Circadian rhythms and treatment implications in depression

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A B S T R A C T
In humans almost all physiological and behavioural functions occur on a rhythmic basis. Therefore the possibility that delays, advances or desynchronizations of circadian rhythms may play a role in the pathophysiology of psychiatric disorders is an interesting field of research. In particular mood disorders such as seasonal affective disorder and major depression have been linked to circadian rhythms alterations. Furthermore, the antidepressant efficacy of both pharmacological and non-pharmacological strategies affecting endogenous circadian rhythms, such as new antidepressant medications, light-therapy and sleep deprivation, is consistent with the idea that circadian alterations may represent a core component of depression, at least in a subgroup of depressed patients. This paper briefly describes the molecular and genetic mechanisms regulating the endogenous clock system, and reviews the literature supporting the relationships between depression, antidepressant treatments and changes in circadian rhythms.

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1. Introduction
Living organisms show cyclic rhythmicity in a variety of biological and behavioural processes; the sleep–wake cycle is one of the most obvious rhythmic physiological functions. Rhythms that approximate the 24-hour dark–light cycle are called circadian (from Latin circa diem), whereas those that are longer or shorter are defined, respectively, ultradian and infradian. Cyclic rhythmicity is produced by an oscillator that comprises interacting cellular components, which interact to generate a rhythmic output. In both animals and humans oscillators have been identified in brain as well as in peripheral tissues. In mammals, a central pacemaker has been localized in the suprachiasmatic nucleus (SNC) of the hypothalamus, a cluster of about 10,000 neurons located at the midline above the optic chiasm (Hastings, 1997); this is often referred to as the “master clock” (Klein et al., 1991). The destruction of the SCN by experimental procedures in animals or by pathological processes in humans disrupts the ability to express any overt circadian rhythm (Klein et al., 1991). Neurons of the central pacemaker have an intrinsic rhythmicity, usually longer than 24 h that can respond directly or indirectly to external time givers, or zeitgebers in an adaptive process known as entrainment. This process leads to the synchronization of the intrinsic rhythmicity of the SCN to 24-hour daily. Beside the central master clock peripheral circadian clocks have been identified in the liver, the gastrointestinal system, the respiratory system, fat tissue, the thyroid gland and the adrenal gland. All these systems undergo the cyclic rhythmicity of the SCN; hence, they are also defined as slave clocks to emphasize their strong dependence by the master clock of the SCN.

Light is one of the most powerful zeitgebers able to influence the output of multiple oscillator systems, through entrainment of the master clock. Food availability as well as social schedules or social exchanges, or even the earth’s magnetic field are important time givers for peripheral oscillators, (Schulz and Steimer, 2009). Light may act directly as a zeitgeber at peripheral oscillators in simple organisms like Drosophila, in which many different tissues are photoreceptive. In animals of grater size and complexity, the range of tissues exposed and responsive to light is reduced. In mammals, only the retina is light responsive and conveys light information to the SCN through a specific monosynaptic pathway, the retino-hypothalamic tract that originates from a distinct population of light sensitive retinal ganglion cells containing the photopigment melanopsin and releasing glutamate (Hattar et al., 2002). In addition to the glutamatergic retina input, the SCN also receives a dense serotonergic innervation from the median raphe nucleus (Moore and Speh, 2004) that appears to convey non-photic timing stimuli to the SCN. These two major inputs seem to act on the SCN in a mutually inhibitory manner in which each one can inhibit the phase changes induced by the other (Smith et al., 2001).

The major output of SCN is to the paraventricular nucleus (PVN) of the hypothalamus, which translates the SCN signals into hormonal and autonomic signals for peripheral organs through the autonomic nervous system and the corticotrophin-releasing factor secreting neurons, which are part of the hypothalamic-pituitary-adrenal axis.
Light also directly inhibits the production of the pineal hormone melatonin, which has been defined as the “darkness” hormone. In fact, in humans, the secretion of melatonin by the pineal gland is minimal during day hours, progressively increases with the onset of the dark phase to reach a peak in the second phase of the night, and then gradually decreases to daytime levels in the morning. Melatonin transmits information about the occurrence and duration of darkness, being considered as a marker of the absence of the photic zeitgeber. Moreover, as the duration and the amplitude of the nocturnal melatonin peak increase with the lengthening of the dark phase of day/night cycle, a lengthening melatonin secretion indicates that fall/winter is coming, while progressive shortening of melatonin signal indicates that the season is moving to spring/summer (Simonneaux and Ribelayaga, 2003). Therefore, melatonin is also able to communicate to the cells of the organism the change of seasons over the year. Melatonin has itself a zeitgeber function, being secreted under the hierarchical dependence of SCN and influencing the intrinsic rhythmicity of the SCN in return, through the action on specific melatonin receptors located on SCN neurons (Schulz and Steimer, 2009).

At molecular level, the circadian oscillator system involves numerous interlocked transcriptional and post-transcriptional regulatory feedback loops including several proteins and their coding genes such as the Circadian Locomotor Output Cycles Kaput (CLOCK) and the Brain and Muscle ARNT-like protein 1 (BMAL1), the Period, Timeless, Cryptochrome, the Neuronal PAS domain protein-2 (NPAS-2), and the recently identified Fer2 and nocturnin genes (Cermakian and Boivin, 2003; Harms et al., 2004; McClung 2007; Nagoshi et al., 2010). In the central nervous system, the result of this complex regulatory system is the rhythmic modulation of neurotransmitters and neuromodulators, through changes in the amount of substances released, in the neuronal firing rate, or in the cellular metabolism rate (Reppert and Weaver, 2002). This impacts behavioural and neurobiological functions including mood, learning, memory, motor activity, hormone secretion, temperature, food intake and sleeping, which in turn undergo an intrinsic rhythmicity, mainly on a circadian basis.

2. Circadian rhythm disturbances in depression

In healthy subjects, mood may vary across the 24-hour cycle showing a typical deterioration in evening if compared with morning hours (Tölle and Goetze, 1987; Gordijn et al., 1994; Boivin et al., 1997; Buyssse et al., 1997); moreover, it has been proved that, in healthy people, the daily variation in mood depends on the interaction between the circadian phase and the duration of prior wakefulness (Boivin et al., 1997). If mood regulation in healthy people is directly affected by circadian processes, it is not surprising that circadian disturbances may have a role in the pathophysiology of mood disorders. Indeed, alterations of endogenous circadian rhythms in major depression have been described for the first time about 25 years ago (Van Cauter and Turek, 1986), and a meta-analysis showed that circadian rhythm disturbances are most likely to distinguish subgroups of depressed patients from controls (Benza et al., 1992).

The most consistent circadian alterations that have been described in patients with major depression includes changes in daily mood variation, brain activity, core body temperature, hormone secretion, sleep–wake cycle, motor activity and seasonal mood variation. Many patients with depression show a regular daily pattern of mood, usually with worse mood in the morning (Tölle and Goetze, 1987; Gordijn et al., 1994), and, notably, a pattern of worse mood in the morning is mentioned in formal DSM-IV criteria for the melancholic subtype of major depression. On the contrary, a minority of depressed patients show the opposite trend defined as “reverse diurnal variation” and characterized by worsening mood in the evening (Joyce et al., 2005). In a recent post-hoc analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study, it has been reported that 21.6% of depressed patients enrolled into the study experienced diurnal mood variation and that, as compared to patients without diurnal mood variation, they exhibited a more severe depression and were more likely to meet the criteria for the melancholic subtype of depression if the definition was expanded to include also afternoon and evening worsening of mood (Morris et al., 2007). Also patients with other forms of depression actually appear to report a pattern of diurnal mood variation (Leibenluft et al., 1992). A recent investigation, using a two-factor model of mood categorized according to positive affect (PA) and negative affect (NA), indicated that depressed patients show lower overall levels of PA, which increases over the course of the day as in healthy controls but with a backwards shifted acrophase, and higher overall NA levels with maximum values occurring in the late morning and then decreasing over the rest of the day (Peeters et al., 2006). The investigation of the biological and metabolic correlates of diurnal mood variation showed that depressed patients exhibit peculiar patterns of activation in regional brain glucose metabolism across day time. In particular, an increased activation of a dorsal neural network involved in affective regulation was found to be associated with evening mood improvement in depressed individuals (Germain et al., 2007).

Alterations in core body temperature circadian rhythm have been largely reported in depression. The most common observed circadian abnormalities are represented by elevation of mean nocturnal body temperature, decreased period amplitude and phase-advance in its overall 24 hour pattern, although these changes were not confirmed by all the studies (Dietzel et al., 1988; Goetze and Tölle, 1987; Souètre et al., 1988; Duncan, 1996). A normalization of elevated nocturnal body temperature has been reported in patients undergoing mood improvement (Avery et al., 1982). Moreover, in subjects experiencing a depressive episode, nighttime changes in body temperature have been found inversely correlated with nighttime changes in plasma levels of the thyroid stimulating hormone (TSH) (Souètre et al., 1988). The mean plasma concentrations of TSH during sleep, its nocturnal peak and the amplitude of its circadian rhythm have been reported to be lower in depressed subjects as compared to both normal controls and remitted patients (Souètre et al., 1989). Finally, the time of the nocturnal TSH peak has been found to be advanced during a depressive episode (Souètre et al., 1989).

In healthy subjects, the circadian rhythm of cortisol is characterized by a maximal secretion in the morning, a progressive decline of production over the day to reach the nadir in the evening, immediately after falling asleep, and a subsequent gradual increase over the night up to the morning peak. Patients with major depression exhibit an overall increased cortisol secretion, with the largest effect at the nadir of the circadian rhythm, and an early onset of the nocturnal secretory episode. These changes suggest a phase advance of the cortisol circadian rhythm in depression (Van Cauter et al., 1996; Koenigsberg et al., 2004). Moreover, in depressed patients the 24-hour cortisol secretion appeared to be more variable (Peeters et al., 2006) and less strongly related to social zeitgebers (Stetler et al., 2004).

Because of its pivotal role in the endogenous clock system, melatonin has been largely investigated in depression as well as in bipolar disorders. Decreased plasma levels of melatonin and a phase advance or a trend toward a phase advance in melatonin circadian rhythm have been described in patients with major depression (Claustret et al., 1984; Parry and Newton, 2001); though this was not confirmed by all the studies (Thompson et al., 1988; Carvalho et al., 2006). Moreover, bipolar patients and their offspring have been shown to exhibit an enhanced sensitivity to the suppressant effect of light on melatonin secretion (Lewy et al., 1985; Nurnberger et al., 1988).

Subjective and objective sleep–wake cycle alterations are by far the most widely reported circadian disturbances associated with depression. Epidemiological studies estimate in 50–90% the percentage of depressed patients who complain about impairment of sleep quality and/or duration (Casper et al., 1985; Riemann et al., 2001). The majority of depressed patients report difficulty falling asleep, staying
asleep and early awakening whereas only 6% to 25% of them complain about hypersomnia (Roberts et al., 2000; Tsuno et al., 2005). Insomnia is not only subjectively experienced but also reflected in altered objective sleep architecture. In particular, a shortened latency between sleep onset and the first rapid eye movements (REM) sleep episode characterizes depressed individuals, who also exhibit an increased duration of REM sleep, an increased number of eye movements during REM sleep, and a decreased slow-wave sleep (SWS) compared to healthy controls (Riemann et al., 2001; Shaffer et al., 2003; Tsuno et al., 2005). REM sleep abnormalities show a trend toward normalization after mood improvement (Buyse et al., 1997), and even a total restoration of sleep architecture has been reported after remission (Knowles et al., 1986). However, persistence of REM sleep and SWS alterations during remission has been also found, and this has been associated with an increased risk of relapses and recurrences (Giles et al., 1987; Buyse et al., 1997; Kupfer et al., 1990).

Motor activity shows a typical circadian rhythm in humans, and most although not all investigations have documented a phase advance (early daily peak) of the circadian motor activity rhythm in bipolar disorder patients in both the depressive and the manic phases as well as during euthymia (Wolf et al., 1985; Salvatore et al., 2008).

Seasonal affective disorder (SAD) is a disorder with a circannual period and patients with SAD present with apparent chronobiological abnormalities; hence, it is currently assumed that SAD is a disorder of seasonal biological rhythms (Levitan, 2007). In “winter depression”, the most common type of SAD, patients experience major depressive episodes starting with the onset of winter, followed by remission in the spring. Sleep disturbances, quantitative changes and phase delays in cortisol and melatonin secretion patterns, and increases in the minima of the nocturnal body temperature as well as a phase delay of its 24-hour rhythm are the most commonly reported abnormalities of circadian rhythms in SAD patients (Dahl et al., 1993; Avery et al., 1997; Schwartz et al., 1997).

Finally, both diurnal and seasonal variations have been detected also for suicide, which showed increasing rates with the increasing amount of bright sunlight (Chew and McCleary, 1995; Preti and Miotti, 2001).

3. Circadian genes and depression

The role of disrupted circadian rhythms in the pathophysiology of depression is also supported by recent findings in the field of molecular biology and genetics of the complex machinery regulating biological clocks. Transgenic mice overexpressing the gene of the glycerone synthase-kinase-3β (GSK-3β), a recently recognized central regulator of circadian rhythms and a target of the mood stabilizer lithium (Quiroz et al., 2004), show a slight depression-like behaviour and an increased startle response that are reminiscent of a mania-like behaviour (Prickaerts et al., 2006). Moreover, mice carrying a mutation in the CLOCK gene exhibit mania-like behaviours such as decreased need of sleep and motor hyperactivity, which are reverted by chronic administration of lithium and are rescued by expressing a functional CLOCK protein specifically in the ventral tegmental area of those CLOCK mutant mice (Roybal et al., 2007).

The role of genes involved in the endogenous clock system has been investigated in both bipolar disorder and major depression. Bipolar patients with CC genotype of the CLOCK gene T3111C single nucleotide polymorphism (SNP) show a greater severity of insomnia during antidepressant treatment, higher recurrence rate of affective episodes and reduced need for sleep as compared to patients carrying CT and TT genotypes (Benedetti et al., 2003; Serretti et al., 2003, 2005). A significant, although modest, association of BMAL1 and TIM gene SNPs with bipolar disorder has been found by a study on a family-based sample of bipolar patients (Mansour et al., 2006). An independent haplotype analysis confirmed the BMAL1 association with bipolar disorder, and found a new association with PER2 gene SNPs (Nievergelt et al., 2006). Moreover, it has been reported that bipolar patients with the TT genotype of the GSK3β-50 SNP show an early onset of the disorder and a worse response to lithium treatment compared to patients with TC or CC genotypes (Benedetti et al., 2004, 2005). Finally, recent studies suggest an increased risk for SAD in patients carrying some SNPs of PER2, NPAS2 and BMAL1 genes (Partonen et al., 2007).

4. The circadian hypotheses of depression

Because of the occurrence of the above reported dysregulations in several endogenous circadian and seasonal rhythms in depressed individuals, circadian hypotheses for the pathogenesis of depression have been put forward. Although rhythm abnormalities observed in depressed patients are highly variable, including phase advance or delay as well as amplitude changes, the “phase advance” of endogenous circadian rhythms seems to be the most consistently reported as shown by the shortening of the latency of the REM phase after falling asleep, the early morning awakening, the early morning rise of ACTH and cortisol secretion and the nocturnal elevation of prolactin and growth hormone levels in depressed patients (Wehr and Goodwin, 1983; Linkowski et al., 1985; Mendlewicz et al., 1985). Therefore, a “phase advance” hypothesis of depression has been proposed.

Alternatively, “the internal phase coincidence” hypothesis, postulated that depression arises when awakening occurs during a sensitive phase of the circadian period (Borbély and Wirz-Justice, 1982). This model was supported by the finding that the reduction of the mismatch in circadian and sleep phases by advancing sleep episodes leads to mood improvement in depressed patients (Wehr et al., 1979).

The “social rhythm” hypothesis of depression, instead, underlines the key role of the disruption of social rhythms in triggering depressive episodes. This social zeitgeber theory specifically postulates that depressive episodes arise as a consequence of life events disturbing social zeitgebers (social factors such as the timing of meals, work schedules, social demands, personal relationships) which, in turn, derail an individual’s social rhythms. These disruptions can place substantial stress on the body’s capacity to maintain stable biological rhythms, particularly sleep–wake, energy, alertness and appetite rhythms. Whereas in most individuals such rhythms will restabilize shortly after the destabilizing events, in predisposed subjects, they may precipitate a major depressive episode. This hypothesis is supported by the evidence that social rhythms are disrupted and less regular in patients with affective disorders, as well as during stressful life events (Shear et al., 1994; Frank et al., 1995, 1997), and by the finding that increased regularity of social rhythms is associated with higher quality of sleep and less severe depressive symptoms (Monk et al., 1994; Brown et al., 1996).

5. Circadian rhythms and antidepressant treatment

It is possible to speculate that a disruption in physiological circadian rhythmicity characterizes at least a subgroup of depressed patients, thus opening the way to treatment interventions that, restoring normal endogenous rhythmic patterns, would resolve depressed states. Therefore, chronotherapeutic interventions, including pharmacological and non-pharmacological therapies, have been developed.

As for non-pharmacological treatments, sleep deprivation, light therapy and interpersonal and social rhythm therapy (IPSRT) have shown antidepressant effects. A one-night application of total sleep deprivation (TSD) improves mood in 50–60% of patients with depressive disorders (Wehr, 1990; Wu and Bunney, 1990), but that therapeutic effect is largely transient, since over 80% of responders experience a relapse after the first night spent sleeping after TSD monotherapy (Svestka, 2008). Concomitant antidepressant medication has been shown to reduce the relapse rate to 59% of depressed patients treated with TSD (Wu and Bunney, 1990). A recent study in
healthy volunteers established that the antidepressant effect of TSD correlates with the morningness–eveningness chronotype (Selvi et al., 2007), since subjects with the eveningness chronotype showed mood improvement whereas those with the morningness chronotype experienced mood worsening. Furthermore, it has been very recently shown that euthymic bipolar patients had evening preferences and this phenotypic chronotype was significantly associated with longer sleep latency (Giglio et al., 2010). These findings should be taken into account in delivering TSD to depressed individuals, and chronotype issues are worth of further investigations in the treatment of affective disorder patients. Partial sleep deprivation (PSD), that is deprivation of sleep for at least 1 h in the second half of the night, has been shown to induce a marked improvement of depressive symptoms, although smaller than TSD (Giedke et al., 1990, 1992). Selective REM sleep deprivation (SD) was initially supposed as more effective than TSD, but several studies found no difference in antidepressant effect between the two variants and a more delayed onset of the clinical efficacy for REM SD (from 5 to 10 or even 14 days) (Reynolds et al., 1990). In order to prolong the transient antidepressant effect of SD several strategies have been proposed. The one which demonstrated the best efficacy was the sleep phase advance method. It consists in progressively advancing the sleeping hour after experiencing a SD, starting from 5 p.m. and shifting forward each following day for the total duration of 7 days. The sleep advance method prevented relapse in 60–80% of responders to SD. (Vollmann and Berger, 1993; Riemann et al., 1996; Albert et al., 1998) and a sleep phase advance of 3 days has been shown to be as effective as a 7 days cycle (Voderholzer et al., 2003).

Light therapy is actually considered the first choice treatment for the winter-onset form of SAD and its outstanding positive effect has led to the conclusion that, at this moment, it represents the most successful clinical application of the resynchronization of circadian rhythms in psychiatry. A recent meta-analysis confirmed that a significant reduction in depression symptom severity is associated with bright light treatment in both SAD (effect size 0.84) and non-seasonal depression (effect size 0.53) (Golden et al., 2005). Light therapy moves from the hypothesis that most patients with SAD become depressed in fall/winter at least in part because the winter later dawn causes a delay in the patients' endogenous circadian rhythms with respect to clock time and to sleep–wake cycle (Lewy et al., 2006). Therefore, providing a corrective phase advance should be useful in realigning endogenous rhythms with the sleep–wake cycle. In SAD patients, exposure to bright light in the morning causes a phase advance of endogenous circadian rhythms and has robust antidepressant effects, which are correlated with the magnitude of the phase advance (Terman et al., 2001). However, some SAD patients are actually phase-advanced, and this may explain why bright light scheduled in the evening, which causes a phase-delay of endogenous rhythms, has been proven to have equally antidepressant effects as morning exposure (Wirz-Justice et al., 1993). Light therapy has also been associated with reduced suicidal ideation (Lam et al., 2000). Guidelines for the treatment of SAD patients with bright light have been recently provided (Lewy et al., 2007).

IPSRT was specifically designed to maintain regular daily rhythms a well as identify and manage potential precipitants of rhythm disruptions, according to the social zeitgeber theory that depressive episodes arise as a consequence of life events disturbing social zeitgebers (Ehlers et al., 1988). Therefore, restoring the depressed patient’s social zeitgebers, such as personal relationships, meal, exercise and social demands, would result in normalization of biological rhythms and improved mood. Two preliminary studies have shown that, although increasing bipolar individuals’ social rhythm regularity did not improve the mood, participants treated with IPSRT experienced longer episode-free periods and were more likely to remain well in the two year preventive maintenance study phase (Frank et al., 1997, 2005).

As for pharmacological treatments, several lines of evidence indicate that antidepressant medications and mood stabilizers influence circadian rhythms, possibly by acting on serotonin ascending pathways from the median raphe nuclei, which modulates the sensitivity to light of SCN clock neurons (Racagni et al., 2007). Despite of large individual drug variability, tricyclic antidepressants (TCAs) generally shorten sleep latency and improve sleep duration and continuity in depressed patients; moreover, almost all TCAs share the property to increase REM latency and decrease the total amount of REM sleep, thus contributing to normalize the disrupted sleep architecture that characterizes a subgroup of depressed patients. As for selective serotonin reuptake inhibitors (SSRIs), fluoxetine has been shown to modulate the activity of the biological clock through phase advances of SCN neuronal firing (Sprouse et al., 2006), and to increase the hippocampal expression of CLOCK and BMAL1 genes (Uz et al., 2005) after chronic administration. Mood stabilizers such as lithium and valproate have also shown chronobiological properties. In particular lithium has been shown to lengthen the period of circadian rhythms in rodents (LeSauter and Silver, 1993) and the period of firing of cultured SCN neurons (Abe et al., 2000) as well as to inhibit the GSK-3β, a regulator of the circadian clock (Quiroz et al., 2004), while valproate has been detected to influence the expression of several circadian genes in the amygdala (Ogden et al., 2004).

As melatonin has shown chronobiological properties in both mice and humans, an antidepressant effect of the pineal hormone has been supposed. However, studies investigating melatonin in the treatment of depression generally found an improvement of sleep, but no antidepressant effects when melatonin was used either in mono-therapy (de Wries and Peeters, 1997; Dolberg et al., 1998) or in combination with existing antidepressant drugs in patients with treatment-resistant depression (de Wries and Peeters, 1997; Dolberg et al., 1998; Dalton et al., 2000). Agomelatine, a recently synthesized antidepressant drug, is a potent agonist at melanotenic MT1 and MT2 receptors and an antagonist at 5-HT2c, which are highly expressed in the SCN (Millan et al., 2003). The antagonistic effect at 5-HT2c receptor may explain the above mentioned lack of antidepressant activity of exogenous melatonin, which acts only through MT1 and MT2 receptors, and it allows inference that agomelatine antidepressant action is not mediated through those mechanisms known for TCAs, SSRIs, and monoamine oxidase inhibitors. Moreover, agomelatine has shown to possess sleep–wake cycle regulating properties and to be able to restore abnormal circadian rhythms in several models of disrupted circadian rhythms. In particular, agomelatine has shown to restore the activity pattern in an animal model of delayed sleep-phase syndrome (Armstrong et al., 1993), as well as the stress-induced changes in body weight, hypothalamo-pituitary-adrenal axis activity, locomotor activity and core body temperature in animal models of depression (Fuchs et al., 2006). In recent studies on major depressed patients agomelatine increased the duration of SWS and normalized its night distribution (Quera Salva et al., 2007) as well as demonstrated a rapid improvement of subjective evaluation for both getting to sleep and quality of sleep (Lemoine et al., 2007). All these data are indicative of agomelatine’s potential to renormalize circadian rhythms including sleep–wake cycle alterations.

6. Conclusions

Although a causal link between endogenous rhythm disruption and depression has not been firmly established, experimental evidence converge and support the hypothesis that circadian rhythm dysregulations may play a critical role in the pathophysiology of this disorder (Boyle and Barriball, 2010). Furthermore, the antidepressant efficacy of both pharmacological and non-pharmacological strategies affecting circadian rhythms is consistent with the idea that circadian alterations may represent a core component of depression, at least in a subgroup of depressed patients. However, it must be pointed out that
most of the circadian abnormalities observed in the depressed state normalize with recovery; hence, it cannot be excluded that they arise as consequence of depression and do not represent primary determinants of the affective disorder. However, even if so, the presence of disrupted endogenous rhythms might potentially contribute to the maintenance of depressive symptoms and might affect the course and/or the prognosis of patients affected. Therefore, circadian abnormalities of depressed patients are worth of clinical and therapeutic consideration.

Future research should specifically address the issue whether inducing circadian rhythm abnormalities may generate animal models of depression and/or may precipitate depressive symptoms in euthymic patients and/or in healthy subjects, that could be prevented or reverted by antidepressant medications. This would provide further strength to the circadian hypothesis of depression. Moreover, a more profound knowledge of the connections between biological clock functions and mood regulation will not only provide deeper understanding of the etiopathogenetic processes that characterize depression, but will contribute also to the development of more effective antidepressant treatment strategies. Indeed, the currently used antidepressant drugs, acting more or less specifically on brain monoamines, are frequently associated with significant limitations, such as low remission rates, high risk of relapses, slow onset of response, discontinuation symptoms and side effects, especially sleep disturbances. Normalization of endogenous circadian rhythms seems to represent a possible new direction for the development of either pharmacological or non-pharmacological innovative therapeutic strategies to treat depression.

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