



CLINICAL REVIEW

Chronotherapeutics in a psychiatric ward[☆]

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KEYWORDS

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Summary Psychiatric chronotherapeutics is the controlled exposure to environmental stimuli that act on biological rhythms in order to achieve therapeutic effects in the treatment of psychiatric conditions. In recent years some techniques (mainly light therapy and sleep deprivation) have passed the experimental developmental phase and reached the status of powerful and affordable clinical interventions for everyday clinical treatment of depressed patients. These techniques target the same brain neurotransmitter systems and the same brain areas as do antidepressant drugs, and should be administered under careful medical supervision. Their effects are rapid and transient, but can be stabilised by combining techniques among themselves or together with common drug treatments. Antidepressant chronotherapeutics target the broadly defined depressive syndrome, with response and relapse rates similar to those obtained with antidepressant drugs, and good results are obtained even in difficult-to-treat conditions such as bipolar depression. Chronotherapeutics offer a benign alternative to more radical treatments of depression for the treatment of severe depression in psychiatric wards, but with the advantage of rapidity of onset.

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What is psychiatric chronotherapeutics

Psychiatric chronotherapeutics are controlled exposures to environmental stimuli that act on biological rhythms in order to achieve therapeutic

effects in the treatment of psychiatric conditions. First introduced at the 2nd meeting of the International Society for Affective Disorders in the year 2004, when an international Committee on Chronotherapeutics was formed under the chair of Anna Wirz-Justice in order to promote and achieve consensus on the use of these techniques¹ the term chronotherapeutics refers to non-pharmaceutical and biologically-based clinical interventions including sleep deprivation (SD) or wake therapy, sleep phase advance (SPA), light and dark therapy (LT, DT).

The use of psychiatric chronotherapeutic techniques in everyday psychiatric work is a rather new

[☆]Dedicated to Anna Wirz-Justice in recognition of her contributions to the field made during her career at the Psychiatric University Clinics Basel.

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Nomenclature	
(5-HT) serotonin	(ECT) ElectroConvulsive Therapy
(5-HTTLPR) polymorphism in the promoter gene for the 5-HT transporter	(LT) light therapy
(ACC) anterior cingulate cortex	(NE) norepinephrine
(DA) dopamine	(SAD) Seasonal Affective Disorder
(DLPFC) dorsolateral prefrontal cortex	(SCN) suprachiasmatic nuclei of the hypothalamus
(DT) dark therapy	(SD) sleep deprivation
	(SPA) sleep phase advance
	(PET) positron emission tomography

achievement and is almost exclusive of the treatment of mood disorders. Mainly developed in European countries over the last five decades,² these techniques evolved both from empirical observation of impressive clinical changes following random exposure to environmental stimuli (e.g., immediate mood improvement in sleep-deprived depressed patients),³ and from neurobiological models of behaviour.³

Interest in the clinical use of these techniques in real-world settings (psychiatric wards, outpatient services) stemmed from their efficacy, rapidity of action, and lack of side effects.⁴ Their clinical usefulness was questioned by the short duration of the antidepressant effects, with a high probability of early relapse 1 or 2 days after treatment discontinuation.⁵ However, these transient therapeutic effects were observed in experimental settings aimed rather at studying the fascinating mechanisms of action of these treatments,⁶ and not at promoting long-standing changes in psychopathological conditions.

Meanwhile in the “real world” of psychiatric clinical work, a number of investigators over a number of years combined the different chronotherapeutic interventions in different ways as well as adding them to conventional psychiatric treatments. This led to long-lasting therapeutic effects, thus providing clinicians with new and affordable therapeutic instruments (as summarised in consensus statements).⁷ Progress in biological psychiatry produced sound evidence for the multiple mechanisms of action of these treatments, thus changing their status from empirically-driven “jumps in the dark” to neuroscience-based clinical interventions.

This paper will review (a) techniques and (b) mechanisms of action of chronotherapeutics of mood disorders, which both sustain the early hope of research on biological rhythms in psychiatry that chronobiological interventions could become a benign alternative to more radical treatments of depression.⁸

You cannot avoid chronotherapeutics

The light–dark cycle exerts a synchronising effect on the biological clock: every morning environmental light acts as a zeitgeber to reset the circadian pacemaker via glutamatergic inputs to the neurons of the suprachiasmatic nuclei of the hypothalamus (SCN) via the retino-hypothalamic tract.⁹ A cascade of cyclical events, into the brain and in the whole organism, is triggered and will continue during the day influencing neurotransmitter turnover, hormonal production, and the rest–activity and sleep–wake cycles.

Behaviour, in turn, exerts a zeitgeber effect, though indirectly. Activity enhances the firing of raphe serotonergic neurons, which modify SCN activity.^{10,11} Brain serotonin (5-HT) turnover, which mediates this non-photoc entrainment of the clock and modulates the response of the SCN to photic inputs,¹² follows a cyclical pattern^{13,14} with the highest activity during behavioural arousal and the lowest during sleep.^{15,16} In a similar way, dopamine (DA) turnover follows a circadian rhythmicity influenced by light,¹⁷ while in turn signalling mediated by the dopamine D2 receptor potentiates circadian regulation by clock genes.¹⁸ The SCN regulates circadian variations in noradrenergic locus coeruleus impulse activity,¹⁹ while in turn norepinephrine (NE) provides circadian regulation of the sleep–wake cycle.²⁰ Cholinergic neurons are involved in the generation of REM sleep,^{21,22} and acetylcholine follows a circadian rhythm²³ and plays a role in modulating the photic information reaching the SCN²⁴ and in entraining the clock. EEG power density during sleep is correlated with SCN neuronal activity, and both vigilance state transitions and SD influence SCN function²⁵ and gene expression in the whole brain: the transition from sleep to waking can affect basic cellular functions such as RNA and protein synthesis, neuronal plasticity, neurotransmission, and metabolism.²⁶

Confirming the classical belief that man and his environment are inseparable, it is then impossible to avoid exposure to environmental stimuli that act directly on brain neurotransmitter function and the transcription of clock genes. We can only choose if we want to let these zeitgeber stimuli to be given by chance, or if we want to control exposure to them. Since the neurotransmitters that undergo circadian rhythms (5-HT, DA, NE) are the same that are targeted by psychiatric drugs, a strict control of the exposure to those stimuli that influence their turnover could be recommended in patients affected by psychiatric conditions.

Many research data confirm this. Going by chance, patients affected by mood disorders can be lucky or not depending on their current psychopathological conditions, because stimuli that phase-advance rhythms tend to elevate mood, while stimuli that phase-delay rhythms tend to induce depression. When patients are euthymic, phase-shifts can be the precipitating factor of new illness episodes: transmeridian travellers who needed a psychiatric treatment after flight had mania after phase-advancing eastward flights, and depression after phase-delaying westward flights, irrespective of airport location (London area,²⁷ or the Hawaii islands²⁸). When patients are depressed, exposure to sunlight can become an underestimated and uncontrolled antidepressant treatment, again irrespective of the location of the hospital: in Canada depressed patients in sunny rooms had a mean 2.6 days shorter hospitalisation than patients in dimly lit rooms,²⁹ and in Italy bipolar depressed inpatients assigned to rooms with eastern windows (exposed to direct sunlight in the morning) had a mean 3.7 days shorter hospital stay than patients in rooms with western windows,³⁰ with maximal differences in summer and autumn (7 days) and no difference in winter, when morning sunlight is dimmer and later. Single case studies have confirmed a relationship between mood, hours of sunlight, and solar irradiation in patients affected by non-seasonal mood disorders,^{31,32} with more sunlight associated with better mood.

If the method of exposing patients to environmental stimuli by chance should then be rejected, the decision on how to do it cannot be left to the patients themselves. Following their psychopathological biases, depressed patients with seasonal affective disorder tended to limit their exposure to sunlight during wintertime,³³ thus probably increasing the severity of their condition, but self-administered unmonitored exposure to light for therapeutic purposes has been found to cause marked mood oscillations.³⁴ The above considera-

tions leave no choice to the clinical psychiatrist: exposure to stimuli that act on biological rhythms in mood-disordered patients should be controlled in order to achieve therapeutic effects with the same attention usually reserved for drug administration.

Structured chronotherapeutic techniques

Clinical suggestions about the usefulness of chronotherapeutics can be found in classical psychiatric texts. Vincenzo Chiarugi in 1794,³⁵ antedating by 10 years Pinel's reforms at the Bicêtre by abolishing all severe forms of restraint at the Bonifacio asylum in Florence, recommended increasing exposure to outdoor light in depressed patients, and to avoid exposure to light and noise in agitated patients by putting them in dark rooms. In modern times, Schulte in 1959³⁶ first reported antidepressant effects of SD and Wehr et al. in 1979³⁷ of sleep phase-advance; the scientific approach to the treatment of depression with bright light started in the '80s³⁸⁻⁴⁰; and mood-stabilising effects of extended bed rest and antimanic effects of light restriction have been described only recently.⁴¹⁻⁴³

Many structured chronotherapeutic modalities have been developed since then (see Table 1), and many reviews are available on this topic (see recent reviews^{2,7,44-46}). Coming from experimental settings to everyday clinical practice in inpatient settings, two issues need to be defined: (1) who will obtain the maximal benefit (which population, and at which time point of the illness course), and (2) which technique, or which combination of techniques, will obtain the best and safest results.

Clinical population to be treated

Beneficial antidepressant effects of different chronotherapeutic approaches have been described in all depressive conditions.

SD is antidepressant in endogenous, reactive, unipolar, bipolar, secondary, and schizoaffective depression⁴; in depression in the elderly⁴⁷ and secondary to Parkinson's disease⁴⁸ or schizophrenia⁴⁹; and in depression associated with pregnancy and postpartum⁵⁰ and premenstrual dysphoric disorder.⁵¹

Predictors of response to SD include the presence of diurnal mood fluctuations (consistently reported by independent research groups⁵²⁻⁵⁵), endogenous subtype,⁵⁶ an abnormal dexamethasone suppression test,⁵⁷ lower interleukine-6 levels⁵⁸: i.e., the same clinical and biological features that predict good response to antidepressant drugs.⁵⁹⁻⁶² In all conditions the response is quick and dramatic, and

Table 1 Chronotherapeutic techniques in the treatment of mood disorders.

Intervention	Therapeutic response	
	Latency	Duration
Sleep deprivation (SD)	Hours	Until sleep restored (~1 day)
Phase advance (PA) of the sleep-wake cycle SD followed by PA	~2 days	Tolerance after ~2 weeks
	Hours	Until discontinued (~1 week)
Repeated SD	Hours	Until discontinued (~1 week)
Light therapy (LT) (Seasonal Affective Disorder)	Days	Weeks/months
LT (non-seasonal depression)	~3 days	Until discontinuation
Combined LT and drugs (non-seasonal depression)	~3 days	Months (hastens drug response)
Combined SD and drugs	Hours	Months (hastens drug response)
Combined chronotherapeutics (SD, LT, PA) and drugs	Hours	Months (hastens drug response)
Dark or rest therapy (bipolar mania and rapid cycling)	Hours	Until discontinuation (days)

Modified from Wirz-Justice, 2005.¹⁹⁹

will become clinically evident with a latency of 1 day (i.e., the day after the first night awake) or 2 days (i.e., after recovery sleep).⁶³ The only known contraindications to treatment is epilepsy, because of the high risk of seizure induction.⁶⁴ The relative lack of risks and the reproducibility of the antidepressant effects suggested even a diagnostic use for SD, which will not ameliorate the clinical picture of neurologic conditions that can mimic depression, such as Alzheimer disease.^{65,66} It is, however, recommended that a careful medical examination precede SD, because the unspecific stress associated with staying awake all night could unexpectedly precipitate unsuspected medical conditions.^{67,68} The expected increase in sleepiness during the SD procedure and the day after SD will be easily managed into the ward, but discourages demanding activities (such as driving cars, etc.) in case the patients are allowed to exit the hospital setting.

In a similar way, benefits from LT have been reported in seasonal and non-seasonal major depressive episodes (see Terman's contribution in this issue), and in many heterogeneous depressive conditions including the mood fluctuations linked with pregnancy,⁶⁹ premenstrual dysphoric disorder,⁷⁰ attention deficit hyperactivity disorder,⁷¹ schizophrenia,⁷² schizoaffective disorder,⁷³ alcoholism,⁷⁴ Parkinson's disease,⁷⁵ stroke,⁷⁶ or Alzheimer disease.⁷⁷⁻⁷⁹

The optimal target for chronotherapeutics seems then to be the classical depressive syndrome, broadly defined: nothing new in psychiatry, given that antidepressant drug treatments and electroconvulsive therapy (ECT) are active both in primary affective disorders and in secondary depression,⁸⁰ and the brain metabolic changes associated with primary major depression are common to normal sadness and to depression secondary to medical conditions.^{81,82}

Acute response rates to chronotherapeutics range from two-third to three-quarters of patients, similar to those reported for drug treatments.⁷ Given that at least 40% of patients treated for depression do not respond to the initial trial of antidepressant drug medication⁸³ and at least one half of this percentage do not respond satisfactorily to several further treatment trials,⁸⁴ the rapid and safe administration of chronotherapeutics should then be tested as a first-line treatment strategy in the majority of depressive syndromes.

Nevertheless, consistent findings showed that diagnosis is a predictor of response to chronotherapeutics, with bipolar depressed patients receiving higher benefit than unipolars both from SD^{85,86} and from LT.⁸⁷ This elective sensibility is clinically uncoupled from the susceptibility for mania that defines the disorder, and is specific to chronotherapeutics: bipolar patients switch from depression into mania at a lower rate with chronotherapeutics than with antidepressant drugs,⁸⁸ but show equal or lower response rates to antidepressant drugs than unipolars.^{89,90}

Prospective trials showed that patients affected by bipolar disorder are expected to spend, in the long term, roughly one-third of follow-up weeks with depressive symptoms, which will present themselves in varying degrees of severity despite medication-based psychiatric care,^{91,92} that discontinuation of antidepressant treatment in the first 6 months after remission will result in relapse in more than a half of responders,⁹³ but that continuation of antidepressants will double the risk of manic switches.⁹⁴ Bipolar depression is thus a relatively understudied and difficult-to-treat condition, yet the depressive phases of bipolar disorder

can be very disabling, with significant associated comorbidity and suicide risk, impairment in functioning, and infringement on quality of life.⁸⁹

Probably because of the difficulty treating bipolar depression with standard drug treatments, chronotherapeutics have been widely tested in this conditions, and have proved useful even in patients resistant to several antidepressant drugs, with sustained response rates comparable to those obtained with full-dosage antidepressant drug treatment.⁹⁵ Mood stabilisers, the first-choice treatment for bipolar disorder, can successfully sustain the effect of chronotherapeutics and can help to manage the low risk of manic switches. Chronotherapeutics should therefore be considered the treatment of choice for the depressive phase of bipolar disorder, the safety and efficacy of which has been extensively studied over the years in roughly 500 cases published by our group at the Center of Mood Disorders of the San Raffaele Hospital in Milano⁷ (see Acknowledgments).

Optimal treatment schedule

Three basic techniques of proven efficacy are available for chronotherapeutics: SD (total or partial), SPA, and LT (see Terman's contribution to this issue). All these techniques induce rapid antidepressant effects, which can be perceived by the patients in a matter of hours or days, but all share a high risk of relapse upon discontinuation of treatment; in the case of SD, the most rapid and powerful, this will occur soon after restoring normal sleep. Repetition of treatment was proven unsuccessful, both because of reported tolerance to the therapeutic effects,⁹⁶ and because after eventual discontinuation patients however relapsed,⁹⁷ with only 5–10% of treated patients maintaining a stable euthymia.^{98,99} In a similar way, the acute antidepressant effects caused by an advance of the sleep phase cycle could be followed by tolerance when prolonged over weeks, but the few available data prevent conclusions on this issue.³⁷ A more successful strategy to maximise response and prevent relapse is to combine the different chronotherapeutic modalities as well as adding them to other treatment strategies (Table 1).

The early relapse after SD can be prevented by combining it with subsequent LT or SPA. Early studies on SD and light showed that the beneficial effects of SD became clinically relevant when patients were exposed to morning light,¹⁰⁰ and that exposure to bright light during SD could lead to a more prolonged improvement of responders.¹⁰¹

Bright LT during and after SD was then shown to stabilise the antidepressant effect of both partial^{102,103} and repeated total SD.¹⁰⁴ Not surprisingly, a concordance of response to SD and LT in the same patient has been reported.¹⁰⁵ In a similar way, SPA has been shown to prevent the early relapse after SD.^{106,107}

Once a stable acute response with combined chronotherapeutics has been obtained, the clinical focus becomes the prevention of delayed relapse, which is known to be maximal during the first 6 months after response to antidepressant treatments both in unipolar and in bipolar depression.⁹³ Current leading opinions recommend a up to 1 year continuation therapy with the same drug to which the patient responded¹⁰⁸ despite a reported rate of tachyphylaxis in more than 10% of treated patients.¹⁰⁹ After chronotherapeutics, the long-term relapse prevention can be obtained with drugs.

Total SD has been successfully associated with antidepressant drugs with a serotonergic,^{99,110,111} noradrenergic,¹¹² mixed serotonergic-noradrenergic,^{63,113,114} and dopaminergic¹¹⁵ mechanism of action. In the first days after the beginning of drug treatment, when no therapeutic effect is expected due to the latency of action of antidepressants, SD will cause acute antidepressant effects and drugs will prevent relapse after recovery sleep. In a similar way LT has been shown to hasten response to serotonergic antidepressants in non-seasonal depression.^{111,116} Chronotherapeutics will thus hasten the achievement of euthymia and reduce the burden of perceived depression at the beginning of treatment. Once stable euthymia has been obtained, drugs will then be continued according to clinical need.

In the case of bipolar depression, the combination with antidepressant drugs is not necessary (thus avoiding the risk of triggering mania) because the long-term response rates to combined chronotherapeutics (e.g., repeated SD plus LT) is independent of concomitant antidepressant medication.⁹⁵ Lithium alone, the mainstay for the long-term treatment of bipolar disorder, is sufficient to prevent both acute relapse (after SD,¹¹⁷ and after combined SD+LT¹⁰⁴) and delayed relapse (after repeated SD,⁹⁸ after repeated SD+LT,⁹⁵ and after TSD+repeated SPA.¹¹⁸ To reduce or avoid the use of antidepressant drugs in hospitalised severe bipolar depression, the benefits from chronotherapeutics need to be maximised by combining repeated SD (three cycles in a week) with LT and lithium, thus reaching continued remission rates 9 months later that are comparable to those obtained with long-term antidepressant treatments.^{93,95}

Finally, special caution is recommended in special populations, where data are lacking: an acute worsening of delusions has been reported in delusional patients after SD without drugs,¹¹⁹ and it is not clear which techniques will be more efficient and tolerated during pregnancy, or in acute suicidal patients. A paradoxical acute worsening of suicidal ideation and/or attempts, and of completed suicide, can be expected with all antidepressant treatments, and the FDA Public Health Advisory of March 22, 2004 "Worsening Depression and Suicidality in Patients Being Treated With Antidepressant", stated that "Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases". Every clinical psychiatrist knows that antidepressant treatments may increase the intensity of drives before leading to the remission of the depressive syndrome and of the depressive cognitive distortions (hopelessness/helplessness) linked with suicidal ideation. There is no reason to think that chronotherapeutics should be an exception to this rule, even if two studies described rapid amelioration of depressive cognitive distortions after SD alone¹²⁰ or combined with SPA.¹²¹ Like for drug antidepressant treatments, LT has been reported both to alleviate suicidal tendencies¹²² and to worsen transient but dangerous suicidal ideation.^{123,124} No report associated therapeutic SD with a worsening of suicidality. Given its ability to shorten the latency of action of combined drugs, chronotherapeutics could then be of potential usefulness in preventing suicide associated with depression, but careful clinical management of suicidal patients is recommended with this as with any other antidepressant treatment, and further study is needed before firm conclusions can be drawn on this topic.

Mechanisms of action

Nearly 50 years after the modern re-discovery of their therapeutic potential, the mechanisms of the antidepressant action of chronotherapeutics are still considered unknown. This is not dissimilar to the state of knowledge regarding antidepressant drugs. Not that chronotherapeutics lack effects on brain function, but rather because researchers do not agree on which of the multiple effects is responsible for the clinical mood amelioration. Notwithstanding the chronobiological literature about the phase advance hypothesis, the critical phase theory and about the two-process model of

sleep in its relation to SD effects,² several studies described neurobiological and brain imaging effects using the same methodological approaches as in drug research. Most probably all these mechanisms contribute to the clinical outcome, with available literature suggesting that chronotherapeutics and antidepressant drugs share targets and mechanisms of action.

Neurobiological mechanisms

The synergistic interaction between chronotherapeutics and antidepressant drugs observed in clinical studies supports a major role for monoamines in the mechanism of action of chronotherapeutics, and neurobiological studies have shown that SD was able to increase the levels of almost all the neurotransmitters targeted by antidepressant drugs: serotonin (5-HT), NE, and DA.

In particular, changes in the activity of brain 5-HT pathways after SD¹²⁵ include an increase in serotonergic neuronal activity in the dorsal raphe nucleus,¹²⁶ an increase in brain 5-HT turnover,^{127–129} an increase in extracellular 5-HT,¹³⁰ and an increase in behavioural responsiveness to 5-HT precursors both in animal models¹³¹ and in depressed humans,¹³² with a reduction in sensitivity of 5-HT_{1A} inhibitory autoreceptors.^{126,133} In patients affected by bipolar depression the further blockade of 5-HT_{1A} autoreceptors obtained by administering the 5-HT_{1A}- β adrenoceptor blocking drug pindolol enhanced the antidepressant efficacy of SD,⁹⁹ an effect similar to that obtained by combining pindolol and serotonergic antidepressant drugs.¹³⁴

In a similar way, studies of 5-HT function in patients affected by Seasonal Affective Disorder (SAD) treated with LT suggested a role for 5-HT. Serotonergic afferents mediate activity-dependent entrainment of the mouse circadian clock,¹⁰ and in depressed humans LT tended to normalise the blunted growth hormone response to sumatriptan,¹³⁵ the cortisol and prolactin response to *m*-chlorophenylpiperazine,¹³⁶ the abnormal activation-euphoria response (but not the blunted responsiveness of the hypothalamic-pituitary-adrenal axis) to *m*-chlorophenylpiperazine in winter depression,¹³⁷ and the levels of tetrahydrobiopterin, an essential cofactor in the hydroxylation of tryptophan and, therefore, in the synthesis of 5-HT.¹³⁸ Both tryptophan and catecholamine depletion reversed the beneficial effects of LT,^{139–141} while, in SAD patients with natural summer remission, tryptophan depletion was reported both to cause the recurrence of depressive symptoms¹⁴² or

to show no effects.¹⁴³ Administration of a low tryptophan diet during SD followed by a tryptophan free amino acid mixture after TSD did not reverse the TSD effects, but seemed able to prevent relapse after recovery sleep.¹⁴⁴ Though ethically criticisable, these relapse-inducing studies support the hypothesis of a major involvement of 5-HT neurotransmission, and produced effects similar to those described after tryptophan and catecholamine depletion in depressed patients who responded to serotonergic or to noradrenergic antidepressant drugs.¹⁴⁵

A clear-cut demonstration that SD and LT share the neurobiological mechanisms of action of drugs targeting the 5-HT system comes from psychiatric pharmacogenetic studies of the influence of a polymorphism in the promoter gene for the 5-HT transporter (5-HTTLPR) on antidepressant response to serotonergic treatments in Caucasian populations.¹⁴⁶ A 44 base pairs deletion was associated with reduced transcriptional efficiency and decreased expression of 5-HT transporter protein, and with a bias against antidepressant response which influences, in the same direction and with similar effect sizes, the antidepressant response to the 5-HT uptake inhibitors fluvoxamine,¹⁴⁷ paroxetine,^{148,149} fluoxetine,¹⁵⁰ citalopram,¹⁵¹ sertraline,¹⁵² and to SD alone or combined with LT.^{6,153}

But 5-HT is not the only monoamine targeted by SD, which also increases synaptic levels of NE,¹⁵⁴ tyrosine hydroxylase and NE transporter mRNA in the locus coeruleus,¹⁵⁵ and the urinary excretion of catecholamine metabolites in depressed patients,¹⁵⁶ thus suggesting the possible involvement of NE in the antidepressant effect of SD in humans.¹⁵⁷ Some reports suggested that also LT modified the urinary output of norepinephrine,^{158–160} and catecholamine depletion caused relapse in SAD patients who responded to light therapy.¹⁴⁰ Sounder data link SD effects to DA activity, which is enhanced in animals.¹⁶¹ In depressed patients, lower levels of homovanillic acid in the spinal fluid before TSD were associated with better clinical effects of SD¹⁶²; plasma levels of prolactin, which is inhibited by DA agonists, were reported to decrease after SD^{163,164}; SD responders and nonresponders showed a different prolactin response to sulpiride¹⁶⁵; single photon emission computerised tomography before and after SD showed a significantly different D2 receptor occupancy in responders and nonresponders, thus suggesting an enhanced dopamine release in responders,¹⁶⁶ and an increase in eye-blink rate after SD, suggesting DA activation, was reported to be proportional to the clinical effects of SD.¹⁶⁷

This led to hypothesise that the clinical effects of SD could be due to psychostimulant effects similar to that obtained with dopamine-stimulating substances.¹⁶⁸ The clinical relevance of the DA enhancement to obtain antidepressant effects from SD was however not supported both by pharmacogenetic studies showing that DA receptor D2, D3, and D4 gene variants are not associated with the antidepressant effect of SD,^{169–171} and most importantly, by two trials which attempted to enhance and sustain the antidepressant effect of SD by combination with the dopaminergic drug amineptine, but could only produce transient improvements^{115,172} in front of the long term benefits obtained when combining chronotherapeutic techniques with lithium. Moreover lithium, the most powerful agent to improve the effects of chronotherapeutics in psychiatric practice, downregulates D2-like receptor signalling,¹⁷³ and reverses the activating effects of psychostimulants.¹⁷⁴ However, the only negative interaction of SD and LT with antidepressant drugs were reported when these chronotherapeutic treatments were combined with trimipramine,¹⁷⁵ which shows in vitro DA antagonistic properties.¹⁷⁶ The role of enhanced DA in the mechanism of action of SD awaits further studies to be elucidated, and some findings suggest its involvement in LT effects too: in seasonal affective disorder LT increased visual contrast sensitivity, possibly by inducing retinal sensitisation,¹⁷⁷ and normalised the blunted winter thermoregulatory heat loss,¹⁷⁸ which both are DA-dependent processes.

Other factors can be involved in the clinical response to SD. Brain levels of thyroid hormones in animals are enhanced by antidepressant of different classes, including SD,¹⁷⁹ and in depressed humans SD is able to produce highly significant increases in both TSH, levothyroxine, and triiodothyronine,^{180,181} though the clinical relevance of this finding remains controversial.¹⁸² In normal humans adenosinergic mechanisms could contribute to individual differences in SD-induced changes in neurobehavioral function,¹⁸³ but a possible involvement of adenosine in the antidepressant effects of SD remains hypothetical.¹⁸⁴

Finally, systematic screening showed that SD robustly increased the expression of immediate-early genes and transcription factors, genes related to energy metabolism, growth factors and adhesion molecules, chaperones and heat shock proteins, vesicle- and synapse-related genes, neurotransmitter and hormone receptors, neurotransmitter transporters, and enzymes¹⁸⁵: the search for the neurobiologic mechanisms of action of chronotherapeutics has only just begun.

Localisation of the effects in specific brain areas

An impressive group of brain imaging studies showed that the antidepressant response to SD is associated with changes in the functioning of specific brain areas.^{186–190} In particular, five different groups with a total of seven published studies on SD effects with positron emission tomography (PET), HMPAO-SPECT, or functional magnetic resonance imaging reported that responders had increased relative localised metabolic activity in the general location of the ventral/anterior cingulate cortex (ACC) compared with non-responders or normal controls at baseline: the higher the baseline levels, the greater the decrease induced by SD, the better the antidepressant effect. These results are consistent with the wide and consistent literature on PET measures of metabolic activity in perigenual ACC in major depression at baseline and after recovery, which showed higher metabolic rates at baseline and a decrease after pharmacological treatment that was proportional to the clinical amelioration.¹⁹¹ In a pivotal study, changes obtained with a single SD were then obtained, in the same subjects, with a 1-month paroxetine drug treatment.¹⁹²

The cingulate cortex is widely implicated in the detection of unfavourable outcomes, response errors, response conflict, and decision uncertainty.¹⁹³ Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) showed that activity in this area during perceptual processing of fearful stimuli is tightly coupled with that of limbic structures, contributing to feedback circuits implicated in the extinction of negative affect¹⁹⁴ and in providing a neural basis for mood-congruent cognitive biases in depression.¹⁹⁵ Changes of neural activity in these areas seem to be a correlate of depression and of depression recovery: neural responses to stimuli were modified by antidepressant response to venlafaxine, their baseline intensity being correlated with response.¹⁹⁶ Our group showed that successful repeated SD combined with LT caused major changes in cingulate neural responses to morally tuned words, an effect influenced by 5-HTTLPR,¹⁹⁰ thus confirming that SD and antidepressant drugs target neural activity in the same brain areas. By administering positive and negative stimuli to the patients, we observed that chronotherapeutics normalised the pattern of neural response in ACC and dorsolateral prefrontal cortex (DLPFC). These areas are implicated in the cognitive control of emotions, and in normal conditions their activation in response to negative stimuli attenuates the experience of emotion both in the context of

voluntary suppression¹⁹⁷ and when emotional distractors interfere with cognitive tasks¹⁹⁸ by inhibiting subcortical nuclei.¹⁹⁴ While at baseline DLPFC abnormally activated more for positive than for negative stimuli, after 1 week of successful chronotherapeutics it reverted this pattern and activated more for negative than for positive stimuli, the change being proportional to clinical response.¹⁹⁰ In agreement with these findings, responders to SD showed greater baseline amygdalar perfusion and greater reduction after treatment.¹⁸⁹

Conclusions

Though several issues need to be defined (see Research Agenda), existing literature about the clinical efficacy and the mechanism of action of chronotherapeutics for the treatment of mood disorders warrant the usefulness of wide application in psychiatric wards. With respect to traditional antidepressant drug treatments, chronotherapeutics target the same neurotransmitter systems (5-HT, NA, DA), target the same brain structures, are influenced by the same biological factors (e.g., 5-HTTLPR pharmacogenetics), are influenced by the same clinical factors (e.g., previous history of resistance), have the same response rates, but seem to be more rapid and with fewer side effects than other treatment options. Chronotherapeutics can thus be considered powerful therapeutic instruments for the clinical psychiatrist.

Research agenda

Issues to be defined in the future include:

- (1) Is there a dose–response curve for chronotherapeutics? (e.g., longer light exposure is more effective than shorter? repeated SD is more effective than single?)
- (2) Which is the best sequential treatment for the patients? (i.e., should we start with LT or with SD, with single or repeated applications, etc.)
- (3) Which is the efficacy of chronotherapeutics in patients affected by more than one psychiatric condition? (e.g., comorbid mood and anxiety disorders)
- (4) What is the efficacy of chronotherapeutics in special populations? (including pregnancy, suicidal patients, medical conditions, secondary depression, etc.)
- (5) Which side effects should be expected when chronotherapeutics are used in large patient populations?

(6) What is the efficacy of chronotherapeutics in conditions other than mood disorders?

Practice points

- (1) Psychiatric chronotherapeutic techniques include light therapy (LT), sleep deprivation (SD), and sleep phase-advance (SPA). All these techniques cause antidepressant effects.
- (2) Chronotherapeutics are powerful biological treatments that target the same brain mechanism as do antidepressant drugs, and should be administered under medical supervision and after a medical assessment.
- (3) Effects of chronotherapeutics are transient, but can be stabilised by combining techniques among themselves and with common drug treatments. Day-to-day changes in the clinical picture should be monitored.
- (4) The treatment of severe depression with chronotherapeutics should be done under hospitalised condition on a psychiatric ward.
- (5) Chronotherapeutics target the broadly defined depressive syndrome, but best results are observed in bipolar depression.
- (6) PCT can be combined with most antidepressant drugs and lithium salts to speed up response.

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