our group developed a treatment schedule based on repeated SD combined with LT and lithium salts. It consists of repeated 36-h SD, three cycles during 1 week, resulting in a lengthening of the sleep–wake period from the usual 24–48 h. On the first, third and fifth day patients stay awake from 7 am until 7 pm the following day. They are then allowed to sleep during the night of the second, fourth and sixth day. SD is carried out in normal ambient light, but patients are administered LT during the SD night, to counteract sleepiness, and in the morning after recovery sleep, half an hour after awakening, between 8–9 am from day 1 to day 7. If patients are not being treated with ongoing lithium salts, they start them at the beginning of the chronotherapeutic procedure, with the aim of preventing relapse. Many other effective treatment strategies, which combine SD with other manipulations of the sleep–wake and of the light–dark rhythms, have been proposed [12]. Recently Wu and colleagues extended SD, LT and phase advance combined therapy to lithium-intolerant bipolar patients on mood stabilizers other then lithium [57].

In unipolar patients, repeated total SD once a week has also been proposed as a prophylactic treatment to sustain response and prevent relapses [58,59].

In conclusion, combined chronobiological treatments with SD and LT are useful for endogenous depression, both unipolar and bipolar. Considering its rapid efficacy and the low risk of manic switches, it should be considered as a first-line strategy to treat bipolar depression. The only known contraindication to treatment is the presence of epilepsy, because of the high risk of seizure induction linked to sleep reduction [60]. Moreover, literature evidence suggests caution in administering SD to psychotic depressed patients. Although they were found to react more favorably than nonpsychotic depressives to total SD combined with clomipramine, they also showed a larger negative response after recovery sleep compared with other patients [61]. Moreover, anecdotal reports about delusional depressed patients treated with SD showed that in some cases, an 'increased intensity of drives' after SD was paralleled by a worsening of psychotic symptoms [62,63]. No definite conclusion can be drawn on the latter topic, but caution and a careful antipsychotic strategy, possibly including combined medications, is suggested by the available literature.

Neurobiological mechanisms

The synergistic interaction between SD and antidepressant drugs observed in clinical studies supported a major role for monoamines in the mechanism of action for SD, and neurobiological studies in human subjects and in animal models have shown that SD was able to increase the activity of all the neurotransmitter systems targeted by antidepressant drugs: serotonin, norepinephrine and dopamine [18,64]. The implication of monoamines in the mechanism of action of SD is confirmed by the findings that biological factors affecting the activity of these pathways, such as genotypic variants [19,65,66], basal neurotransmitter levels [67] or the extent of receptor occupancy [68], affect the clinical antidepressant response.

Moreover, SD increases the levels of thyroid hormones [69] and interacts with glycogen synthase kinase-3β [70], glutamate [71] and the sleep-related mechanisms that regulate synaptic homeostasis [72], which are emerging as specific targets for the treatment of mood disorders.

The antidepressant response to SD was shown to be associated with specific functional and metabolic changes in the brain cortex [18]. In particular, major changes were observed in the ventral/anterior cingulate and medial prefrontal cortex. Responders to SD show increased relative localized metabolic activity compared to nonresponders or normal controls at baseline in these areas, with higher baseline levels leading to a greater decrease induced by SD and a better antidepressant effect [48,73,74]. This metabolic changes are paralleled by changes in spectroscopic correlates of glutamatergic activity in the cingulate cortex [71], and in neural correlates of brain activity in response to emotional tasks [65]. Moreover, a decrease in the perfusion of the cingulate [75] and amygdala [76], which is specific of antidepressant response, parallels the metabolic changes in the cortex.

These results are consistent with the finding that metabolic changes in the cingulate cortex are proportional to the clinical amelioration during pharmacological antidepressant treatments [77,78].

Sleep phase advance therapy

Sleep phase advance therapy consists of advancing the timing of the sleep–wake cycle. Studies on small samples showed SPA to improve the antidepressant effects of drug treatments and to ameliorate depression [79,80]. On the contrary, an acute sleep phase delay was shown to worsen mood in normal subjects [81], leading to the onset of clinically relevant depressive symptoms in a minority of subjects [82]. Moreover, a study on mood episodes triggered by phase shifts induced by transmeridial flights showed that flights from east to west (which tend to phase delay circadian rhythms) increased the risk of depression incidence, while the opposite was true for hypomania [83].

Sleep phase advance was shown to improve the response to total SD [84]. Other studies demonstrated that SPA therapy for 2–3 weeks alleviated depressive mood in 75% of patients, even without a preceding successful total SD [79]. However, previous SD creates an improvement of mood that facilitates the patient compliance to the following procedure. Moreover, the rapidly achieved improvement enables limiting the rather unwieldy SPA procedure to 1 week, with a gradual return to the conventional sleep schedule.

To date, the only theory to explain the antidepressant effects of SPA is based on the phase advance hypothesis of depression [85]. This theory assumes that an abnormal phase relationship between the circadian system and sleep could be involved in the pathogenesis and in the maintenance of depression. Following this perspective, a phase advance of the sleep–wake cycle could make sleep coincide with other, already advanced biological rhythms, thus synchronizing them, and improving depression by promoting a better 'internal timing' [86].

However, while clear-cut evidence suggests that disrupted temporal organization impairs behavior, cognition and affect, and that these mechanisms play a crucial role in bipolar disorder [87], it is still unclear how these mechanisms may be implicated in mental disorders, and sound basic research is needed understand the neural mechanisms of this interaction and the role that they play in the pathogenesis of the illness [88]. Moreover, some clinical studies suggest that patients affected by mood disorders could have heterogeneous abnormalities in their internal timing, thus leading to the need for individualized manipulations of sleep–wake rhythms to achieve the optimal synchrony [89].

Light therapy

Clinical aspects

Light therapy derives from basic research showing that hamster seasonal hibernation or reproduction rhythms could be created or reversed by manipulating daylength – more specifically, by changing the duration of melatonin secretion to simulate a winter or summer night. Patients affected by seasonal affective disorder (SAD) who showed depressive episodes during winter, were hypothesized to have abnormal responses to diminishing daylength in fall. Thus, they were supposed to benefit from morning light exposure signaling a spring dawn. The treatment has been remarkably successful and has now been established worldwide as the therapy of choice for winter depression and is typically self-administered at home on a schedule recommended by the clinician [90,91]. It has a latency of action of only a few days [92] and a low side-effect profile [93].

Treatment studies have focused on parameters that influence response in SAD, including exposure schedule, duration, intensity and wavelength spectrum. The established form of bright LT provides broad-spectrum white, UV-filtered, diffuse illumination. The dose of 10,000 lux (bright light) for 30 min [94,95] demonstrated the biggest antidepressant efficacy. Lower intensities can also be effective, but they require substantially longer exposure durations [96,97]. The consensus is that bright light has an antidepressant effect greater then placebo (dim) light when administered at all times of day, but that morning light is superior to evening light [12]. Better response rates are achieved when patients are treated with LT timed according to their personal circadian phase (internal time), which is linked to the circadian rhythm of melatonin secretion. Bright LT 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 [98]. In terms of circadian rhythms, a greater phase advance of melatonin onset means a better clinical improvement, and the phase advance to earlier light exposure is larger than that to later light exposure. Since melatonin onsets can vary between patients by as much as 6 h, this information is useless unless the patient's circadian rhythm phase is known. Direct measurement of the melatonin rhythm is not always practicable and the clinician may need an on-the-spot assessment. A practical solution is found in the Horne-Ostberg Morningness–Eveningness Questionnaire (MEQ) score [99], which measures diurnal preference for activities in healthy subjects and correlates strongly with melatonin onset [90]. This has provided an algorithm for timing light treatment.

Although bright LT can be considered to be the treatment of choice for SAD, with rapid improvement and generally mild side effects, there remains a significant number of nonresponders and partial responders [90]. Some treatment failures undoubtedly result from nonoptimum dosing and timing. In fact, to maximize the therapeutic effect, compliance is a *sine qua non* condition. Despite an agreement to awaken for light treatment at a specific hour, patients may ignore the alarm, considering additional sleep to be the priority of the moment, and may delay or skip treatment. In order to bypass these compliance problems, dawn simulation therapy was developed. It consists of a slow, incremental light signal in the bedroom at the end of the sleep interval, with maximum intensity two orders of magnitude lower than in post-awakening bright LT (e.g., 300 vs 10,000 lux). First described by Terman and colleagues [100], dawn simulation has been studied with procedural variations in several controlled trials [101]. The basic therapeutic strategy is to set the time of the sunrise signal earlier than outdoors in winter. As with bright LT, there is an antidepressant response and normalization of hypersomnic, phase-delayed and fractionated sleep patterns [100]. Since dawn simulation appears to

match postawakening bright light in efficacy in seasonal depression, it may become the next-generation LT given its convenient use while the patient sleeps [91].

The use of bright LT has now expanded beyond SAD [91], with evidence for therapeutic effects in late luteal phase dysphoric disorder [102], bulimia nervosa [103], sleep–wake cycle disturbances [104] and Alzheimer's dementia [105]. Both open-label [106] and controlled [107] studies have successfully employed LT for major depressive disorder during pregnancy, which offers a safe somatic treatment alternative to antidepressant drugs, even if the woman does not show an history of seasonal mood oscillations.

Recent studies have also provided evidence for the efficacy of bright LT in nonseasonal major depression. Confirming the results of the earliest studies [108], the American Psychiatric Association Committee on Research on Psychiatric Treatments [109] and a Cochrane review [110] concluded that LT for nonseasonal depression is efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials. When combined with standard antidepressant drug treatment for unipolar depression, LT hastens recovery, with benefits that can be perceived by the patients during the first week of treatment [111,112].

Neurobiological mechanisms

The therapeutic use of light arose from researches showing that light is a strong timing cue (zeitgeber). In mammals, a primary circadian pacemaker, the master clock, located in the suprachiasmatic nuclei of the anterior hypothalamus [113], drives all circadian rhythms in the brain and body. Light can synchronize the master clock to the external 24-h light/dark cycle by inputs going from the retina through the retinoic–hypothalamic tract [114] and can shift the biological clock to earlier or later depending on whether it is administered in the early morning or in the evening. Patients suffering from SAD are supposed to become depressed in fall/winter, at least in part because the late dawn in winter causes a delay in their endogenous circadian rhythms in regards to clock time and the sleep–wake cycle [89]. LT could show its antidepressant efficacy, providing a corrective phase advance and realigning endogenous rhythms with the sleep–wake cycle. In fact, exposure to bright light in the morning causes a phase advance of endogenous circadian rhythms, which is proportional to clinical improvement in depressed patients: the bigger the phase advance, the better the clinical improvement [98]. Moreover, bright light scheduled in the evening, which causes a phase-delay of endogenous rhythms, has been proven to have equally antidepressant effects as morning exposure in those uncommon SAD patients who are phase-advanced [115].

Different hypotheses focus on the role of chronobiological alterations in the pathogenesis of not only SAD, but also nonseasonal major depression [116]. The circadian phase-shift hypothesis [117] is based on concept that some affective disorders might be partly due to a mismatch in circadian rhythms [118]: during a depressive episode the master clock is time advanced in relation to those rhythms related to the sleep–wake cycle, which is influenced by melatonin production and by the external timing. LT in the morning, acting as a phase advance of these last rhythms, could realign the mismatch, resulting in clinical improvement.

Dark therapy

Dark therapy, in which complete darkness is used as a mood stabilizer in bipolar disorder affected by mania, has support from several preliminary studies. Two case reports showed that extended bed rest and darkness could stabilize timing and duration of sleep, and rapidly improve mood swings in rapid cycling patients who were exposed to a regimen of 14 h of enforced darkness and rest from 6 pm to 8 am each night [119,120]. Our group demonstrated that adding dark therapy to the usual antimanic therapy resulted in a significantly faster decrease of Young Mania Rating Scale scores when patients were treated within 2 weeks from the onset of the current manic episode. When the duration of the current episode was longer, dark therapy had no effect. Follow-up confirmed that good responders needed a lower dose of antimanic drugs and were discharged earlier from the hospital [121].

Expert commentary

Chronotherapeutics works. With respect to traditional antidepressant drugs, chronobiological treatments target the same neurotransmitter systems (5-hydroxytryptamine, noradrenalin, dopamine) and the same brain structures; they are influenced by the same biological factors (e.g., serotonin-transporter-linked polymorphic region pharmacogenetics) and the same clinical factors (e.g., previous history of resistance). Moreover, they have the same response rates, but seem to be more rapid and with fewer side effects than other treatment options. A single week of treatment – which can be combined with medication if necessary – can get depressed patients, even drug resistant patients, out of hospital under remission, with a lower relapse rate months later.

In recent years, an increasing literature regarding the safety and the efficacy of chronobiological treatments in everyday psychiatric settings supports the inclusion of these techniques among the first-line antidepressant strategies for patients affected by mood disorders. These techniques have passed the experimental developmental phase and reached the status of powerful and affordable clinical interventions for everyday clinical therapy of depressed patients.

Nevertheless, to date these techniques have not been used diffusely worldwide. Even if in 2004 the International Society for Affective Disorders convened a Committee on Chronotherapeutics to advance the use of SD (wake therapy) and LT in major depression, with the hope that a consensus statement would get colleagues interested [15] and a treatment manual for a step-by-step implementation of chronotherapeutic methods for treating depression has been written [12], not much has changed. It should be hoped that these treatments will be considered to be possible first-line interventions for mood disorder in the near future.

Five-year view

Despite its great potential for clinical use, many issues regarding chronotherapeutics need to be assessed with further research.

In particular, concerning total SD, the available literature does not provide a definition of dose–response relationships comparing total with partial SD, or the definition of how many cycles of SD are needed to obtain the best antidepressant effect.

Moreover, further studies should be conducted to compare the efficacy of the techniques proposed over decades, in order to optimize the treatment.

Several questions remain unanswered concerning the use of LT in the treatment of nonseasonal depression. As for seasonal depression, treatment studies focusing on parameters that influence response, including exposure schedule, duration and intensity of light should be carried out in order to optimize the treatment. Given that the photo-period continuously changes over the seasons, with a phase-delay of natural morning light exposure during fall and winter and a phase-advance during spring and summer, whether the season of treatment and the season of recurrence influences the antidepressant efficacy should be studied. Moreover, the efficacy of dawn simulation in nonseasonal depression should be estimated.

Finally, the many neurobiological mechanisms involved in the response to chronotherapeutics still remain obscure. Explanation of this issue could be useful to understand the pathogenesis of mood disorders. It would be useful to carry out additional preclinical studies that include animal models of circadian gene dysfunction, as well as clinical studies, which further explore the relationship between circadian dysfunction and pathological states.

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Key issues

- Research into circadian rhythms and sleep have led to the definition of nonpharmacological therapies for mood disorders that can be used in everyday practice. These strategies, named chronotherapeutics, are based on controlled exposures to environmental stimuli that act on biological rhythms, and demonstrate good efficacy in the treatment of illness episodes. They include manipulations of the sleep–wake rhythm (such as partial and total sleep deprivation [SD], and sleep-phase advance) and of exposure to the light–dark cycle (light therapy [LT] and dark therapy).
- It is still unclear how many hours of SD are needed to achieve its full antidepressant effect. The typical antidepressant SD is called 'total' SD because wake is prolonged throughout the night of treatment. It begins with the extension of daytime wake into the night and lasts about 36 h until the evening of the day after. The amelioration in mood is usually followed by a high rate of symptomatological relapse in the morning after awakening from recovery sleep, even when a complete response had been achieved the evening before.
- Many strategies have been developed in order to prevent this short-term relapse. A treatment strategy based on the combination of repeated SD with light therapy and lithium seemed to be the better strategy to reach sustained remission rates.
- The reported response rates to SD are similar to those observed with antidepressant drugs, ranging from 50 to 80% of treated patients. Positive antidepressant effects of the treatment have been reported in different depressive conditions, but better results have been demonstrated in endogenous major depression and in the treatment of bipolar disorder.
- Light therapy was first developed and has been established as the treatment of choice for winter seasonal affective disorder (SAD). The use of LT has then expanded beyond SAD, with recent studies providing evidence for the efficacy of bright LT in nonseasonal major depression.
- Treatment studies have focused on parameters that influence response in SAD, including exposure schedule, duration, intensity and wavelength spectrum. The established form of bright LT provides broad-spectrum white, UV-filtered, diffuse illumination. The dose of 10,000 lux (bright light) for 30 min demonstrated the biggest antidepressant efficacy. Better response rates are achieved when patients are treated with LT timed according to personal circadian phase (internal time).
- Dark therapy, in which complete darkness is used as a mood stabilizer in bipolar disorder affected by mania, has support in several preliminary studies.

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