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Antidepressant chronotherapeutics for bipolar depression

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The need for chronotherapeutics

Chronotherapeutics refers to treatments based on the principles of circadian rhythm organization and sleep physiology, which control the exposure to environmental stimuli that act on biological rhythms, in order to achieve therapeutic effects in the treatment of psychiatric conditions. These nonpharmaceutical and biologically based clinical interventions include manipulations of the sleep-wake cycle such as sleep deprivation and sleep phase advance, and controlled exposure to light and dark. The antidepressant effects of chronotherapeutics are evident in difficult-to-treat conditions such as bipolar depression, which has been associated with extremely low success rates of antidepressant drugs in naturalistic settings and with stable antidepressant response to chronotherapeutics in more than half of the patients. Recent advances in the study of the effects of chronotherapeutics on neurotransmitter systems, and on the biological clock machinery, allow us to pinpoint its mechanism of action and to transform it from a neglected or “orphan” treatment to a powerful clinical instrument in everyday psychiatric practice.

Keywords: bipolar disorder; antidepressant; sleep deprivation; light therapy; sleep phase advance; dawn simulation; serotonin; glutamate; dopamine; noradrenaline

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Reduced a positive answer to early doubts about the therapeutic usefulness of chronotherapeutics and about the temporary nature of the achieved benefits. These effects of chronotherapeutics have been particularly evident in difficult-to-treat conditions such as bipolar depression, which has been associated with extremely low success rates of antidepressant drugs in naturalistic settings. Bipolar patients spend a substantial proportion of their time ill, with depression representing their predominant abnormal mood state, but with the repeated use of antidepressant drugs being related to poor prospective response to naturalistic treatment. The clinical need for treatment of their disabling condition and the interplay between the risk of treatment-emergent mania and the risk of relapse when discontinuing drug treatments often leads to prolonged and highly complex medication regimens to achieve a sustained response. Nevertheless, there is still a real clinical need for fast-acting antidepressant effects to counteract the rapid breakthrough depression experienced by the patients: hence the interest in chronotherapeutics, which act without the delay inherent to traditional antidepressant treatments.

Paralleling these clinical achievements in recent years, basic research in the last decade has substantially improved knowledge about the biological mechanisms that control the molecular machinery of the master clock, and link it with the neurotransmitter systems that are involved in mood regulation and targeted by antidepressant drugs. Confirming the classical belief that man and his environment are inseparable, it is now established that exposure to environmental stimuli that act on the transcription of clock genes will lead to major changes in the same brain neurotransmitter function involved in psychiatric conditions; and that from a clinical point of view the choice will be restricted between the potentially detrimental random exposure to these stimuli, which could even precipitate bipolar illness episodes, and the direct control by the psychiatrist in order to achieve a therapeutic effect. The present review focuses on recent achievements in the chronotherapeutic treatment of bipolar depression and on the recently discovered molecular mechanisms that clearly link chronotherapeutics with the usual antidepressant drug treatments of this disorder.

Techniques

The first studies published in clinical samples used single chronotherapeutic techniques to treat depression, but the clinical need for rapid and sustained improvement of patients prompted the combination of different techniques among themselves and with usual antidepressant drug treatments.

Sleep deprivation

Antidepressant effects of sleep deprivation were first reported in 1959, but the first experimental trials to test its clinical efficacy were performed in the 1970s. The amazingly rapid effects of the treatment, which is usually able to restore euthymia in the morning soon after a single night awake, are closely linked to the wake period and are usually rapidly lost after restoring an undisturbed night sleep. To achieve the best results the wake period includes the extension of daytime wakefulness into the night, and lasts about 36 hours until the evening of the day after (total sleep deprivation), but it can also be limited to the second half of the night and the following day, thus allowing sleep during the first half of the night, with little disadvantage: in both cases, the mood amelioration is obtained during the prolonged wake, and in the presence of light. This link between mood and wake, together with the observation that during the nights of undisturbed sleep patients sleep better and deeper than usual, justified the recent use of the term “wake therapy” to refer to this treatment. In the absence of combined treatments, not more than 5% of responders to wake will maintain a stable euthymia in the days of subsequent normal sleep, thus limiting the diffusion of this technique alone. Soon in the early studies, however, SD was observed to produce rapid benefits in the broadly defined depressive syndrome: in endogenous, reactive, unipolar, bipolar, secondary, and schizoaffective depression; in the elderly and in children; in depression secondary to Parkinson’s disease or schizophrenia; or associated with pregnancy and postpartum and premenstrual dysphoric disorder, and with better effects observed in endogenous primary depression compared with reactive and/or secondary depression, and in the treatment of Bipolar Disorder compared with Primary Depressive Disorder. In order to prevent the relapse into depression after SD, single-night SD or repeated SD was combined with serotonergic antidepressants, lithium salts, or other chronotherapeutic techniques. The simple repetition of SD over time has been tested for many schedules, including twice in 1 week, or twice a week for 3 weeks.
for a month, or for twice in 1 week followed by partial SD twice, etc. Repeated SD once a week has also been proposed as a prophylactic treatment: preliminary studies in small samples showed that SD reduced the frequency of relapses and increased the duration of normothymia in roughly one half of the patients.

Our group developed a treatment schedule based on repeated total SD, three times during 1 week, resulting in a lengthening of the sleep-wake period from the usual 24 to 48 hours. When combined with light therapy and with lithium salts, the mainstay for the long-term treatment of bipolar disorder, this therapy is able to trigger an acute response also in patients drug resistant to both serotonergic and tricyclic antidepressants, and to lead to a stable euthymia for 9 months in roughly 60% of bipolar patients without a history of drug resistance. Despite early concerns due to the close link between sleep loss and the onset of mania, this result is achieved with a risk of switch which is around 6% and leads to easily controlled manic reactions, thus comparable to the reported switch rate for placebo. Considering the 15%-to-25% risk of treatment-emergent mania linked with antidepressant treatment in bipolar patients, and the 30% of responders maintaining euthymia when discontinuing drug treatments before 6 months, these data warrant the highest clinical interest in using these techniques as first-choice treatments for bipolar depression.

**Light therapy**

The scientific approach to the treatment of depression with bright light started in the 1980s. Early on, antidepressant bright light therapy (LT) was administered 1 to 2 hours before the usual time of awakening. This phase-advancing administration of light in the early morning was then proven to have better antidepressant effects than the simple increase of the subjective photoperiod obtained by exposing the patients to light in the evening. A correlation was then observed between the magnitude of phase advances to morning LT and improvement in depression ratings, with maximum effects with phase advances of 1.5 to 2.5 hours (about 7.5 to 9 hours after the dim-light melatonin onset the evening before). Since scores on the Morningness-Eveningness Questionnaire (MEQ) are strongly correlated with sleep midpoint and melatonin secretion, a predictive algorithm based on MEQ scores was then developed to define the individual optimal timing of LT administration, and proven successful even when used in common clinical settings, and when giving light in combination with antidepressants. Over the years, other treatment algorithms have been proposed, and research is currently identifying the most effective treatment schedule as a function of seasonality and other individual characteristics.

Given that LT is, however, useful, even when given at midday, the clinical use of LT followed a pattern of evolving applications in any kind of depressive syndrome. The APA Committee on Research on Psychiatric Treatments and a Cochrane review concluded that light treatment for nonseasonal major depression is efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials. When combined with standard antidepressant drug treatments LT hastens recovery, with benefits that can be perceived by the patients during the first week of treatment. After 1 month of treatment, patients treated with light show a net benefit, in respect to placebo, that can be quantified in a approximately 30% better reduction in the severity of depression: remarkably, these values are very similar for early studies performed with the combination of light and tricyclic antidepressants, and for new studies combining light and selective serotonergic drugs. The benefit is also clinically evident in drug-resistant patients, when adding light to ongoing albeit ineffective antidepressants. Similar to SD, LT in nonseasonal major depression does not show a sustained effect after discontinuation, with a complete offset of effect after 1 month, but the relapse can be easily prevented when combining LT with common antidepressant drugs. Again, similarly to SD, LT caused marked benefits in the broadly defined depressive syndrome, including very different psychopathological conditions such as antepartum depression as well as post-stroke depression in the elderly. In the case of bipolar depression, the efficacy of LT alone is questioned, with studies showing either better benefits than in unipolar patients, or worse effects, but the combination of LT with other chronotherapeutic techniques and with lithium salts was proven to lead to stable mood ameliorations and euthymia, even in drug-resistant patients. Moreover, some observations suggested that bipolar patients could be sensitive to the antidepressant properties of light at intensities as low as 300 to 500 lux, far below the usual 10000-lux standard used in LT of unipolar patients: a finding in agreement
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with the proposed supersensitivity of the biological clock to the effects of light as a possible trait marker for bipolar disorder.79 Other studies explored the interaction of LT with the circadian changes of sensitivity of the biological clock to the effects of light and defined “dawn simulation” protocols based on the administration of low intensity (400 lux) LT during the last period of the patient’s sleep episode, a treatment with a comparable efficacy to that of bright white LT.80,81

Sleep phase advance and combined treatments

Antidepressant effects of sleep phase-advance (SPA) have been predicted by chronobiological studies of depression (suggesting a misalignment between the biological clock, biological rhythms, and the sleep-wake rhythms) and first described in 197976; the simple act of going to bed and waking up 5 hours earlier leads to a sustained marked improvement of mood in a bipolar depressed patient, an effect then confirmed in unipolar endogenous depression.79 Remarkably, recent studies on large samples in the general population showed that earlier parental set bedtimes are a protective factor against depression and suicidal ideation during adolescence,82 thus suggesting a major role for the disruption of the circadian timing in the pathophysiology of depression.83 Probably because of the difficult match of a phase-advanced sleep schedule with social and environmental cues and expectations, SPA has never spread into clinical settings. When combined with a previous SD, SPA is however able to sustain its effects and prevent the relapse that might occur after restoring night sleep.84 A short SPA protocol, performed over 3 days, has been shown to be sufficient to achieve this effect and to be synergistic with lithium salts in sustaining a stable euthymia in bipolar depressed patients.85 This protocol can easily be associated with antidepressant medications,86 and more recent pilot trials explored the possibility of a “triple chronotherapeutics” for bipolar depression: SD followed by SPA and combined with morning LT, given as adjunctive treatment to lithium and antidepressants, significantly enhanced antidepressant response.87

Mechanisms of action

The mechanism of action of chronotherapeutics has been widely explored for SD, and suggests convergence of effects between SD and all known antidepressant strategies. Many effective antidepressant treatments target several mechanisms, and a multitarget approach to treatment could overall be better suited for a multifactorial illness such as depression88; chronotherapeutics is no exception, and is able to influence the same mechanisms that are targets for other antidepressants.

Brain monoamines and glutamate

SD potentiates all the monoaminergic systems that are targeted by antidepressant drugs and that have been involved in the pathogenesis of depression, and effects of SD on monoamines are part of its mechanism of action. Research on this topic directly measured changes in monoaminergic neurotransmission in animal models, or studied SD effects in humans with challenge methods, brain imaging, or pharmacogenetic approaches. These methods allowed definition of convergent effects in animal and humans, either healthy or depressed, of SD on serotonin (5-HT), noradrenaline (NA), and dopamine (DA).

In animal models, SD increase 5-HT neurotransmission87 by enhancing the activity of 5-HT neurons in the dorsal raphé nucleus,88 increasing brain extracellular 5-HT79 and 5-HT turnover,89 reducing the sensitivity of 5-HT1A inhibitory autoreceptors,90,91 and increasing the behavioral responsiveness to 5-HT precursors.92 In a similar way, SD was shown to increase synaptic levels of NA79 and tyrosine hydroxylase and NA transporter mRNA in the locus coeruleus,93 and to increase DA activity and behavioral response to DA agonists,94,95 with an increase of DA receptor binding sites during the early stages of SD (following 12 to 24 hours awake)96 and a subsequent subsensitivity after more prolonged wake,97 suggesting downregulation after prolonged stimulation.

Clinical psychobiology confirmed these effects in depressed humans and linked them with the efficacy of chronotherapeutics. SD increased the prolactin response to intravenous tryptophan infusion100 and decreased plasma levels of prolactin, which is inhibited by DA agonists, thus suggesting DA hyperactivity during SD.102,103 D2 receptor occupancy decreased in responders to SD, thus suggesting an enhanced DA release in responders,104 levels of homovanillic acid in the spinal fluid predicted the clinical effects of SD,104 and eye-blink rate after SD increased in responders, suggesting DA activation.105 The NA metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG) and MHPG sulfate107 increased after SD pro-
portionally to severity of depression and clinical response to treatment. Human pharmacogenetics confirmed that gene variants that improve neurotransmission by increasing receptor or transporter density, or decreasing neurotransmitter degradation, also improve the clinical efficacy of SD in bipolar depression when given alone or combined with bright light therapy. This was proven for genotypes influencing the density of the 5-HT transporter and of the 5-HT receptor, or the efficiency of the catechol-O-methyltransferase (COMT) in clearing NA and DA from the synapse. Interestingly, the role of these genetic influences has effect sizes comparable to those observed on response to antidepressant drugs, thus strongly suggesting a shared mechanism of action of chronotherapeutics and monoaminergic drugs.

Following this line of reasoning, the most striking confirmations of shared influences on monoamines come from combined treatments with chronotherapeutics and drugs. SD showed synergistic interactions with drugs that increase the activity of brain 5-HT, NA, and DA systems; conversely, DA antagonists block the behavioral and antidepressant effects of SD. Similar synergistic effects have been described for light therapy, which significantly potentiates serotonergic antidepressants, and can prevent the mood-lowering effect of acute tryptophan depletion, which reduces brain 5-HT.

Finally, an increasing interest on glutamatergic neurotransmission in depression stemmed from trials reporting antidepressant effects of the NMDA antagonists ketamine and the glutamatergic modulator riluzole. Glutamatergic neurotransmission follows a strict circadian rhythm, and in animal models it is first enhanced and then markedly depressed during SD. In vivo single proton magnetic resonance spectroscopy (1H-MRS) indicated that glutamatergic transmission is altered by SD, as shown by reduced glutamate concentrations, the changes being proportional to both perceived and observed mood amelioration in bipolar depression. Remarkably, these effects were observed in the anterior cingulate cortex, a brain area which has been widely implicated in providing a neural basis for mood-congruent cognitive biases in depression, and where chronotherapeutics was shown to profoundly change metabolism and neural reactivity to stimulus words in responders to treatment.

**Biological clock and long-lasting effects on biological rhythms**

The hypothesis that several psychiatric conditions may involve primary or secondary changes in biological clocks, and the observations that biological rhythms show a range of abnormalities in mood disorders, make the biological clock a primary candidate to explain the mechanism of action of chronotherapeutic techniques. The molecular machinery which constitutes the biological master clock in the suprachiasmatic nuclei (SCN) is being elucidated, but the systematic study of the relationship between clock and therapeutic interventions in psychiatry is just beginning.

Growing evidence supports the hypothesis that changes in brain monoaminergic functioning influence the function of the biological clock molecular machinery, and the clock and the control of biological rhythms are emerging targets for antidepressant drug treatment. New animal models have been used to test the interactions between circadian genes and mood-related neurotransmitter systems, and, conversely, to explore the effects of light on brain circuitries and of antidepressant and mood-stabilizing drugs on the clock. Serotonin modulates the response of the circadian system to light and mediates modification of the period and phase of the central clock by behavioral arousal, while, in turn, the biological clock gene network is expressed in serotonergic raphe neurons, with a close interplay between the two systems leading to strong circadian and seasonal rhythms in serotonergic function. Dopaminergic activity also follows a strong rhythm, and manipulations of clock genes within brain dopaminergic structures leads to abnormal animal behaviors that closely resemble human bipolar disorder, while some genetic variants of the same clock genes are associated with a worse bipolar phenotype in human patients. The locus coeruleus produces a relatively constant tonic noradrenergic firing throughout all behavioral states, except during rapid eye movement (REM) sleep when NA discharge is absent, and it was hypothesized that modifications of NA activity during chronotherapeutics could be necessary for its effects.

Remarkably, all antidepressant chronotherapeutic interventions cause a phase advance of biological rhythms. Light therapy in the morning is the main environmental synchronizer of the internal clock and influences timing and entrainment of the SCN circadian clock by inducing
The circadian pacemaker is sensitive to short-duration light pulses with a nonlinear relationship between light duration and the amount of resetting, and a 1-hour bright white light pulse phase shifts the circadian pacemaker following a clear-cut phase-response curve\textsuperscript{144}: phase advances are obtained when administering light in the morning, and phase delays when administering it in the evening (the so-called type I phase response).\textsuperscript{146} SD directly targets the sleep-wake rhythm and can influence SCN function by modifying vigilance state transitions and sleep states,\textsuperscript{147} specifically modifies the binding of the molecular components of the biological clock,\textsuperscript{148} and is clinically synergistic with the administration of phase-advancing morning light\textsuperscript{149}; in agreement with these findings, an actimetric advance of the activity-rest circadian cycle correlates with positive antidepressant response to SD.\textsuperscript{150} Surprisingly, very little data are available on the effects of antidepressant drugs on the biological clock, but a single study showed that fluoxetine induces a phase advance of the SCN in rats,\textsuperscript{151} while the antidepressant agomelatine can induce a phase advance in normal humans,\textsuperscript{152} thus supporting the hypothesis that chronotherapeutics and drug-induced changes on monoamnergic function may result in similar long-lasting effects on the master clock of depressed patients, possibly correcting yet poorly understood abnormalities in the phase-angle relationships between biological rhythms.\textsuperscript{151,152}

**Brain plasticity and metabolism**

Genes of the biological clock are expressed in many brain structures other than in the SCN\textsuperscript{153,154} and their genetic variants can bias “non-clock” brain functions such as information processing and decision making in bipolar depression.\textsuperscript{155} Several findings suggest that at the cellular level clock genes could provide a mechanism for the control of circadian gene expression and of responsiveness to stimuli,\textsuperscript{156} which in psychiatric conditions may influence the complex relationship between susceptibility and precipitating factors for depression, thus biasing core characteristics of the illness such as age at onset,\textsuperscript{157} recurrence of illness,\textsuperscript{158} or its occurrence in specific risk periods such as the postpartum period.\textsuperscript{159} The close link between the clock machinery and core metabolic cellular processes is confirmed by the study of protein modulators such as glycogen synthase kinase 3-β (GSK3-β), which is a core constituent of the mammalian circadian clock and affects circadian rhythm generation by modifying the stability of circadian clock molecules.\textsuperscript{160} This kinase is also an essential element of the Wnt/beta-catenin pathway, which is involved in the control of gene expression, cell behavior, cell adhesion, and cell polarity, and plays major roles in neurodevelopment and in regulation of neuronal polarity, neuronal plasticity, and cell survival.\textsuperscript{161} It regulates the activity of many targets including transcriptional factors, enzymes, and cytoskeletal proteins,\textsuperscript{162} and is considered a primary regulator in a range of cellular processes including differentiation, growth, motility, and apoptosis.\textsuperscript{163} GSK-3 influences the susceptibility of neurons to harmful stimuli (neuronal resilience), because increasing GSK-3 activity increases apoptosis in neuronal cells, while inhibiting GSK has neuroprotective effects,\textsuperscript{164} and because its inhibition occurs in response to brain-derived neurotrophic factor (BDNF) and other neurotrophins.\textsuperscript{165} These mechanisms provide a target for the convergent effects of chronotherapeutics and antidepressant drugs on the biological clock and on neurotransmitter systems. Control of the phosphorylation/activity status of GSK-3β is considered an important mechanism of serotonin (5-HT) and dopamine (DA) action on brain and behavior,\textsuperscript{166} because GSK3-β is inhibited by lithium, valproate, and several antidepressants such as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants.\textsuperscript{167,168} Confirming the role of these mechanisms for bipolar disorder and chronotherapeutics, promoter gene variants were associated with less detrimental clinical features, including a delayed onset of illness,\textsuperscript{169} a better clinical response to lithium,\textsuperscript{170} and a better response to sleep deprivation\textsuperscript{171}; this effect was so strong as to overcome the detrimental influence on SD response of genotypes negatively affecting serotonergic function.\textsuperscript{172,173}

Molecular mechanisms involved in brain plasticity are likely to play a major role in antidepressant response and long-term mood stabilization of bipolar patients.\textsuperscript{174} Accumulating evidence suggests then that plastic processes occurring during wakefulness result in a net increase in synaptic strength in many brain circuits, and that synaptic strength is downscaled to baseline levels during sleep,\textsuperscript{174} when effective cortico-cortical connectivity is broken down.\textsuperscript{174} In agreement with the predictions of this “synaptic homeostasis hypothesis” of sleep,\textsuperscript{175} a recent study showed that in healthy humans prolonged wakefulness is associated with significant changes in the state of cortical circuits involving a steady...
Cronoterapia antidepresiva para la depresión bipolar

La cronoterapia se refiere a los tratamientos basados en los principios de la organización del ritmo circadiano y de la fisiología del sueño, mediante el control de la exposición a los estímulos ambientales que actúan sobre los ritmos biológicos con el fin de conseguir efectos terapéuticos en el tratamiento de los cuadros psiquiátricos. Esta terapia incluye manipulaciones del ciclo sueño-vigilia como la privación de sueño y el avance de fase del sueño así como la exposición controlada a la luz y a la oscuridad. Los efectos antidepresivos de la cronoterapia son evidentes en cuadros de difícil tratamiento como la depresión bipolar, la cual se ha asociado con resultados de éxito extremadamente bajos para los fármacos antidepresivos en estudios naturalistas y con una respuesta antidepresiva estable a la cronoterapia en más de la mitad de los pacientes. Avances recientes en el estudio de los efectos de la cronoterapia en los sistemas de neurotransmisión y en la maquinaria del reloj biológico, permiten identificar su mecanismo de acción y transformarlo desde un rechazo o un “tratamiento huérfano” a un poderoso instrumento clínico en la práctica psiquiátrica cotidiana.

Chronotherapeutics for bipolar depression - Benedetti

In conclusion, chronotherapeutics has now been proven to be a powerful clinical instrument for the treatment of depression in everyday clinical practice. Rapidity of effects and lower rates of switch into mania with respect to available antidepressant drugs make chronotherapeutic combinations a first-choice option for the hospital treatment of patients with a major depressive episode in the course of bipolar disorder. Antidepressant efficacy in nearly one half of drug-resistant patients makes it mandatory for the clinician to prescribe these treatments to these difficult-to-treat patients. Single techniques, such as light therapy, can be easily prescribed to outpatients in combination with the usual antidepressant drug treatments. In all cases, chronotherapeutic techniques should be combined with mood-stabilizing treatments, such as lithium salts, which are the mainstay of the long-term psychiatric management of bipolar disorder and which can enhance and sustain the acute antidepressant effects of chronotherapeutics.
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