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Circadian rhythms and depression

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Some core symptoms of major depression show a circadian rhythm in their clinical manifestations or are closely linked to the circadian system functioning, such as sleep-wake cycle. Moreover, abnormalities in circadian rhythmicity of core body temperature and some endocrine- metabolic parameters have been detected in depressive patients compared to healthy controls. The circadian rhythm disturbances described in depressive states as well as the efficacy and fast onset of action of chronobiological based treatments point out the circadian system as an important therapeutic target in the treatment of depression. The aim of this work is to review the biological and clinical data that link major depression to circadian rhythm abnormalities, the mechanisms that may underlie the abnormalities of circadian rhythm physiology seen in depressive states and the different therapeutic approaches to depression that involve the circadian system in their mechanisms of action.

Key words:
Depression. Mood disorders. Circadian rhythms. Chronobiology.

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Ritmos circadianos y depresión

Determinados síntomas nucleares de la depresión mayor muestran ritmicidad circadiana en su expresión clínica o están íntimamente vinculados al funcionamiento del sistema circadiano, como las alteraciones del ciclo sueño-vigilia. Asimismo, en los sujetos depresivos se han detectado alteraciones en los ritmos circadianos de temperatura corporal y varios parámetros endocrinometabólicos en comparación con individuos sanos. Las anomalías en los ritmos circadianos descritas en los estados depresivos, así como la eficacia y rapidez de acción de tratamientos basados en cronobiología, señalan al sistema circadiano como una importante diana terapéutica en el tratamiento de la depresión. El objetivo del presente trabajo es revisar los datos clinicobiológicos que vinculan a la depresión mayor con alteraciones de los ritmos circadianos, los mecanismos que pueden conducir a las anomalías de la ritmicidad fisiológica descritas en los estados depresivos y los diferentes abordajes terapéuticos de la depresión que implican al sistema circadiano en su mecanismo de acción.

Palabras clave:
Depresión. Trastornos del humor. Ritmos circadianos. Cronobiología.

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INTRODUCTION

Major depression is the most frequent mental disorder and constitutes one of the main causes of disability worldwide.[1] The most recent estimates of lifetine prevalence are approximately 13% in the European population.[2] Depression is considered a complex disorder resulting from the interaction between genetic, physiological, psychological and environment factors whose clinical manifestations include affective, cognitive, somatic and behavior symptoms. Some core symptoms of depression show circadian rhythm in their clinical expression, such as diurnal mood variation, or are closely linked to the circadian system functioning, such as the sleep-wake cycle alterations. In addition, alterations have been described in the circadian rhythms of several biological markers in depressed patients. Thus, taking the neurobiological aspects of the circadian system into consideration is fundamental in the approach to the physiopathology and therapy of depressive conditions.

The `present work reviews the physiological characteristics of the circadian system and the clinical and biological findings linked to depression with circadian rhythm alterations are indicated and the mechanisms that may lead to these abnormalities of the physiological rhythm are indicated. Finally, different therapeutic approaches in the treatment of depression that involve the circadian system in its action mechanism are presented.

PHYSIOLOGY OF THE CIRCADIAN SYSTEM

The circadian system is responsible for the generation and maintenance of the body's circadian rhythms and for its synchronization with the environment. The characteristics of the circadian system are similar in all mammals, which, subjected to cyclic changes due to the rotation and transfer movements of the planet around the sun, must anticipate and improve their adaptation to these changes. Thus they have cyclic variations in several physiological and behavior functions that are called biological rhythms.[3] The rhythms whose period, or complete duration of a cycle, is within 20 and 28 hours are called circadian. The rhythms expressed by live organisms are not a passive consequence of the environmental conditions but rather have an endogenous origin. The circadian system is made up of an internal biological clock as the principal piece, that has an intrinsic capacity to vary. In it, some entry pathways of information from the receptors that capture the signals from the environment and some exit pathways aimed at the physiological systems responsible for manifesting the biological rhythms of an individual function as a pacemaker.

The principal internal biological clock or *pacemaker* in mammals is found in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. On the molecular level, it consists in an autoregulatory transcription/translation feedback loop that generates cycles of approximately 24 hours when there are no environmental stimuli.[4] In brief, the principal transcriptional activator is a dimer between the CLOCK (*circadian locomotor output cycles kaput*) proteins and BMAL1 (*brain and muscle ARNT-like protein 1*) that stimulates the transcription of the genes *Per* (*Period*). The PER (PER1, PER2, PER3) proteins dimerize with a cryptochrome (CRY1,CRY2), and are phosphorylated in the cytoplasm by the casein-kinase I (CKI) and glycogen-synthase-kinase 3β (GSK3 β), generating changes in their stability. The complex PER/CRY is capable of inhibiting the transcription of CLOCK/BMAL1, providing the element of negative regulation of the circadian clock feedback circuit. There are other secondary circuits that regulate and modulate these genes, which are the principal components of the molecular clock mechanism. Although the central circadian pacemaker is located in the SCN, all these genes are expressed in other brain cells and organs where they function as peripheral clocks that respond to non-photic stimuli.[5,6]

The genetically determined endogenous periodicity is slightly different from 24 hours (usually somewhat longer). Thus, the clock responsible for maintaining the time organization of the internal body processes must be synchronized daily with the external environment through structures that are capable of capturing and conducting the stimuli of the setting. The environmental signals or external rhythmic stimuli capable of modifying the duration of the cycle or period in which the endogenous clock oscillates, directing it or guiding it, are called *zeitgebers*. Due to this readjustment, the biological rhythms are maintained in a specific time order or relation of a determined phase (the phase is the time relationship between a determined moment of a cycle, for example when the maximum value occurs, and a specific time reference and would indicate the «time» of the endogenous clock). The main *zeitgeber* or most potent synchronizing agent for the SCN is the light-dark cycle. In the case of human being, in addition to other stimuli such as motor activity and temperature, social factors constitute one of the most potent *zeitgebers* capable of modifying spontaneous behavior.

The time information from the principal clock is transmitted towards the different effector systems and peripheral oscillators through which the rhythms in the rest of the body will be manifested and amplified. In human beings, many physiological parameters present circadian rhythmicity, among them the sleep-wake cycle, body temperature, heart rate, blood pressure, levels of several hormones, alert state and performance of activities. The rhythmic expression of these circadian variables in humans only partially reflect the principal biological clock behavior since they may be influenced by other factors such as environmental light, situations of stress, fatigue, sleep, exercise, food intake, etc, through a phenomenon known as masking.[7]

Efferent projections of the SCN reach the pineal gland, where melatonin is synthesized and secreted during the night, proportionally to the extension of the dark phase. Melatonin secretion is inhibited by light. Melatonin is the fundamental hormone for the synchronization of the endogenous rhythms since the duration of its secretion acts as a time signal that is translates the duration of the photoperiod to the body. Due to its robust pattern of circadian secretion, melatonin has been proposed as the biological marker of choice to determine the phase and period of the circadian system.[8]

IMPLICATIONS OF THE CIRCADIAN RHYTHMS IN DEPRESSION

Daytime mood variation, alterations of the sleep-wake cycle and periodic recurrences are clinical observations that have classically related depressive states with the circadian system. Furthermore, in depressive subjects, alterations have been detected in the circadian rhythms of the body temperature and several endocrine-metabolic parameters such as cortisol secretion, thyroid stimulating hormone, melatonin and monoamines, in comparison with healthy individuals.

Circadian component of the core symptoms of depression

In healthy individuals, the sleep-wake cycle and sleep architecture, attention capacity, concentration and work memory, appetite control mechanisms, intakes and weight

are regulated by the circadian system and they interact.[9-11] Several symptoms within the diagnostic criteria of major depression are clearly related with the circadian rhythmicity. In fact, the guide symptom of depression is depressive mood and a significant proportion of patients have regular changes in the intensity of depressive mood during the day. These mood changes often come with parallel changes in psychomotricity, attention capacity and anxiety symptoms that frequently accompany depression. On the other hand, sleep alterations are practically constant in depression. Depressive patients with melancholic symptoms characteristically have early morning awakening and morning worsening in their mood state. Both symptoms form a part of the diagnostic criteria of this depressive subtype. Thus, endogenous or melancholic depression has classically been linked to abnormalities in biological rhythms.

The frequency of the appearance of the circadian mood variation varies based on the clinical characteristics of the depression, as well as the severity of the symptoms or depressive subtypes. In classical studies, morning time worsening of the mood status is present in 65%[12] to 90%[13] of the melancholic patients. In a recent study conducted on an extensive sample of outpatients diagnosed of major depressive disorder without psychotic symptoms, 22% of the patients had daytime mood variation. These patients showed greater severity of the symptoms and had more likelihood of fulfilling criteria for depression with melancholic characteristics when compared with patients without daytime mood variation.[14] Typical diurnal mood variation with morning worsening and evening improvement not only involves the mood status but also is seen in the psychomotricity, executive function and other neuropsychological functions in depressive patients.[15,16] On the other hand, when the circadian variation of mood is expressed as morning improvement and evening worsening, is known as «inverse» or «typical». This «inverse» variation has often been associated with neurotic depression, dysthymia, anxiety, and the depressive episodes with atypical symptoms.[17] The daytime variation of mood is a predictor of positive response to some antidepressant drugs. Depressive patients with evening improvement of mood respond better to sleep deprivation than those without daytime variation or with «inverse» variation.[18,19] Other studies indicate typical diurnal mood variation as a predictor of a positive response to antidepressant drugs[20] and the association of «atypical» or «inverse» with poor response to serotonergic antidepressants.[21] The utility implied by the manipulation of endogenous rhythms as a marker of response to treatment stresses the relationship of the daytime variation of depressive mood with the circadian system.

The sleep-wake cycle is the most obvious circadian rhythm in human beings and it is estimated that about 80% of depressive patients suffer insomnia,[22] whether expressed as trouble falling asleep, (initial insomnia); trouble remaining asleep through the night (middle insomnia); and/or waking up too early (terminal insomnia). Equally, the presence of insomnia is a risk factor for the appearance of depressive episodes[23] and is a prodromic symptom of new recurrences in patients with major depressive disorder.[24] Several characteristic changes have been described in polysomnographic registries of the sleep architecture in depressive patients in comparison with healthy individuals, such as decrease in sleep efficiency, decrease in slow wave sleep, shortening of REM sleep latency, abnormal distribution of REM sleep during the night with accumulation of it during the early phases, increase in REM sleep density and lower delta activity in the first sleep cycle with greater activity in the second one.[25] This abnormal REM sleep has been interpreted as a result of a phase advance of the endogenous circadian system and of abnormal phase relationships between several circadian rhythms.[26] However, some sleep alterations observed in depression also appear in other mental disorders, the abnormalities of REM sleep seem to be more specific for depressive disorders.[27]

Alterations of body temperature and endocrine-metabolic circadian rhythms

Abnormalities have been described in both the circadian phase in the amplitude of the circadian rhythm of body temperature in depressive patients. The most frequently replicated finding is elevation of nighttime body temperature compared with physiological flattening of the curves in healthy individuals.[28,29] However, the question of whether these alterations represent functional changes in the endogenous oscillator or are a consequence of the influence of other factors is subject to debate.

The physiological circadian pattern of cortisol secretion in healthy individuals shows a maintained increase during the night with a maximum peak or acrophase in the morning and decrease during the day. On the contrary, several changes that differ based on the diagnostic subtype have been observed in depressive patients. One of the classical and most consistent biological findings in depression with melancholic characteristics is the inability of suppressing plasma cortisol with 1 mg of dexamethasone.[30] The existence of cortisol hypersection[31,32] and alterations in the circadian rhythm of secretion,[33] with an advance in the nadir phase position (lowest point) of the cortisol and ACTH rhythms[34] have been consistently described in depression. Alterations in cortisol secretion in severe depressions have been related with the existence of a central dysfunction in form of hypothalamic-pituitary-adrenal axis hyperactivity (HPA).[35] A recent study in twins has shown that probands with a background of depression have a daytime curve of cortisol secretion that is significantly different from that of cross-twins without a background of depression, suggesting that the circadian dysfunction of the HPA axis may be a marker of susceptibility for depression.[36]

Another hormone axis in which alterations have been observed in depressive patients is hypothalamic-pituitary-

thyroid axis (HPT), in form of flattening of response of TSH to TRH, not associated to a clinical or subclinical hypothyroidism, and a decrease in the amplitude with flattening of normal nocturnal elevation of TSH plasma concentrations in depressive patients.[37-40]

Equally, a circadian profile with abnormal secretion of the growth hormone (GH) has been observed in depression, above all at the expense of the nocturnal period.[41,42]

Several studies have detected a decrease in the amplitude of the circadian rhythm of melatonin and a significant reduction in the nocturnal plasma secretion of melatonin in depressive patients.[43,44] However, these findings have not been replicated in other works.

MECHANISMS OF ALTERATION OF THE CIRCADIAN RHYTHMS IN DEPRESSION

Abnormalities observed in circadian rhythms in depressed subjects suggest the probable existence of alterations in the physiology of the circadian system involved in the etiopathogeny of depression. Among these alterations, a central dysfunction in the generation of circadian rhythms or abnormal response of the circadian system to the stimuli involved in the adjustment of the main clock with the external environment setting such as light or sleep-wake cycle can be indicated. However, current knowledge does not make it possible to draw definitive conclusions at present regarding the existence of a possible direct causal relationship between alterations of the circadian system and depression. The abnormalities observed could mean vulnerability or causal factors, could be a consequence of depressive status, of reciprocal interactions, or manifestation of other conditions that directly affect both biological rhythms and mechanisms involved in mood state regulation. Circadian alterations may also reflect either masking phenomena in relationship with the sleep disorders present in depression or internal desynchronization phenomena of several circadian rhythm in the same individual.[45] On the other hand, depression in general terms is a heterogeneous concept that includes several depressive subtypes. Thus, there may be an unequal participation of the circadian system based on the different clinical and demographic characteristics of the patients considered. In addition, correct functioning of the circadian system depends on the *zeitgebers* or environmental stimuli in charge of maintaining the endogenous clock synchronized daily with the external environment in 24-hour routines; availability or frequency of exposure to these stimuli may be affected secondarily to other characteristic symptoms of depressive episodes such as psychomotor inhibition, decrease of activities, lack of initiative, anhedonia and social withdrawal. All these factors may induce or contribute to the circadian alterations described in depression.

The chronobiological approach in etiopathogeny of depression does not exclude other well-established classical hypotheses such as monoaminergic; on the contrary, it constitutes an approach that is complemented by other theories since, for example, brain monoaminergic neurotransmission systems show a circadian metabolic pattern,[46] and SCN receive serotoninergic afferences from raphe nuclei, whose most accepted function is the modulation of the sensitivity of circadian system to light.[47] Furthermore, some antidepressant drugs that act on the serotoninergic pathway also have a modulator effect on the circadian system[48] and may modify the clock gene expression.[49]

Different and non-excluding, hypotheses have been proposed to explain chronobiological alterations observed in depressive patients. In the initial studies, it was proposed that the principal chronobiological dysfunction associated to affective disorders could be a decrease in the amplitude of endogenous rhythms,[44] but most of the studies that supported this hypothesis were performed under conditions that did not make it possible to control the influence of masking, external (light-dark cycle) or internal (sleep-wake cycle) phenomena. Studies conducted in patients with seasonal affective disorder (SAD) under constant routine protocols have not revealed differences consistent with the amplitude of the endogenous rhythms regarding the control subjects.[50]

The hypothesis of internal coincidence supposes that there is a relationship of abnormal phases between the circadian system and the sleep-wake cycle. Currently, there is considerable evidence that supports the existence of abnormalities in the phase position of different circadian rhythms in depression. Thus, phase advances of the circadian rhythms of several physiological variables (temperature, cortisol, REM sleep) regarding the sleep-wake cycle in both unipolar and bipolar depressions have been described. The phase advance hypothesis was proposed at the beginning of the 1980's as a pathognomonic alteration of melancholic depression.[51] This would justify symptoms such as evening improvement of mood, early awakening and some neurohormonal findings. The phase advance of circadian rhythms of body temperature and several hormones is still being replicated in recent studies.[52] The hypothesis of phase delay in circadian system has been applied to the seasonal affective disorder, pointing out that treatment with bright morning light would correct the phase position in this depressive subtype.[53]

A dual theoretical model has been proposed to explain the regulation of normal sleep through two interacting physiological processes, «S process» or homeostatic factor that determines the tendency to sleep based on the duration of the previous wake period and a «C process» or circadian factor that establishes the initiation of sleep under endogenous pacemakers control. Slow wave sleep would be regulated by S process and REM sleep would mostly be regulated by C process. Alterations in sleep architecture de-

tected in depression have been related with a failure in these components balance. The hypothesis of the deficiency of the homeostatic process of sleep attributes it to an S process disorder that would be responsible for reduction of REM sleep latency, although changes in phase ratio between both processes have also been involved.

Social zeitgebers, such as work, social demands or interpersonal relationships, may act directly or indirectly on the SCN. These zeitgebers, above all in the industrialized societies, determine eating cycles, sleep hours, physical exercise and exposure to environmental light, so that these factors have the potential capacity to alter the circadian rhythms. Some of the psychosocial aspects involved in the onset and/or maintenance of affective episodes, such as life events, or lack of adequate social support systems, could act as precipitating or maintaining factors through of circadian rhythms disturbance.[55,56]

The recent discovery of the molecular clock responsible for the generation of circadian rhythms indicates genes related with circadian clock molecular machinery as candidates in the study of genetic vulnerability to depression.[57]

Along this line, associations have been detected of some polymorphic variants in genes belonging to human molecular clock in patient with affective disorders with chronobiological variables such as seasonability and chronotype or daily preference;[58] with variables of course such as number of recurrences,[59] with the evolution of insomnia during antidepressive treatment,[60] age of onset of the disorder,[61] sleep and activity patterns,[62] response to mood stabilizing treatment[63,64] and susceptibility to suffering bipolar disorder.[65-67] Although some of these findings are not conclusive and need to be replicated, they involve genetic variants in molecular clock genes in genetic vulnerability to suffer certain depressive phenotypes and/or functional abnormalities in the circadian system.

RESYNCHRONIZATION OF THE CIRCADIAN SYSTEM IN THE TREATMENT OF DEPRESSION

The abnormalities in the biological rhythms described in the depressive states indicate the circadian system as an important therapeutic target in the treatment of depression. Therapeutic strategies aimed at resynchronizing the circadian clock have been developed along this line in order to normalize the changes of the circadian rhythms that appear in the depression.

Non-pharmaceutical treatments

In recent decades, different non-pharmacological interventions have been developed based on the knowledge that maladaption between endogenous biological rhythms with the external environment and alterations of circadian rhythms are associated to depressive symptoms. These interventions have been used both as alternative treatment and as adjuvants of antidepressive psychodrugs. Standing out among these interventions are sleep deprivation, bright light therapy and interpersonal social rhythm therapy.

Sleep deprivation

Application of sleep restriction regimes has been shown to have a significant and rapid onset (in hours or days) antidepressive effect. Response rates of 60% after one night of total sleep deprivation (TSD) have been calculated.[68] Furthermore, antidepressive effects have been observed with sleep manipulations that are not as strict as the TSD, such as partial sleep deprivation restricted to second half of the night or selective deprivation of REM sleep. Efficacy of these manipulations compared with TSD is debated. The principal indication of treatment with sleep deprivation is the acute treatment of major depression, although some effect has also been demonstrated in the prevention of relapses using regular sleep deprivation sessions in association with antidepressants. On the other hand, the combination of TSD and fluoxetine associate a faster onset in the improvement of the depressive symptoms than treatment with only serotoninergic antidepressants.[69]

The best predictor of positive response to this treatment is the daytime variation of mood with morning worsening and evening improvement, characteristic of the depression with melancholic symptoms,[70] although its efficacy is not restricted to this depressive subgroup.

The scarce duration of the results is the principal disadvantage and contrast to the almost immediate antidepressive response in responding patients. In 50%-80% of patients who respond to sleep deprivation, the symptoms have early total or partial reappearance. To avoid or lessen these early relapses in responding patients, several strategies are recommended, among them association with antidepressants, mood stabilizers, bright light treatment[70] or modifications in the hours of sleep to induce a phase advance.[71]

The mechanism of close action of the TSD is unknown, although changes in the brain monoamine activities have been involved in animal models with increases of serotoninergic activity in the raphe neurons[72] and in the dopaminergic receptors of the striate nucleus.[73]

Bright light therapy

Bright light treatment has mainly been studied in depressive patients who have a seasonal pattern in their de-

pressive recurrences, preferentially in fall and winter, with remission (or shift to hypomania/mania in the case of bipolar depression) during the months of spring and summer. This clinical picture is known as Seasonal Affective Disorder (SAD)[74] and is frequently associated with atypical depressive symptoms such as appetite increase with craving for carbohydrate rich foods, weight gain and hypersomnia which are, in turn, predictors of good response to light.[75] Bright light therapy is recommended as first line treatment in SAD,[76] with a 60% to 90% response rate. On the contrary, the role of light therapy in non-seasonal depressions has not been established. However, the results of recent studies support its efficacy in major depression with no seasonal pattern as coadjuvant treatment of pharmacological antidepressive treatment, strengthening its efficacy[77] and accelerating response to serotonin reuptake inhibitors (SSRI).[78]

Light is the principal *zeitgeber* to connect the circadian rhythms in humans so that its antidepressive effects have been related with the capacity to induce changes in the internal phase position. Exposure to bright light in the morning produces phase advances in the circadian rhythms, while evening exposure provokes phase delays.[79] Its application in the early morning has been shown to be superior in regards to antidepressive efficacy in patients with SAD.[80] The treatment consists in exposure to 2,000-10,000 lux for 30-120 minutes/day and its duration is established based on the therapeutic response, usually from two to four weeks.

Social and interpersonal rhythm therapy

Social and interpersonal rhythm therapy (SIPRT) was designed for both acute and maintenance treatment of bipolar disorder (BD), with special emphasis on the prevention of both manic and depressive recurrences.[81] It focuses on the intervention on the principal factors associated to affective episodes recurrences, that would be lack of drug treatment compliance, stressful life events and social rhythms maladaption. SIPRT is based on the hypothesis of social *zeitgebers* in mood disorder. This stresses the relationship between both stressful and positive life events that suppose a marked change in daily routines and changes in the biological rhythms. Thus, disturbance in daily routines would negatively affect physiological function of circadian system in charge of adequately maintaining sleep-wake rhythms, appetite, eating, energy and alert level synchronized, which are distinctive of eutimic states. Individuals vulnerable to suffering a mood disorder would find it difficult to adapt to changes in the circadian rhythms. In fact, changes in daily routines, basically sleep-wake cycle, have been associated to precipitation of affective episodes.[82] Thus, efforts aimed at stabilizing social rhythms should form an important part of the treatment. SIPRT has been shown to be effective in the reduction of the risk of recurrences in BD[83] and has been associated with a significant reduction in suicide attempts in patients with BD.[84] SIPRT includes three complementary strategies: psychoeducation, social rhythm therapy (SRT) and interpersonal therapy (IPT), which, together, help patients to obtain better control on their mood states, coping with the interpersonal relationships more effectively, leading a more organized life with special stress on the maintenance of regular routines and anticipating possible changes in these routines in order to be able to apply a series of strategies aimed at improving adaptation to them. The cornerstone of SRT is a weekly *social rhythm metric (SRM)* that is used as a diagnostic measure of evaluation of treatment efficacy and as a therapeutic tool. The patients fill out a form weekly in which they record the hours in which they perform each one of the following daily activities: waking up, having their first contact with another person, beginning of daily occupations (work, school, etc), the main meal of the day and going to sleep. Parallelly, they evaluate the grade of involvement of other persons in these activities and the mood states and energy levels associated to each one of these situations. This instrument makes it possible to identify the connections between the stability and instability of the rhythms and the mood states and thus recognize which alterations in the routines may lead to alterations in the mood states and vice versa in order to establish skills to restore normality in the circadian rhythms and psychopathological condition.

Antidepressant drugs and treatment of circadian rhythms

Chronopharmacology supposes the existence of a link between the action of a drug and the circadian rhythms of the body. Chronobiotic agents are considered to be those substances capable of influencing the circadian system functioning. Since the 1970's, it has been known that lithium salts, a first line treatment in bipolar disorder and effective potentiator of antidepressive treatment in unipolar depression, lengthen the circadian period in plants.[85] These effects on the circadian system have also been demonstrated in humans,[86] even on the level of individual neurons in the SCN.[87] The properties on the circadian rhythms of lithium have been attributed to the inhibition of glycogen synthase kinase 3 (GSK3 β),[88] which in turn modulate the activity of severe molecular clock components.[89] On the other hand, the data referring to the chronobiotic properties of the antidepressive drugs are more controversial.[90] Recent studies indicate that fluoxetine produces phase advances in the circadian activity in a similar way to the application of bright light in the morning.[48] This information is supported by others who have indicated that the SCN receives innervations from serotonergic neurons of the raphe nuclei[91] and that the local application of serotoninergic receptor agonists in the SCN produce phase advances of the circadian activity.[92]

Antidepressants of common use at present have a series of limitations, among them a several week delay in the onset of their action, several undesired effects and symptoms associated to their discontinuation or withdrawal, which affects correct treatment compliance.[93] Side effects such as blurred vision, constipation, dizziness, dry mouth, shaking and micturation problems are more frequent with tricyclic antidepressants (TAD) than with SSRI, while symptoms such as nausea, headache, increase stool rhythm and insomnia are more frequent with SSRI.[94] On the other hand, serotonin-norepinephrine reuptake inhibitors (SNRI) would have a profile of intermediate side effects, although they are better tolerated than TADs. With long term antidepressant treatment, sexual dysfunction, weight gain, sleep alteration, fatigue, apathy, and cognitive symptoms that limit the quality of life and social functioning of the patients often appear.[95]

Sleep alterations make up one of the most prevalent symptoms of depression. In general, both polysomnographic measurement and subjective impressions on sleep quality in depressive patients improve after 3 or 4 weeks of effective antidepressant treatment.[25] Several types of antidepressants alter the physiological architecture of sleep. These effects are fundamentally on the REM sleep (*rapid eye movement*).[96] However, their influence on slow wave sleep, clearly affected in depression, is more controversial. The most consistent effects on sleep of most of antidepressants, including TADs and SSRIs, include REM sleep suppression and increases in the onset of REM sleep latency.[97,98] Some antidepressants with 5-HT receptor antagonist activity, as mianserine, mirtazapine, nefazodone, and trazodone, promote the onset and sleep continuity,[99] although they also affect the histaminergic pathway to a greater or lesser degree. This could produce excessive daytime somnolence and a significant weight repercussion. The current SSRIs and SNRIs have no effect on sleep alterations at the onset of the treatment and may even worsen the insomnia. This often entails associating benzodiazepines or hypnotics to the treatment.[25] On the other hand, almost 50% of the depressive patients have not achieved complete remission of the symptoms after two trials of treatment in monotherapy, two thirds have remitted after the establishment of four therapeutic strategies, while one third has remained symptomatic.[100] These modest efficacy values together with the undesired effects indicted manifest the need for new treatments that overcome all these limitations. This has lead to the development of new drugs with action mechanisms that present an alterative to those of the antidepressants used most in the clinical practices, such as the SSRIs, SNRIs and TADs.

Action of the melatoninergic pathway is a new approach in the treatment of depression that affects the functioning of the circadian system in order to normalize its activity. Melatonin has chronobiotic effects so that its external administration can guide the circadian pacemakers inversely to the action of the light. Its action differs based on the time of its administration, producing a phase advance of the circadian system in the evening and a delay at daybreak.[101] Melatonin has been shown to be useful in the treatment of some circadian disorders such as jet-lag or sleep alterations associated to working in shifts, but it lacks antidepressive efficacy, which has attributed to its extremely short half life. Agomelatine is a novel antidepressant with mechanism of antidepressant action involving melatonergic MT1 and MT2 receptors agonist activity and serotonin 5-HT2C receptor antagonist,[102,103] that has demonstrated efficacy in the treatment of major depressive treatment in several controlled clinical trials.[104-106] Agomelatine is a drug currently approved by the Spanish Drug Agency for the treatment of depression with robust effects on the circadian system as it has been demonstrated to resynchronize the circadian rhythms in preclinical models of depression,[107] induce phase advances of several circadian rhythms in healthy individuals[108] and restore sleep pattern in depressive subjects by distribution of slow wave sleep in the first cycles without suppressing REM sleep.[109] Beyond the effects on circadian system through the agonist action on the malatoninergic receptors and on the $5HT_{2C}$ receptor in the suprachiasmatic nucleus, the antagonism on the $5\text{-}HT_{2c}$ receptors stimulates the noradrenergic and dopaminergic transmission to the prefrontal and mesolimbic level. Therefore, agomelatine also differs from the SSRIs and SRNIs in regards to its activity on the serotoninergic pathway. Thus, agomelatine does not have the side effects typically associated to the use of SSRI. It has a neutral effect on weight and sexual function while it shows favorable effects on sleep, increase its quality early without producing daytime somnolence.[110] That is why the combination of antidepressive efficacy with additional benefits on sleep from the early phases of treatment and an excellent tolerability profile mean a clear advantage over the antidepressant drugs that are currently available, stressing the success of the circadian system as therapeutic target in the treatment of depression.

CONCLUSIONS

In recent decades, a large amount of clinical and biological data has been generated. This shows how alterations in circadian rhythms play an important role in pathophysiology and the symptomatic expression of depression. However, there are still questions to answer in the complex relationship between the endogenous pacemakers and the appearance of depressive symptoms. The substantial improvements of some depressive patients after the application of therapeutic interventions based on the manipulation of the circadian rhythms suggest that circadian abnormalities of these patients may be a determining factor in the response to treatment. However, the development and application of therapies aimed at correcting circadian system alterations present in the clinical depression has been given little thought up to now. Non-pharmaco-

logical therapies that act on the circadian system in the treatment of depression are not very extended in the daily clinical practice in our setting. One factor that may explain the limited application of these chronotherapeutic interventions, such as sleep deprivation or therapy with bright light, may be their transient efficacy. This would make it necessary to maintain them over time, with the application problems that this causes in some care settings. Another aspect to be considered is the preferential efficacy of light therapy in some depressive subtypes, such as seasonal depression. This may have limited its application in other depressive subtype. Furthermore, a psychobehavioral approach such as social and interpersonal rhythm therapy is underused overall in daily practice although it has a preferential application in bipolar disorder. However, the data that support its utility in the prevention of depressive recurrences stress the importance of the generalization of its use. The rapid increase of knowledge on the molecular substrate of the circadian system that has occurred in recent years offers new and promising opportunities for the development of therapeutic alternatives to cope with the challenges that continue to occur at present in the treatment of depression, including agents that act by modifying the expression of genes belonging to the circadian molecular machinery. In this sense, the response and remission rates achieved with the commonly used antidepressants at present and their action speed must be improved as well as their tolerability, basically regarding their effect on sleep, sexual function and weight balance. All of this would have a benefit in the increase of treatment compliance both in the acute phase and in the maintenance one for the prevention of relapses and recurrences, with the consequent benefit for the depressive patients. Availability of an antidepressive drug of proven efficacy and excellent tolerability whose action mechanism acts directly on the circadian system, such as agomelatine, will assure the application and extension of specific approach of the alterations of biological rhythms present in depression in the current clinical practice.

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