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# Prospects for Circadian Treatment of Mood Disorders

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**Abstract**

Disruption of circadian clocks is strongly associated with mood disorders. "Chronotherapies" targeting circadian rhythms have been shown to be very effective treatments of mood disorders, but still are not widely used in clinical practice. The mechanisms by which circadian disruption leads to mood disorders are poorly characterized and therefore may not convince clinicians to apply chronotherapies. Hence, in this review, we describe specific potential mechanisms, in order to make this connection more credible to clinicians. We believe that four major features of disrupted clocks may contribute to the development of mood disorders: 1) loss of synchronization to environmental 24-hour rhythms, 2) internal desynchronization among body clocks, 3) low rhythm amplitude, and 4) changes in sleep architecture. Discussing these attributes and giving plausible examples, we will discuss prospects for relatively simple chronotherapies addressing these features that are easy to implement in clinical practice.

**Keywords:** Circadian Clock, Mood Disorders, Depression, Mania, Bipolar Disorder, Chronotherapy

**Key Messages:**

1. In this review, we describe specific potential mechanisms by which disrupted clocks may contribute to the development of mood disorders: 1) loss of synchronization to environmental 24 hour rhythms, 2) internal desynchronization among body clocks, 3) low rhythm amplitude, and 4) changes in sleep architecture.

2. We provide prospects for relatively simple chronotherapies addressing these features that are easy to implement in clinical practice.

## 1. Introduction

The potential role of circadian clocks in mood regulation has been extensively discussed. There is strong evidence from animal and human studies that disturbances of circadian clocks are associated with the development of mood disorders like major depressive disorder (MDD), bipolar disorder (BD), and seasonal affective disorder (SAD) [1]. For instance, disruption of the sleep-wake cycle is such a characteristic feature of MDD and is one of the core symptoms that define the disorder [2]. Furthermore, patients with mood disorders strongly benefit from "chronotherapies" targeting the circadian system. However, whereas there is considerable evidence that circadian clocks play a role in mood control and in the pathophysiology of mood disorders, therapeutic interventions targeting circadian clocks of patients are not yet routine in clinical practice.

We believe that one reason for the under-representation of so called chronotherapies in medical practice is the lack of discussion of causal chains plausibly linking circadian rhythmicity and brain functions. Circadian intervention may become a more attractive therapeutic option for clinicians if they are provided with concrete explanations how disrupted circadian rhythms can contribute to mood disorders.

Accordingly, this review presents plausible and tangible mechanistic connections between circadian disturbances and mood disorders, thereby helping therapists and patients to understand why aligned and stable circadian clocks might be important. McClung has recently discussed various molecular connections between circadian clocks and mood regulation [3]. Expanding on this, we will discuss more general mechanistic links within the framework of fundamental circadian principles, forming a sound conceptual basis for implementing chronotherapies and circadian principles into clinical practice.

## 2. General information about circadian clocks

Life has adapted to recurring daily changes caused by the Earth's rotation. To optimally anticipate these daily changes, most living organisms evolved "circadian" (ca. 24 h) clocks that control almost all biological processes. To synchronize internal circadian rhythms to environmental fluctuations, circadian clocks are permanently reset by external cues, so-called *Zeitgebers* (time givers, e.g. light/darkness, meal times, activity patterns). In response to these *Zeitgebers*, individuals can adopt very different timing preferences ("chronotypes") for daily routines and sleep, i.e. a tendency to 'eveningness' with a delayed sleep time, or 'morningness' with an early sleep time [4]. In mammals, the internal circadian timekeeping system is organized hierarchically, with the master circadian clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, and subsidiary clocks in almost every cell of the body [5]. Rhythms in SCN neurons are mainly synchronized by light signals perceived by melanopsin-expressing retinal ganglion cells [6, 7].

At the molecular level, the circadian clock mechanism is based on a transcriptional-translational feedback loop comprising "clock proteins" which regulate their own biosynthesis in a rhythm approximating 24 h. Central clock genes include *Brain Muscle Arnt-like Protein 1* (*Bmal1*), *Circadian Locomotor Output Cycles Kaput* (*CLOCK*), *Neuronal PAS Domain Protein 2* (NPAS2), *Period* (*PER1*, *PER2, and PER3*), and *Cryptochrome* (*CRY1* and *CRY2*). BMAL1 and CLOCK (or NPAS2) dimerize and bind to E-box elements in the promoters of target genes, including *Per* and *Cry*, thereby inducing transcription of those genes. In the cytoplasm, PER and CRY proteins form complexes which translocate back to the nucleus and repress BMAL1/CLOCK(NPAS2)-dependent transcriptional activity, thus inhibiting transcription of their own genes. Gradual degradation of PER/CRY complexes eventually diminishes this negative feedback, allowing a new molecular cycle to start [8]. An additional loop including both activating and inhibiting regulatory elements is formed by retinoic acid-related orphan receptors ROR ($\alpha$, $\beta$, and $\gamma$) and nuclear receptors REV-ERB ($\alpha$ and $\beta$). Controlled by the rhythmic activity of these clock genes, many physiological and behavioral processes display

circadian oscillations, e.g. in body temperature, hormones, and rest/activity, as well as affective and cognitive functions. In mammals, for example, the SCN orchestrates rhythmic release of the hormone melatonin from the pineal gland at night [9].

## 3. Connections between circadian clocks and mood regulation

### *3.1. Humans*

Although there is strong evidence that mood disorders are associated with both genetic and environmental disturbances of circadian clocks, causality remains to be determined. Environmental disruptions of circadian rhythms, such as shift work, also increase the risk of mood disorders [10]. In patients with SAD, seasonal changes in photoperiod provoke relapse into a depressive episode [11]. SAD may be caused by SCN-mediated alterations of circadian rhythmicity which perturb the affective state [12]. Although not detected by GWAS after strict correction for multiple comparisons, associations between individual clock gene polymorphisms and mood disorders have been found in a number of studies have not revealed associations to clock genes, in targeted genotyping studies, e.g. sequence variations in *PER2*, *ARNTL*, and *NPAS2* increase the risk of developing SAD [13, 14]. Similarly, BD has been linked to polymorphisms of clock genes [15], including *ARNTL* and *PER3* [16]. In an alternative approach providing greater sensitivity than GWAS, considering all clock genes together as a system has tended to confirm an association between clock genes and mood disorders [17]. Additionally, it may be that only a subgroup of MDD patients develop depression because of disrupted circadian rhythms; accordingly, significant associations with clock genes may be present only in this subgroup.

Beyond genetic and environmental associations, the therapeutic efficacy of chronotherapies targeting circadian rhythms in mood disorders patients provides further evidence for a strong connection between circadian clocks and mood regulation. For example, social rhythm therapy aims to stabilize and regularize daily rhythms of mood disorder patients and was proven to have

high efficacy [18]. Some components of this therapy are described below in more detail. Moreover, even standard pharmacological treatment of depressive symptoms often improves circadian function of patients [1, 19]. This suggests a bidirectional relationship between circadian rhythm abnormalities and mood disturbances, encouraging the development and implementation of new therapeutic approaches for mood disorders by normalization of circadian rhythms.

### *3.2. Animals*

Further support for a relationship between circadian rhythms and mood dysregulation arises from animal models in which circadian rhythms can be manipulated more freely, and mood-related behavior and its brain mechanisms studied more intensively [20].

#### *3.2.1. Abolishing Rhythms Changes Mood*

The *Clock*$^{\Delta 19}$ mutant mouse has a long endogenous circadian period (~ 27 h) with eventual arrhythmia if kept in constant darkness [21]. These mice display a behavioral phenotype closely resembling bipolar mania in humans, with hyperactivity, reduced anxiety- and depression-related behavior and an enhanced preference for the consumption of drugs of abuse [22-24]. However, other symptoms comprising the rapid alternation between mania and depressive-like behavior, sleep abnormalities or grandiosity are not covered by this mouse model. In contrast, *Per2*$^{Brdm1-/-}$ mice have short period free-running rhythms that ultimately become arrhythmic in a constant environment [25] but also display mania-like behavior.

#### *3.2.2. Genetic Manipulations of Rhythmicity Influence Mood*

Various other clock gene mutant mice also show altered affective behavior. For instance, *Per1*$^{Brdm1-/-}$ mice have a short circadian period and show an enhanced preference for alcohol consumption after stressful events [26, 27]. Mice deficient in D-box binding protein (DBP), which also have a shorter period, show depressive-like behavior at baseline but mania-like behavior under stress conditions, which might make this mouse a promising model for BD [28]. The *after hours (Afh)* mutant mouse, carrying a mutation of *Fbxl3,* exhibits a long free-running

period (~26.5 h) [29] and mania-like behavior [30]. Knockout of CK1δ/ε induces a long circadian period whereas a mutation of CK1ε (tau) causes a short period [31, 32]. Whereas forebrain overexpression of CK1δ leads to a decrease in reward-seeking behavior [33], genetic deletion of CK1ε leads to enhanced reward-seeking behavior [34]. Finally, mutations in the GSK3α/β genes, which phosphorylate multiple clock genes and regulate circadian rhythms, are also associated with changes in mood-related behavior [35-37].

#### *3.2.3. SCN-specific reduction of rhythms induces depression-like behavior*

Although studies of circadian mutant mice suggest a causal role for circadian clocks in mood regulation, clock genes have pleiotropic effects, so behavioral changes in these mice may not necessarily be due to changes in clock function. Circumventing this issue, we showed that a reduction of circadian rhythm amplitude specifically in the SCN is sufficient to evoke depression-like behavior in mice [38]. This mouse provides a model with intact clock genes in all non-SCN brain regions and peripheral organs, as well as normal brain development and anatomy. Therefore, abnormalities in affective state can be attributed solely to changes of circadian oscillation output signals from the SCN central pacemaker.

#### *3.2.4. Changes in Light-Dark Cycles Influence Mood*

Manipulations of external light/dark conditions are widely used to modify circadian rhythms in animals. Such an experimental approach is especially useful to mimic seasonal changes in daylength, providing animal models for SAD. In particular, diurnal rodents often exhibit depression-like behavior in short days [39]. Exposure to constant light (LL) both disturbs circadian clocks and induces depression-like behavior, implying a connection between circadian rhythms and mood regulation [40]. However, rodents exposed to constant darkness (DD) also show depression-like behavior [41, 42]. As circadian rhythms are not disrupted in DD, it is possible that mood-related abnormalities in response to altered lighting may (at least in part) depend on non-circadian factors.

## 4. How Disturbed Clocks May Result in Mood Disorders

As outlined above, data from animal and human studies provide ample evidence that disturbed circadian clocks play a role in the development of mood disorders. However, mechanistic explanations of exactly how disorganized circadian rhythms can lead to mood disorders has not been widely discussed. Here, we extract common elements that are shared by different animal models and human patients that might serve as tangible links between circadian rhythm abnormalities and mood disorders. Identifying concrete and fundamental physiological changes resulting from disrupted circadian rhythms may help clinicians to appreciate the importance of stable and aligned circadian clocks in their patients.

The consequences of clock manipulations in all of the various animal models and human studies can be ascribed to four main possible mechanisms: "external desynchronization" between the animal and the environment, "internal desynchronization" within an animal, low amplitude of circadian oscillations, and alterations in sleep architecture. Although each of these hypothetical mechanisms is based on experimental data, direct evidence favoring one mechanism over another is lacking. This is largely due to the difficulty of investigating one such circadian mechanism isolated from the others. For example, while many studies indicate a relationship between external desynchronization and mood regulation based on investigations of chronotypes and shift work, desynchronization with the environment in such studies is invariably accompanied by internal desynchronization, amplitude effects, and altered sleep patterns. Whereas some studies have begun to use clever experimental paradigms to manipulate external synchronization, amplitude, and sleep architecture independently, so far only few studies have examined the role of internal desynchronization. This may be at least partly due to the difficulty of creating animal models or identifying human markers to monitor misalignment of tissue oscillators within one subject. In this chapter, we will evaluate the presence of these individual mechanisms in different animal models and human studies and explain why they constitute health risks and might contribute to mood disorders.

### *4.1. External desynchronization*

A desynchronization of the individual's endogenous circadian rhythms (e.g. sleepiness) with the external environment (e.g. sunrise) and can produce adverse or pathological states. Animals with clock gene mutations often show changes in period and phase of rhythms, and some lose the ability to synchronize to external oscillations. Other studies use repeated light phase shifts so that animals never fully entrain to daily environmental rhythms. Humans with extreme chronotypes or subject to shift work also experience external desynchronization. And many patients with mood disorders show circadian phase abnormalities, e.g. advanced sleep-wake cycles in mania and delays in bipolar depression [43].

How could external desynchronization and altered light exposure result in depression? In humans, a late chronotype often leads to a lack of morning light exposure due to waking up late in the morning. Light deprivation leads to depression-like behavior and a reduction of monoamine neurons in the brains of the animals [42]. Apoptosis of neurons is particularly pronounced in the nucleus accumbens and also occurs in the raphe nucleus and the ventral tegmental area, brain areas associated with mood regulation. In addition, Dulcis et al. demonstrated that neurons in the hypothalamus of rats switch between dopamine and somatostatin expression in response to exposure to short- and long-day photoperiods, respectively [44]. Furthermore, the reduction of dopamine in the hypothalamus in long days is accompanied by depression-like behavior of these nocturnal animals. Interestingly, long days seem to have effects in nocturnal animals (e.g. mice) that are similar to those of short days in diurnal (day-active) animals (e.g. humans; see above). These rodent studies impressively demonstrate a negative impact of altered light exposure on brain structures, which ultimately leads to depression-like behavior.

Lack of morning light due to a late chronotype may also result in other physiological changes associated with mood disorders. For instance, reduced sunlight exposure can lead to low levels of vitamin D, which is synthesized in the skin upon UV radiation. Some studies have

demonstrated a correlation between low levels of vitamin D and MDD (or the severity of depression symptoms). However, no improvement of symptoms could be demonstrated with vitamin D supplementation, so the causality of the proposed relationship is uncertain [45-47].

Desynchronization with the environment may also lead to lack of social interaction in patients with mood disorders. Being desynchronized with the environment implies, for example, sleep-wake cycles and meal times that strongly differ from patterns of family and friends. Similarly, extreme chronotypes lead to difficulties in adapting to a common work schedule and impair participation in free-time activities. Although mood disorders patients can experience either phase advances or delays, phase delays are most concerning, as sleeping during the early day greatly reduces both light exposure and social contact.

In our view, changes in brain structures caused by lack of light constitute the most plausible mechanism for how a late chronotype can contribute to depression. As described, short winter days (Figure 1A) represent a risk factor for the development of SAD [48], and in rodents alterations in the light/dark cycle are associated with depression-like behavior [44]. Of note, humans with very late chronotypes may be exposed to short photoperiods throughout the entire year (Figure 1B). Thus, depressive states in SAD or in MDD with delayed circadian rhythms might be largely attributable to insufficient light exposure during the day and the consequent lack of photic inputs relayed by the SCN to other brain regions that are involved in mood and motivational processes.

Conversely, as mania is more typically associated with early chronotype, excessive daylight exposure in early morning may trigger manic switches in bipolar patients (Figure 1B). Increasing morning light exposure does not always induce manic switches [49], but dark therapy or use of blue-blocking glasses (which reduce activation of the blue-sensitive retinal photoreceptor responsible for light input to the SCN and other non-visual brain areas), have been found to reduce manic symptoms [50, 51]. Interestingly, exposure to long photoperiod

reduces synchrony of SCN neurons and leads to reduced rhythm amplitude in non-SCN brain regions of mice [52], which may contribute to the behavioral changes in mood disorders.

Together, these studies suggest that exposure to extreme photoperiods alters brain circuits and cause amplitude changes and/or disruption of circadian rhythms, including "internal desynchronization" of circadian oscillators. In the next sections, we will explore how internal desynchronization or reduced amplitude might facilitate mood disorders.

### *4.2. Internal desynchronization*

Prominent human circadian rhythms include sleep-wake behavior, hunger and satiety states, and body temperature rhythms, as well as many molecular oscillations, e.g. in neurotransmitter release and hormone levels. Naturally, these fluctuations peak at different times of day and night. Maintenance of optimal temporal relationships among these many rhythms in various organs, tissues, cells, and even within one cell can be characterized as a state of internal synchronization. Internal synchrony helps the organism to coordinate compatible physiological processes and avoid coincidence of incompatible processes. However, animal and human studies show that temporal synchrony among different tissues and cells is rather fragile and can be manipulated easily by environmental factors [53-55].

Both animal and human studies have substantiated an association between inner circadian misalignment and mood disorders (and other major health problems) and suggest that internal temporal desynchrony might be part of the etiology of MDD [56-58]. For instance, mutations of clock genes in animals disrupt phase relationships among molecules, cells, and tissues [59-61], and often lead to metabolic dysfunctions and pronounced changes in behavior [62, 63]. After light/dark shifts simulating jet lag, different organs and tissues adjust their phase at different rates, leading to transient internal desynchrony [64]. Such disruption of circadian rhythms has severe consequences on health and survival of rodents [65]. Similar considerations apply to human shift workers, who are at elevated risk of mood disorders and other diseases. Due to rapidly changing shift schedules, the clocks of shift workers can presumably never adjust

to a stable phase relationship and are in a state of perpetual circadian misalignment. Also, because food is a strong Zeitgeber for non-SCN circadian clocks [53, 66], as many people eat irregularly, their clocks may also be perpetually misaligned. Importantly, restricting meals to certain hours per day improves body weight and subjective well-being of subjects previously eating irregularly [67]. Interestingly, subjecting rodents to chronic stress also induces circadian misalignment among tissues [68], which may contribute to depression. Indeed, patients with MDD exhibit an altered phase relationship between sleep and body temperature rhythms [69].

Genetically determined properties of the circadian clock may increase vulnerability to internal desynchronization in certain people. Humans only entrain to a relatively small range of *Zeitgeber* periods [70-72] and entrainment to cycles very different from the endogenous period require stronger *Zeitgebers* [73]. Consequently, individuals with a very long or short endogenous period have more difficulty entraining to environmental rhythms, and may also be more vulnerable to internal desynchronization, as some tissues may be more sensitive to *Zeitgebers* than others. In particular, it is possible that some tissues may be well entrained to the 24-h environment while others mainly follow their own internal clocks, leading to a situation where different oscillators drift apart in phase.

There are different possible mechanisms by which temporal desynchronization among molecules, cells, and tissues may induce diseases and mood disorders. Desynchronization of processes on the neural, hormonal, and behavioral level can lead to insufficient coordination of recurring events of daily life, a cardinal function of the circadian system. Loss of normal daily synchronization might demand instead a more energetically costly and less effective ad hoc regulation of physiology and behavior. In patients suffering from mood disorders, their daily routines are often disrupted, probably making unexpected situations even more stressful and demanding, which may then reinforce fatigue and loss of motivation [74].

Temporal desynchronization may also impair communication among different tissues drastically. Under normal circumstances, phases of distinct tissues are aligned such that one

tissue is prepared to receive and process signals from other tissues at a particular time of day. If, however, two tissues are out of phase, it is possible that the receptor for a crucial signal is not present at a time when the signal arises, or vice versa. In the context of mood disorders, this may apply to insufficient communication among different brain areas implicated in affective functions (Fig. 2A). Only proper synchronization of daily signals allows a smooth flow of multi-step processes in the body. For example, if the timing of multiple signals leading to the secretion of a neurotransmitter proceed in the wrong order, the processes that depend on this neurotransmitter secretion may be impaired (Fig. 2B).

### *4.3.Reduced Amplitude*

Altered circadian rhythm amplitudes (mostly decreases) have frequently been observed in mood disorders. A landmark study of postmortem brains from MDD patients and healthy controls showed that clock genes such as *BMAL1*, *PER1-3*, *DEC1/2*, *REV-ERBα*, and *DBP*, are expressed with clear circadian rhythms in mood-related brain regions, but that these rhythms are much less prominent in brains from MDD patients [75]. Importantly, this study demonstrated dysregulation of circadian rhythmicity at a molecular level in brains of MDD patients. However, as only one time point could be measured for each brain, the weaker circadian rhythms observed in the depressed population might be due to either poor synchronization of the depressed individuals with external *Zeitgebers* or lower rhythm amplitude in individual subjects. The interpretation of lower rhythm amplitude within one subject is consistent with our mouse study of the relationship of depression-like behavior and circadian oscillations in mood-regulating brain areas observed over the course of several days within the same animal. Mice susceptible to induction of depression-like behavior by a learned helplessness training procedure were more likely to have weaker rhythms in the nucleus accumbens and the periaqueductal grey, two brain regions crucially involved in mood regulation [76]. Furthermore, chronically elevated stress in mice alters circadian amplitude in the SCN and mood regulating brain areas, including the nucleus accumbens [77]. Conversely,

experimentally reducing amplitude of SCN circadian rhythms by SCN-specific knockdown of *Bmal1* elicited depression-like behavior in mice [38].

Circadian rhythm amplitude in a tissue is influenced by the strength of the individual cellular circadian oscillators within the tissue as well as by coupling among those cellular oscillators [78]. In either case, low circadian rhythm amplitude at the tissue level can contribute to an unstable circadian system and adversely affect mood regulation. Under normal circumstances, circadian clocks are responsible for ensuring proper timing of physiological processes in the body, particularly separating opposing processes in time, e.g. anabolic vs. catabolic pathways or wakefulness vs. sleep. With reduced circadian amplitude, the separation of such opposing processes cannot take place efficiently, resulting in simultaneous occurrence of conflicting processes or conditions (Fig. 3A). For instance, more than 80% of mood disorders patients suffer from sleep problems during the night and fatigue during the day [79]. High cortisol levels are associated with wakefulness and elevated melatonin with sleep, so their rise and fall need to be separated to avoid inappropriately timed wakefulness during the night or sleepiness during the day. Consistent with this idea, in depressed patients the rhythm amplitude of these hormones is decreased in depression [80-83], resulting in a less pronounced contrast between nocturnal sleepiness and diurnal wakefulness.

Second, precisely timed initiation or termination of many physiologically relevant processes is dependent on high amplitude circadian rhythms. Such physiological transitions often require certain threshold levels of activators/inhibitors (e.g. neurotransmitters). Thus, in the event of low rhythm amplitude, threshold levels might not be reached, and the physiological process cannot properly start or stop (Fig. 3B). As mentioned above, cortisol and melatonin rhythms show reductions of amplitude in depression, with relatively constant high levels of cortisol and low levels of melatonin [80, 81]. Thus, due to reduced circadian amplitude, cortisol levels never drop low enough and melatonin levels never get high enough to permit efficient sleep.

Lastly, altered amplitudes may also encourage internal desynchronization among tissue clocks due to differential sensitivity to *Zeitgebers*. Decreased amplitude of a circadian pacemaker increases its sensitivity to resetting [84-86]. Thus, the phase relationships among oscillators of different tissues are changed more easily in response to *Zeitgeber* modulations when rhythm amplitude is low. Conversely, increasing the amplitude of circadian rhythms in patients lowers the risk of both internal and external desynchronization.

In summary, both hypothetical assumptions and empirical data suggest strongly that altered circadian rhythm amplitudes, especially decreased amplitudes, can lead to profound circadian disruption in mammalian tissues. Conversely, increasing the amplitude of circadian oscillators in patients suffering from mood disorders might reduce internal and external desynchronization processes, leading to a stabilization of the circadian system.

### *4.4. Changes in Sleep Architecture*

Sleep architecture refers to the temporal organization of sleep such as number, duration, and timing of rapid eye movement (REM) and non-REM (NREM) sleep episodes. Reduced sleep quality as attributed to abnormal sleep architecture is strongly associated with mood disorders [87]. Current evidence is insufficient to determine conclusively whether the disruption of sleep-wake cycles in MDD patients is a circadian or sleep related phenomenon. Because sleep and circadian clocks influence each other strongly, it may be impossible to separate them definitively. However, it is known that circadian clocks influence sleep architecture [88]. Thus, changes in circadian rhythmicity could lead indirectly to abnormal mood regulation in patients, through their impact on sleep. For instance, human polymorphisms of the clock gene *PER3* have been associated with altered sleep timing and structure [89, 90]. Interestingly, *Per3*$^{-/-}$ mice and mice carrying a human variant of the *PER3* gene exhibit both altered sleep architecture and depression-like behavior [91]. Thus, *PER3* may represent a connecting link between circadian clocks, sleep, and mood regulation. *Clock*$^{\Delta 19}$ mice exhibit severe mania-like behavior [22] and also reduced sleep [92]. *Cry1/2* double-deficient mice

show anxiety-like behavior [93] as well as increased sleep [94]. Interestingly, however, mice lacking *Per1/2* also exhibit anxiety-like behavior, similar to *Cry1/2* double-deficient mice, but their sleep is reduced rather than elevated [94].

A vast clinical literature shows that mood disorders are commonly accompanied by sleep disturbances. For example, ~ 50-90% of depressed patients suffer sleep abnormalities [95]. The nature of sleep problems in patients with mood disorders is manifold [96]. Many depressed patients as well as manic patients suffer from insomnia, whereas a decreased need for sleep is a trademark of manic patients. Also common in depression are longer sleep onset latency and early morning awakenings. Changes in REM and NREM sleep architecture are frequently observed, with REM sleep typically peaking earlier in the night in depressed patients. Such disruptions of sleep timing suggest that some of the sleep problems seen in mood disorders may in part be attributable to abnormalities in circadian rhythms. Although an association between sleep disturbances and abnormal mood regulation is well established, the direction of causality remains unclear. While the above-mentioned impairments of sleep quality can be regarded as symptoms of depression, there is also considerable evidence that sleep directly impacts affective functions. For instance, sleep positively influences the function of many mood-regulating brain areas, including prefrontal cortex, amygdala, and locus coeruleus [97]. Furthermore, it is believed that the improvement of sleep by antidepressants contributes to their therapeutic efficacy [98].

Thus, it is likely that sleep is one direct mechanistic link between circadian clocks and mood regulation: disturbing circadian rhythms leads to sleep abnormalities, which in turn adversely impacts mood regulation. Depending on the disposition and resilience of the individual, these clock-induced alterations of sleep may contribute greatly to development of a mood disorder.

## 5. Clinical Implementation

As mentioned above, episodes of depression and mania in MDD and BD are often characterized by irregular circadian patterns of behavior. Critically, patients are at increased risk for mood episodes after drastic life events that lead to severe changes of daily routines (e.g. sudden loss of partner, giving birth) [18]. Furthermore, rotating work shifts frequently precipitate episodes or exacerbate mood symptoms. Physicians have several therapeutic options to help patients achieve stable circadian rhythms. Essentially, these strategies aim for structuring the daily routines of patients as much as possible.

### *5.1. Regular Sleep*

The timing of sleep and wakefulness is largely controlled by circadian clocks, but sleep and wakefulness also directly or indirectly alter circadian rhythms. Indeed, sleep can act as a *Zeitgeber* for circadian rhythms. Depending on the time of day, naps can cause phase advances or phase delays of melatonin and other hormone rhythms [99-101]. Whether these effects are mediated directly by sleep or indirectly by reduction of light, activity, social contacts, or changes of posture during naps is not clear [101]. Insufficient sleep also alters the temporal organization of the human blood transcriptome, reducing circadian rhythm amplitude [102].

Many mood disorder patients have poor quality sleep and highly irregular sleep times [103, 104], so clinicians should help patients to regularize their sleep as much as possible. Importantly, schedules for sleep and wake-up times should to be tailored to the individual chronotype of each patient, as far as possible. Unfortunately, most people have to get up early on work days, interrupting their natural sleep, and then make up for this disruption by sleeping late on weekends, resulting in repeated back-and-forth phase shifts every week, a phenomenon commonly known as “social jet lag” [105]. But while the longer and delayed sleep on work-free days might feel refreshing for healthy people, the frequent switch between early and late days may become problematic for patients with mood disorders. For these patients, to promote internal synchrony, it is crucial to reduce the schedule shifts between work and work-free days as much as possible. Regular sleep times are also likely to improve sleep quality. Recording

baseline sleep/wake routines of patients by wristband actimeters or sleep diaries can help therapists and patients to develop an individualized ideal sleep schedules. On the basis of these measures, irregularities and anomalies can be identified and improved. Notably, cognitive behavioral therapy for insomnia (CBT-I) also improves depressive symptoms [106].

### *5.2. Regular Meals*

The circadian clocks of many tissues outside the SCN are very sensitive to meal times [53, 66]. To anticipate meal times and to optimize nutrient utilization, organs involved in digestion uncouple from the SCN and gradually adjust their phase to a new meal time over the course of several days [107]. Importantly, the adjustment of tissue clocks takes multiple days, and this process is only beneficial for the organism when the timing of meals settles stably at the new time. Many people, however, eat at remarkably variable times [67]. If meal times vary greatly from day to day, the clocks in digestive organs never have enough time to adjust completely. Consequently, the clocks of their digestive organs are probably in a perpetual state of disequilibrium, constantly adjusting to new meal times. This phenomenon may lead to significant health problems. Moreover, peripheral and brain clocks are closely linked to each other through hormones [108], and food intake promotes changes in glucocorticoids, body temperature, neuronal activity, and other factors that have impact on brain clocks. Thus, food-induced desynchronization of peripheral organs may also affect synchronization among clocks of various brain regions, thereby contributing to development of mood disorders.

Since the impact of meals on peripheral clocks is so strong, clinicians should encourage their patients to maintain a fixed meal time schedule. Patients should be encouraged to avoid snacks and caloric drinks between scheduled principal meals, as any food intake has an immediate impact on peripheral clocks. Obesity is associated with late meal times [109], so breakfast should be encouraged, and late evening meals or snacks discouraged. But it must be acknowledged that, as for sleep timing, ideal meal schedules may vary from person to person, depending on chronotype, personal preference, and constraints imposed by social or work

demands. Nevertheless, it still may be very valuable for patients to minimize day-to-day variability in whatever meal schedule they are willing to adopt.

### *5.3. Increase of Daytime Physical Activity*

Physical activity alleviates depression, and depressed patients are often encouraged to exercise [110]. Possible mechanisms for this therapeutic effect of exercise on mood include augmentation of endogenous opioids [111], normalization of brain structure abnormalities [112], and improving sleep quality [113].

But another possible mechanism is through positive effects of exercise on the circadian system. In mice, exercise enhances the amplitude of circadian rhythms of body temperature, food uptake, and corticosterone secretion [114], three factors involved in synchronizing body clocks. Indeed, physical exercise can alter the phase of clock gene rhythms in peripheral tissues of mice [115]. Importantly, providing mice with access to running wheels significantly decreases age-related desynchrony in SCN and peripheral tissues [116]. In addition, physical activity increases amplitude of SCN and behavioral rhythms, and accelerates phase adjustment after experimental jet lag [116]. Furthermore, access to running wheels enhances amplitude of activity rhythms and reduces depression- and anxiety-like behavior in rats [117], and protects against the development of depression-like behavior in mice [118].

In humans, physical activity also has an impact on the circadian system. Depending on the time of day, exercise alters temperature, heart rate, and melatonin rhythms and changes sleep architecture [119]. As in mice, exercise facilitates re-entrainment after phase shifts [120], arguing for positive synchronizing effects of exercise in humans. Additionally, in young men multivariate regression analysis reveals that physical activity has by far the strongest influence on the amplitude and stability of body temperature oscillations of any parameter studied [121]. However, clinicians should make their patients aware that the timing of physical exercise is critical, e.g. nocturnal exercise can phase shift behavioral and hormonal rhythms in a manner that might be unfavorable for the patient [122, 123]. Together, these results suggest that regular

exercise during the day supports the stabilization of circadian oscillations in patients with weak or irregular daily rhythms.

### *5.4. Light Therapies*

In the face of overwhelming competitive advertising by the pharmaceutical industry, light therapy for depression has been slow to achieve widespread adoption in clinical practice, but it is now clear that it can be as effective as antidepressant medicines [124], and is finally becoming more popular [125]. Twenty years ago, a series of studies established that bright light (especially in the morning) is an effective treatment for SAD [126-128]. More recently, a number of studies and meta-analyses have suggested that light is also effective for MDD [129-131]. In particular, a recent randomized, controlled 8 week trial of daily 10,000 lux bright light for 30 min "as early as possible" after awakening, showed that light can be more effective than fluoxetine (Prozac) for non-seasonal MDD [132]. A few studies indicate that bright light may even be therapeutic for the depression of BD, which is often unresponsive to common antidepressant medicines. For example, a recent randomized, controlled 6 week trial of 7000 lux bright light in mid-day improved sleep and mood in BD, with no manic switches [133]. Conversely, darkness can be therapeutic for mania [51], and a recent study showed promising antimanic effects of blue-blocking glasses [50]. Thus, light/dark therapies for mood disorders show great clinical promise.

It is not known precisely how light/dark therapies work in mood disorders patients, but animal studies suggest some likely neurobiological mechanisms. First of all, it seems probable that the therapeutic effects of light are mediated not by the conventional image-forming visual system, but rather by the more recently described non-image-forming visual system, involving melanopsin-containing, intrinsically photosensitive retinal ganglion cells (ipRGCs) [134-136]. The ipRGCs project to the SCN and are responsible for circadian photoentrainment, so the effects of light/dark on mood could involve adjustment of brain circadian clocks. The finding that early morning timing of light makes it more effective in SAD suggests that the mechanism

may involve circadian phase-dependent shifting of clock phase and improved alignment of brain clocks. It is known, for example, that seasonal changes in day length produce substantial changes in relative phasing of individual SCN neurons in rodents [137]. On the other hand, the fact that some clinical studies (e.g.,[133]) find light effective at mid-day, when no phase shifting of circadian clocks would be expected, suggests that enhancement of brain clock amplitude may be a more important mechanism. This is consistent with the findings of a postmortem human brain study that brain clocks of MDD patients have reduced amplitude [75], and with our work in a mouse model [38].

### *5.5. Wake Therapy*

It is well documented that sleep deprivation has strong and immediate antidepressant effects, alleviating symptoms of MDD in 40-60% of patients. Improvements in mood are often already apparent even during the night of sleep deprivation and are sustained on the following day. After recovery sleep, most patients (50-80%) suffer from a relapse of depression [138]. Interestingly, keeping patients awake in the second half of the night appears to be sufficient to improve depressive symptoms [125]. Since sleep and circadian clocks are tightly intertwined, the effects of wakefulness at night on mood are often attributed to changes of circadian rhythms. However, even short daytime naps which have only little impact on circadian rhythms cause a relapse of symptoms, raising doubt about how much circadian changes contribute to the antidepressant effects of sleep deprivation. On the other hand, some have hypothesized that MDD patients have abnormal clock gene machinery which is reset by sleep deprivation, thereby improving their affective state [139]. However, a combination of chronotherapeutic treatments, such as bright light, sleep phase advance and pharmacotherapy (lithium or antidepressants) has been proven to sustain the antidepressant responses and prevent relapse [140]. Also, the rapid-acting antidepressant ketamine and sleep deprivation produce similar changes in expression patterns of some clock genes [141]. Thus, a combination of neurotransmitter changes during

sleep deprivation and adjustment of circadian rhythms during phase advance therapy may underlie the efficacy of this treatment.

Even though the exact mechanisms are not known, wake therapy is a first line of treatment for depression in many European countries, although rarely used in the United States [142].

### *5.6. Pharmaceuticals to Manipulate Rhythms*

#### *5.6.1. Agomelatine*

Agomelatine is a recently developed antidepressant drug available for use in Europe. It acts as an agonist at melatonin receptors $MT_1$ and $MT_2$ and an antagonist at the serotonin 5-$HT_{2C}$ receptor. Antidepressant actions of agomelatine have been attributed to various mechanisms including adjustment of circadian rhythms. In diurnal and nocturnal rodents, agomelatine expedites resynchronization of behavior after shifts in the light-dark cycle [143, 144]. Furthermore, it is able to adjust the phase of sleep-wake cycles in rodents under entrained conditions [145], increases the amplitude of melatonin and body temperature rhythms [146], and can synchronize rats to a 24 hr schedule when administered in daily doses under constant environmental conditions [147]. Thus, agomelatine has a strong impact on the circadian system.

Importantly, agomelatine normalizes behavioral rhythms, sleep architecture, and neuronal activity in a rat model of depression, which suggests the potential for positive effects on clocks in depressed patients [148]. In humans, early evening administration of agomelatine (like melatonin) phase advances two central synchronizers of peripheral rhythms, core body temperature [149] and cortisol rhythms [150], which might benefit depressed patients with delayed phases. Because of these effects, administration of agomelatine has been suggested as a therapy for several psychiatric disorders that are associated with circadian disturbances [151]. Besides adjustment of circadian rhythms, agomelatine promotes neurogenesis, cell survival, and expression of brain-derived neurotrophic factor (BDNF), which are other possible mechanisms of antidepressant action. Of note, however, a recent study showed that stress-induced changes of circadian rhythms in mood-regulating brain areas of rats were not

normalized by agomelatine administration. Moreover, melatonin itself was not found to have an antidepressant effect [152], raising questions about whether agomelatine's circadian effects underlie its antidepressant action [153]. On the other hand, melatonin could still be therapeutic if its administration is properly timed and dosed to adjust the misaligned circadian phases of certain patients with mood disorders [154].

#### *5.6.2. Lithium*

Lithium is a mood stabilizer widely used in the treatment of BD, and some have speculated that its therapeutic efficacy could be related to its prominent effects on circadian rhythms [155]. Lithium lengthens circadian period and potently increases amplitude of circadian rhythms [156]. These circadian effects of lithium may be related to its inhibition of glycogen synthase kinase 3 (GSK3), a protein kinase that regulates the clock by phosphorylating multiple clock proteins: PER2, REV-ERBα, and CRY2. Lithium also affects the inositol signaling pathway, which is also involved in amplitude and period regulation of circadian rhythms [157]. It is likely that lithium contributes to the stabilization of circadian clocks in BD patients. However, since lithium has many side effects and regulates a large number of processes in the body, better options are needed for primary targeting of circadian rhythms.

#### *5.6.3. Nobiletin*

It has been discovered recently that the flavonoid nobiletin is capable of regulating circadian rhythms. Flavonoids are plant pigments that are ubiquitous natural components of human foods. In mice, nobiletin substantially increases the amplitude of clock gene rhythms in cells and behavioral wheel-running activity rhythms [158, 159]. Interestingly, mice exposed to a high fat diet are protected from metabolic phenotypes when treated with nobiletin [158]. Furthermore, nobiletin resets the liver clock and defends against metabolic abnormalities in cultured cells [160]. Thus, stabilizing body clocks using nobiletin or similar compounds could potentially be useful in mood disorder treatment.

#### *5.6.4. Rev-Erb* Agonists

The experimental compounds SR9009 (Stenabolic) and SR9011 are agonists of the circadian clock proteins REV-ERBα and REV-ERBβ; they alter amplitude of clock gene expression rhythms and change circadian behavior in mice [161]. Interestingly, in rodents, these drugs also reduce anxiety-like behavior, change sleep architecture [162, 163], and prevent the development of obesity, which is often related to mood disorders [161]. As the effects of these REV-ERB agonists on circadian rhythms are pronounced but short-term, more research is required to investigate the potential usefulness of such drugs in mood disorder therapy.

## 6. Conclusion

Many mood disorder patients suffer irregularities in their daily rhythms. These irregularities (e.g., insomnia) may in themselves be unpleasant and uncomfortable for patients. But the disruptions may also trigger or worsen mood episodes. For both these reasons, therapies aiming to improve circadian organization and stability may be beneficial. The circadian clock evolved to help organisms anticipate daily recurring events. If this ability is lost, the body is no longer capable of preparing physiological processes in advance of an event, but rather must react spontaneously to incidents, which may be less efficient and more stressful. Thus, therapies that reduce the day-to-day variability of circadian rhythms are likely to be helpful. However, more evidence is required to establish a direct causal connection between the disruption of circadian rhythms and mood disorders, especially in humans. To prove such causality, more knowledge about underlying mechanisms is needed. In particular, more research is needed to show specific mechanisms by which existing chronotherapies could improve mood by modulating circadian rhythms.

In this review paper, we suggested several concrete mechanisms by which circadian disruptions may contribute to mood disorders: external desynchronization, internal desynchronization, reduced amplitude, and impaired sleep. Importantly, the separation of these mechanisms remains hypothetical since they inevitably influence each other. Therapies to stabilize and

strengthen circadian clocks would be expected to normalize all these pathological mechanisms at once. Therapeutic manipulations may variously affect clock phase, period, or amplitude, but in practice these clock parameters are usually intimately related. Thus, the aim is usually to reach a high amplitude, a stable period close to 24 hours, a phase compatible with environmental conditions, and a small phase variability from day to day. Because of the ubiquitous role of circadian clocks in physiology, adjusting circadian properties to such desired values can solve many problems at once, including mood disorders and other medical conditions.

Fortunately, clinicians and patients have relatively simple therapeutic options available to improve circadian health. The list of options includes regular sleep, meals, and exercise, light therapy, and a few pharmaceuticals such as melatonin. Even though the strategies were discussed separately in this paper, it is advisable to administer several strategies simultaneously. Patients who suffer severe circadian disruptions will gain the greatest benefit if they structure sleep, light, and meal times, and increase amounts of physical activity in parallel. Conveniently, these treatments can target several circadian conditions concurrently. For example, patients committed to (daytime outdoor) physical exercise automatically increase the amount of sunlight. In turn, the increase of sunlight helps to improve rhythm amplitude and, if applied at the right time, shifts the clock to a desired phase. Furthermore, eating and sleeping at regular times helps structuring other daily routines and promotes social synchronization, and will likely also have beneficial effects for metabolic disorders, which are quite frequently comorbid with mood disorders.

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Literature


1. Bechtel, W., *Circadian Rhythms and Mood Disorders: Are the Phenomena and Mechanisms Causally Related?* Front Psychiatry, 2015. **6**: p. 118.
2. Kronfeld-Schor, N. and H. Einat, *Circadian rhythms and depression: Human psychopathology and animal models.* Neuropharmacology, 2012. **62**: p. 101-114.
3. McClung, C.A., *How might circadian rhythms control mood? Let me count the ways.* Biol Psychiatry, 2013. **74**(4): p. 242-9.
4. Roenneberg, T., et al., *Epidemiology of the human circadian clock*, in *Sleep Medicine Reviews*. 2007. p. 429-438.
5. Dibner, C., U. Schibler, and U. Albrecht, *The Mammalian Circadian Timing System: Organization and Coordination of Central and Peripheral Clocks.* Annual Review of Physiology, 2010. **72**: p. 517-549.
6. Berson, D.M., F.A. Dunn, and M. Takao, *Phototransduction by retinal ganglion cells that set the circadian clock.* Science, 2002. **295**: p. 1070-1073.
7. Hattar, S., et al., *Melanopsin-containing retinal ganglion cells: Architecture, projections, and intrinsic photosensitivity.* Science, 2002. **295**: p. 1065-1070.
8. Koike, N., et al., *Transcriptional architecture and chromatin landscape of the core circadian clock in mammals.* Science, 2012. **338**: p. 349-354.
9. Goldman, B.D., *Mammalian photoperiodic system: Formal properties and neuroendocrine mechanisms of photoperiodic time measurement*, in *Journal of Biological Rhythms*. 2001. p. 283-301.
10. Rosenberg, R. and P.P. Doghramji, *Is shift work making your patient sick? Emerging theories and therapies for treating shift work disorder.* Postgraduate Medicine, 2011. **123**: p. 106-115.
11. Lewy, A.J., et al., *The circadian basis of winter depression.* Proceedings of the National Academy of Sciences, 2006. **103**: p. 7414-7419.
12. Porcu, A., et al., *Photoperiod-induced neuroplasticity in the circadian system.* 2018. **1**: p. 1-25.
13. Etain, B., et al., *Genetics of circadian rhythms and mood spectrum disorders*, in *European Neuropsychopharmacology*. 2011.
14. Partonen, T., et al., *Three circadian clock genes Per2, Arntl, and Npas2 contribute to winter depression.* Annals of Medicine, 2007. **39**: p. 229-238.
15. Milhiet, V., et al., *Circadian biomarkers, circadian genes and bipolar disorders.* Journal of Physiology Paris, 2011. **105**: p. 183-189.
16. Nievergelt, C.M., et al., *Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder.* American Journal of Medical Genetics - Neuropsychiatric Genetics, 2006. **141 B**: p. 234-241.
17. McCarthy, M.J., et al., *A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response.* PLoS One, 2012. **7**(2): p. e32091.
18. Frank, E., H.A. Swartz, and D.J. Kupfer, *Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder.* Biol Psychiatry, 2000. **48**(6): p. 593-604.
19. Monteleone, P., V. Martiadis, and M. Maj, *Circadian rhythms and treatment implications in depression.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2011. **35**: p. 1569-1574.
20. Landgraf, D., M.J. McCarthy, and D.K. Welsh, *The role of the circadian clock in animal models of mood disorders.* Behav Neurosci, 2014. **128**(3): p. 344-59.
21. Vitaterna, M.H., et al., *Mutagenesis and mapping of a mouse gene, Clock, essential for circadian behavior.* Science, 1994. **264**(5159): p. 719-25.

22. Roybal, K., et al., *Mania-like behavior induced by disruption of CLOCK.* Proc Natl Acad Sci U S A, 2007. **104**(15): p. 6406-11.
23. Ozburn, A.R., et al., *Cocaine self-administration behaviors in ClockDelta19 mice.* Psychopharmacology (Berl), 2012. **223**(2): p. 169-77.
24. McClung, C.A., et al., *Regulation of dopaminergic transmission and cocaine reward by the Clock gene.* Proc Natl Acad Sci U S A, 2005. **102**(26): p. 9377-81.
25. Zheng, B., et al., *The mPer2 gene encodes a functional component of the mammalian circadian clock.* Nature, 1999. **400**(6740): p. 169-73.
26. Dong, L., et al., *Effects of the circadian rhythm gene period 1 (per1) on psychosocial stress-induced alcohol drinking.* Am J Psychiatry, 2011. **168**(10): p. 1090-8.
27. Zheng, B., et al., *Nonredundant roles of the mPer1 and mPer2 genes in the mammalian circadian clock.* Cell, 2001. **105**(5): p. 683-94.
28. Le-Niculescu, H., et al., *Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism.* Am J Med Genet B Neuropsychiatr Genet, 2008. **147B**(2): p. 134-66.
29. Godinho, S.I., et al., *The after-hours mutant reveals a role for Fbxl3 in determining mammalian circadian period.* Science, 2007. **316**(5826): p. 897-900.
30. Keers, R., et al., *Reduced anxiety and depression-like behaviours in the circadian period mutant mouse afterhours.* PLoS One, 2012. **7**(6): p. e38263.
31. Etchegaray, J.P., et al., *Casein kinase 1 delta regulates the pace of the mammalian circadian clock.* Mol Cell Biol, 2009. **29**(14): p. 3853-66.
32. Loudon, A.S., et al., *The biology of the circadian Ck1epsilon tau mutation in mice and Syrian hamsters: a tale of two species.* Cold Spring Harb Symp Quant Biol, 2007. **72**: p. 261-71.
33. Zhou, M., et al., *Forebrain overexpression of CK1delta leads to down-regulation of dopamine receptors and altered locomotor activity reminiscent of ADHD.* Proc Natl Acad Sci U S A, 2010. **107**(9): p. 4401-6.
34. Bryant, C.D., et al., *Csnk1e is a genetic regulator of sensitivity to psychostimulants and opioids.* Neuropsychopharmacology, 2012. **37**(4): p. 1026-35.
35. Ackermann, T.F., et al., *Hyperactivity and enhanced curiosity of mice expressing PKB/SGK-resistant glycogen synthase kinase-3 (GSK-3).* Cell Physiol Biochem, 2010. **25**(6): p. 775-86.
36. Paul, J.R., et al., *Disruption of circadian rhythmicity and suprachiasmatic action potential frequency in a mouse model with constitutive activation of glycogen synthase kinase 3.* Neuroscience, 2012. **226**: p. 1-9.
37. Polter, A., et al., *Deficiency in the inhibitory serine-phosphorylation of glycogen synthase kinase-3 increases sensitivity to mood disturbances.* Neuropsychopharmacology, 2010. **35**(8): p. 1761-74.
38. Landgraf, D., et al., *Genetic Disruption of Circadian Rhythms in the Suprachiasmatic Nucleus Causes Helplessness, Behavioral Despair, and Anxiety-like Behavior in Mice.* Biol Psychiatry, 2016. **80**(11): p. 827-835.
39. Leach, G., W. Adidharma, and L. Yan, *Depression-like responses induced by daytime light deficiency in the diurnal grass rat (Arvicanthis niloticus).* PLoS One, 2013. **8**(2): p. e57115.
40. Tapia-Osorio, A., et al., *Disruption of circadian rhythms due to chronic constant light leads to depressive and anxiety-like behaviors in the rat.* Behav Brain Res, 2013. **252C**: p. 1-9.
41. Monje, F.J., et al., *Constant darkness induces IL-6-dependent depression-like behavior through the NF-kappaB signaling pathway.* J Neurosci, 2011. **31**(25): p. 9075-83.
42. Gonzalez, M.M. and G. Aston-Jones, *Light deprivation damages monoamine neurons and produces a depressive behavioral phenotype in rats.* Proc Natl Acad Sci U S A, 2008. **105**(12): p. 4898-903.
43. Moon, J.H., et al., *Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder.* EBioMedicine, 2016. **11**: p. 285-295.
44. Dulcis, D., et al., *Neurotransmitter switching in the adult brain regulates behavior.* Science, 2013. **340**(6131): p. 449-53.

45. Anglin, R.E., et al., *Vitamin D deficiency and depression in adults: systematic review and meta-analysis.* Br J Psychiatry, 2013. **202**: p. 100-7.
46. Jorde, R., et al., *Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial.* J Intern Med, 2008. **264**(6): p. 599-609.
47. Kjaergaard, M., et al., *Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial.* Br J Psychiatry, 2012. **201**(5): p. 360-8.
48. Lam, R.W. and R.D. Levitan, *Pathophysiology of seasonal affective disorder: a review.* J Psychiatry Neurosci, 2000. **25**(5): p. 469-80.
49. Benedetti, F., *Rate of switch from bipolar depression into mania after morning light therapy: A historical review.* Psychiatry Res, 2018. **261**: p. 351-356.
50. Henriksen, T.E., et al., *Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial.* Bipolar Disord, 2016. **18**(3): p. 221-32.
51. Barbini, B., et al., *Dark therapy for mania: a pilot study.* Bipolar Disord, 2005. **7**(1): p. 98-101.
52. Evans, J.A., et al., *Shell neurons of the master circadian clock coordinate the phase of tissue clocks throughout the brain and body.* BMC Biol, 2015. **13**: p. 43.
53. Damiola, F., et al., *Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus.* Genes Dev, 2000. **14**(23): p. 2950-61.
54. Archer, S.N. and H. Oster, *How sleep and wakefulness influence circadian rhythmicity: effects of insufficient and mistimed sleep on the animal and human transcriptome.* J Sleep Res, 2015. **24**(5): p. 476-93.
55. West, A.C. and D.A. Bechtold, *The cost of circadian desynchrony: Evidence, insights and open questions.* Bioessays, 2015. **37**(7): p. 777-88.
56. Barclay, J.L., A.H. Tsang, and H. Oster, *Interaction of central and peripheral clocks in physiological regulation.* Progress in Brain Research, 2012. **199**: p. 163-181.
57. Wirz-Justice, A., *Biological rhythm disturbances in mood disorders.* International Clinical Psychopharmacology, 2006. **21**: p. S11-S15.
58. Wulff, K., et al., *Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease-Supplementary information 2.* Nature Reviews Neuroscience, 2010. **11**.
59. Debruyne, J.P., et al., *A clock shock: mouse CLOCK is not required for circadian oscillator function.* Neuron, 2006. **50**(3): p. 465-77.
60. Sujino, M., et al., *CLOCKDelta19 mutation modifies the manner of synchrony among oscillation neurons in the suprachiasmatic nucleus.* Sci Rep, 2018. **8**(1): p. 854.
61. Landgraf, D., et al., *NPAS2 Compensates for Loss of CLOCK in Peripheral Circadian Oscillators.* PLoS Genet, 2016. **12**(2): p. e1005882.
62. Landgraf, D., M.J. McCarthy, and D.K. Welsh, *The role of the circadian clock in animal models of mood disorders.* Behavioral Neuroscience, 2014. **128**: p. 344-359.
63. Barandas, R., et al., *Circadian Clocks as Modulators of Metabolic Comorbidity in Psychiatric Disorders.* Curr Psychiatry Rep, 2015. **17**(12): p. 98.
64. Kiessling, S., G. Eichele, and H. Oster, *Adrenal glucocorticoids have a key role in circadian resynchronization in a mouse model of jet lag.* Journal of Clinical Investigation, 2010. **120**: p. 2600-2609.
65. Davidson, A.J., et al., *Chronic jet-lag increases mortality in aged mice.* Curr Biol, 2006. **16**(21): p. R914-6.
66. Wehrens, S.M.T., et al., *Meal Timing Regulates the Human Circadian System.* Curr Biol, 2017. **27**(12): p. 1768-1775 e3.
67. Gill, S. and S. Panda, *A Smartphone App Reveals Erratic Diurnal Eating Patterns in Humans that Can Be Modulated for Health Benefits.* Cell Metab, 2015. **22**(5): p. 789-98.
68. Tahara, Y., et al., *Entrainment of the mouse circadian clock by sub-acute physical and psychological stress.* Sci Rep, 2015. **5**: p. 11417.
69. Hasler, B.P., et al., *Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: Further evidence for circadian misalignment in non-seasonal depression.* Psychiatry Research, 2010. **178**: p. 205-207.

70. Erzberger, A., et al., *Genetic redundancy strengthens the circadian clock leading to a narrow entrainment range.* J R Soc Interface, 2013. **10**(84): p. 20130221.
71. Wever, R.A., *Fractional desynchronization of human circadian rhythms. A method for evaluating entrainment limits and functional interdependencies.* Pflugers Arch, 1983. **396**(2): p. 128-37.
72. Aschoff, J. and H. Pohl, *Phase relations between a circadian rhythm and its zeitgeber within the range of entrainment.* Naturwissenschaften, 1978. **65**(2): p. 80-4.
73. Gronfier, C., et al., *Entrainment of the human circadian pacemaker to longer-than-24-h days.* Proc Natl Acad Sci U S A, 2007. **104**(21): p. 9081-6.
74. Fried, E.I., et al., *The differential influence of life stress on individual symptoms of depression.* Acta Psychiatr Scand, 2015. **131**(6): p. 465-71.
75. Li, J.Z., et al., *Circadian patterns of gene expression in the human brain and disruption in major depressive disorder.* Proc Natl Acad Sci U S A, 2013. **110**(24): p. 9950-5.
76. Landgraf, D., J.E. Long, and D.K. Welsh, *Depression-like behaviour in mice is associated with disrupted circadian rhythms in nucleus accumbens and periaqueductal grey.* European Journal of Neuroscience, 2016. **43**: p. 1309-1320.
77. Logan, R.W., et al., *Chronic Stress Induces Brain Region-Specific Alterations of Molecular Rhythms that Correlate with Depression-like Behavior in Mice.* Biol Psychiatry, 2015. **78**(4): p. 249-58.
78. Duncan, W.C., *Circadian rhythms and the pharmacology of affective illness*, in *Pharmacology and Therapeutics*. 1996. p. 253-312.
79. Argyropoulos, S.V. and S.J. Wilson, *Sleep disturbances in depression and the effects of antidepressants.* International review of psychiatry (Abingdon, England), 2005. **17**: p. 237-245.
80. Linkowski, P., *Neuroendocrine profiles in mood disorders*, in *International Journal of Neuropsychopharmacology*. 2003. p. 191-197.
81. Souêtre, E., et al., *Circadian rhythms in depression and recovery: Evidence for blunted amplitude as the main chronobiological abnormality.* Psychiatry Research, 1989. **28**: p. 263-278.
82. Emens, J., et al., *Circadian misalignment in major depressive disorder.* Psychiatry Research, 2009. **168**: p. 259-261.
83. Salgado-Delgado, R., et al., *Disruption of circadian rhythms: A crucial factor in the etiology of depression*, in *Depression Research and Treatment*. 2011.
84. Pittendrigh, C.S., W.T. Kyner, and T. Takamura, *The amplitude of circadian oscillations: temperature dependence, latitudinal clines, and the photoperiodic time measurement.* J Biol Rhythms, 1991. **6**(4): p. 299-313.
85. Brown, S.A., et al., *Molecular insights into human daily behavior.* Proc Natl Acad Sci U S A, 2008. **105**(5): p. 1602-7.
86. Vitaterna, M.H., et al., *The mouse Clock mutation reduces circadian pacemaker amplitude and enhances efficacy of resetting stimuli and phase-response curve amplitude.* Proceedings of the National Academy of Sciences, 2006. **103**: p. 9327-9332.
87. Strine, T.W. and D.P. Chapman, *Associations of frequent sleep insufficiency with health-related quality of life and health behaviors.* Sleep Med, 2005. **6**(1): p. 23-7.
88. Landgraf, D., A. Shostak, and H. Oster, *Clock genes and sleep.* Pflugers Arch, 2012. **463**(1): p. 3-14.
89. Archer, S.N., et al., *A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference.* Sleep, 2003. **26**(4): p. 413-5.
90. Viola, A.U., et al., *PER3 polymorphism predicts sleep structure and waking performance.* Curr Biol, 2007. **17**(7): p. 613-8.
91. Zhang, L., et al., *A PERIOD3 variant causes a circadian phenotype and is associated with a seasonal mood trait.* Proc Natl Acad Sci U S A, 2016. **113**(11): p. E1536-44.
92. Naylor, E., et al., *The circadian clock mutation alters sleep homeostasis in the mouse.* J Neurosci, 2000. **20**(21): p. 8138-43.

93. De Bundel, D., et al., *Cognitive dysfunction, elevated anxiety, and reduced cocaine response in circadian clock-deficient cryptochrome knockout mice.* Front Behav Neurosci, 2013. **7**: p. 152.
94. Wisor, J.P., et al., *A role for cryptochromes in sleep regulation.* BMC Neurosci, 2002. **3**: p. 20.
95. Tsuno, N., A. Besset, and K. Ritchie, *Sleep and depression.* J Clin Psychiatry, 2005. **66**(10): p. 1254-69.
96. Rumble, M.E., K.H. White, and R.M. Benca, *Sleep Disturbances in Mood Disorders.* Psychiatr Clin North Am, 2015. **38**(4): p. 743-59.
97. Goldstein, A.N. and M.P. Walker, *The role of sleep in emotional brain function.* Annu Rev Clin Psychol, 2014. **10**: p. 679-708.
98. Nutt, D., S. Wilson, and L. Paterson, *Sleep disorders as core symptoms of depression.* Dialogues Clin Neurosci, 2008. **10**(3): p. 329-36.
99. Buxton, O.M., et al., *Daytime naps in darkness phase shift the human circadian rhythms of melatonin and thyrotropin secretion.* Am J Physiol Regul Integr Comp Physiol, 2000. **278**(2): p. R373-82.
100. Akacem, L.D., et al., *The Timing of the Circadian Clock and Sleep Differ between Napping and Non-Napping Toddlers.* PLoS One, 2015. **10**(4): p. e0125181.
101. Danilenko, K.V., C. Cajochen, and A. Wirz-Justice, *Is sleep per se a zeitgeber in humans?* J Biol Rhythms, 2003. **18**(2): p. 170-8.
102. Moller-Levet, C.S., et al., *Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome.* Proc Natl Acad Sci U S A, 2013. **110**(12): p. E1132-41.
103. Scott, J., et al., *Sleep-wake cycle phenotypes in young people with familial and non-familial mood disorders.* Bipolar Disord, 2016. **18**(8): p. 642-649.
104. Robillard, R., et al., *Ambulatory sleep-wake patterns and variability in young people with emerging mental disorders.* J Psychiatry Neurosci, 2015. **40**(1): p. 28-37.
105. Roenneberg, T., et al., *Light and the human circadian clock.* Handb Exp Pharmacol, 2013(217): p. 311-31.
106. van der Zweerde, T., et al., *Does online insomnia treatment reduce depressive symptoms? A randomized controlled trial in individuals with both insomnia and depressive symptoms.* Psychol Med, 2018: p. 1-9.
107. Stokkan, K.-A., et al., *Entrainment of the Circadian Clock in the Liver by Feeding.* Science, 2001. **291**(5503): p. 490-493.
108. Landgraf, D., A.M. Neumann, and H. Oster, *Circadian clock-gastrointestinal peptide interaction in peripheral tissues and the brain.* Best Pract Res Clin Endocrinol Metab, 2017. **31**(6): p. 561-571.
109. McHill, A.W., et al., *Later circadian timing of food intake is associated with increased body fat.* Am J Clin Nutr, 2017. **106**(5): p. 1213-1219.
110. Wegner, M., et al., *Effects of exercise on anxiety and depression disorders: review of meta-analyses and neurobiological mechanisms.* CNS Neurol Disord Drug Targets, 2014. **13**(6): p. 1002-14.
111. Dinas, P.C., Y. Koutedakis, and A.D. Flouris, *Effects of exercise and physical activity on depression.* Ir J Med Sci, 2011. **180**(2): p. 319-25.
112. Gujral, S., et al., *Exercise effects on depression: Possible neural mechanisms.* Gen Hosp Psychiatry, 2017. **49**: p. 2-10.
113. Kovacevic, A., et al., *The effect of resistance exercise on sleep: A systematic review of randomized controlled trials.* Sleep Med Rev, 2018. **39**: p. 52-68.
114. Yasumoto, Y., R. Nakao, and K. Oishi, *Free access to a running-wheel advances the phase of behavioral and physiological circadian rhythms and peripheral molecular clocks in mice.* PLoS One, 2015. **10**(1): p. e0116476.
115. Wolff, G. and K.A. Esser, *Scheduled exercise phase shifts the circadian clock in skeletal muscle.* Med Sci Sports Exerc, 2012. **44**(9): p. 1663-70.
116. Leise, T.L., et al., *Voluntary exercise can strengthen the circadian system in aged mice.* Age (Dordr), 2013. **35**(6): p. 2137-52.

117. Tal-Krivisky, K., N. Kronfeld-Schor, and H. Einat, *Voluntary exercise enhances activity rhythms and ameliorates anxiety- and depression-like behaviors in the sand rat model of circadian rhythm-related mood changes.* Physiol Behav, 2015. **151**: p. 441-7.
118. Solberg, L.C., T.H. Horton, and F.W. Turek, *Circadian rhythms and depression: effects of exercise in an animal model.* Am J Physiol, 1999. **276**(1 Pt 2): p. R152-61.
119. Yamanaka, Y., et al., *Morning and evening physical exercise differentially regulate the autonomic nervous system during nocturnal sleep in humans.* Am J Physiol Regul Integr Comp Physiol, 2015. **309**(9): p. R1112-21.
120. Miyazaki, T., et al., *Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise.* Am J Physiol Regul Integr Comp Physiol, 2001. **281**(1): p. R197-205.
121. Tranel, H.R., et al., *Physical activity, and not fat mass is a primary predictor of circadian parameters in young men.* Chronobiol Int, 2015. **32**(6): p. 832-41.
122. Van Reeth, O., et al., *Nocturnal exercise phase delays circadian rhythms of melatonin and thyrotropin secretion in normal men.* Am J Physiol, 1994. **266**(6 Pt 1): p. E964-74.
123. Eastman, C.I., et al., *Phase-shifting human circadian rhythms with exercise during the night shift.* Physiol Behav, 1995. **58**(6): p. 1287-91.
124. Pail, G., et al., *Bright-light therapy in the treatment of mood disorders.* Neuropsychobiology, 2011. **64**(3): p. 152-62.
125. Wirz-Justice A, B.F., Terman, *Chronotherapeutics for Affective Disorders: a Clinician's Manual for Light and Wake Therapy*. 2 ed. 2013: Karger: Basel, Switzerland.
126. Terman, M., J.S. Terman, and D.C. Ross, *A controlled trial of timed bright light and negative air ionization for treatment of winter depression.* Arch Gen Psychiatry, 1998. **55**(10): p. 875-82.
127. Eastman, C.I., et al., *Bright light treatment of winter depression: a placebo-controlled trial.* Arch Gen Psychiatry, 1998. **55**(10): p. 883-9.
128. Lewy, A.J., et al., *Morning vs evening light treatment of patients with winter depression.* Arch Gen Psychiatry, 1998. **55**(10): p. 890-6.
129. Tuunainen, A., D.F. Kripke, and T. Endo, *Light therapy for non-seasonal depression.* Cochrane Database Syst Rev, 2004(2): p. CD004050.
130. Golden, R.N., et al., *The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence.* Am J Psychiatry, 2005. **162**(4): p. 656-62.
131. Lieverse, R., et al., *Bright light in elderly subjects with nonseasonal major depressive disorder: a double blind randomised clinical trial using early morning bright blue light comparing dim red light treatment.* Trials, 2008. **9**: p. 48.
132. Lam, R.W., et al., *Efficacy of Bright Light Treatment, Fluoxetine, and the Combination in Patients With Nonseasonal Major Depressive Disorder: A Randomized Clinical Trial.* JAMA Psychiatry, 2016. **73**(1): p. 56-63.
133. Sit, D.K., et al., *Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial.* Am J Psychiatry, 2018. **175**(2): p. 131-139.
134. Stephenson, K.M., et al., *Complex interaction of circadian and non-circadian effects of light on mood: shedding new light on an old story.* Sleep Med Rev, 2012. **16**(5): p. 445-54.
135. Roecklein, K.A., et al., *Melanopsin, photosensitive ganglion cells, and seasonal affective disorder.* Neurosci Biobehav Rev, 2013. **37**(3): p. 229-39.
136. LeGates, T.A., D.C. Fernandez, and S. Hattar, *Light as a central modulator of circadian rhythms, sleep and affect.* Nat Rev Neurosci, 2014. **15**(7): p. 443-54.
137. Coomans, C.P., A. Ramkisoensing, and J.H. Meijer, *The suprachiasmatic nuclei as a seasonal clock.* Front Neuroendocrinol, 2015. **37**: p. 29-42.
138. Giedke, H. and F. Schwarzler, *Therapeutic use of sleep deprivation in depression.* Sleep Med Rev, 2002. **6**(5): p. 361-77.
139. Bunney, B.G. and W.E. Bunney, *Mechanisms of rapid antidepressant effects of sleep deprivation therapy: clock genes and circadian rhythms.* Biol Psychiatry, 2013. **73**(12): p. 1164-71.
140. Wu, J.C., et al., *Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder.* Biol Psychiatry, 2009. **66**(3): p. 298-301.

141. Orozco-Solis, R., et al., *A Circadian Genomic Signature Common to Ketamine and Sleep Deprivation in the Anterior Cingulate Cortex.* Biol Psychiatry, 2017. **82**(5): p. 351-360.
142. Winkler, D., et al., *Usage of Therapeutic Sleep Deprivation: A Survey in Psychiatric Hospitals in Austria, Germany, and Switzerland.* Behav Sleep Med, 2018: p. 1-8.
143. Van Reeth, O., et al., *Resynchronisation of a diurnal rodent circadian clock accelerated by a melatonin agonist.* Neuroreport, 1998. **9**(8): p. 1901-5.
144. Weibel, L., et al., *A melatonin agonist facilitates circadian resynchronization in old hamsters after abrupt shifts in the light-dark cycle.* Brain Res, 2000. **880**(1-2): p. 207-11.
145. Armstrong, S.M., et al., *Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS).* Pharmacol Biochem Behav, 1993. **46**(1): p. 45-9.
146. Castanho, A., et al., *Like melatonin, agomelatine (S20098) increases the amplitude of oscillations of two clock outputs: melatonin and temperature rhythms.* Chronobiol Int, 2014. **31**(3): p. 371-81.
147. Redman, J.R. and A.J. Francis, *Entrainment of rat circadian rhythms by the melatonin agonist S-20098 requires intact suprachiasmatic nuclei but not the pineal.* J Biol Rhythms, 1998. **13**(1): p. 39-51.
148. Mairesse, J., et al., *Chronic agomelatine treatment corrects the abnormalities in the circadian rhythm of motor activity and sleep/wake cycle induced by prenatal restraint stress in adult rats.* Int J Neuropsychopharmacol, 2013. **16**(2): p. 323-38.
149. Krauchi, K., et al., *Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature.* Am J Physiol, 1997. **272**(4 Pt 2): p. R1178-88.
150. Leproult, R., et al., *Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men.* Clin Endocrinol (Oxf), 2005. **63**(3): p. 298-304.
151. De Berardis, D., et al., *Agomelatine beyond borders: current evidences of its efficacy in disorders other than major depression.* Int J Mol Sci, 2015. **16**(1): p. 1111-30.
152. Pringle, A., et al., *Does melatonin treatment change emotional processing? Implications for understanding the antidepressant mechanism of agomelatine.* J Psychopharmacol, 2015. **29**(10): p. 1129-32.
153. Hojgaard, K., et al., *Disturbances of diurnal phase markers, behavior, and clock genes in a rat model of depression; modulatory effects of agomelatine treatment.* Psychopharmacology (Berl), 2018. **235**(3): p. 627-640.
154. Lewy, A.J., *Circadian misalignment in mood disturbances.* Curr Psychiatry Rep, 2009. **11**(6): p. 459-65.
155. Kripke, D.F., et al., *Circadian rhythm disorders in manic-depressives.* Biol Psychiatry, 1978. **13**(3): p. 335-51.
156. Li, J., et al., *Lithium impacts on the amplitude and period of the molecular circadian clockwork.* PLoS One, 2012. **7**(3): p. e33292.
157. Wei, H., et al., *Inositol polyphosphates contribute to cellular circadian rhythms: Implications for understanding lithium's molecular mechanism.* Cell Signal, 2018. **44**: p. 82-91.
158. He, B., et al., *The Small Molecule Nobiletin Targets the Molecular Oscillator to Enhance Circadian Rhythms and Protect against Metabolic Syndrome.* Cell Metab, 2016. **23**(4): p. 610-21.
159. Shinozaki, A., et al., *Potent Effects of Flavonoid Nobiletin on Amplitude, Period, and Phase of the Circadian Clock Rhythm in PER2::LUCIFERASE Mouse Embryonic Fibroblasts.* PLoS One, 2017. **12**(2): p. e0170904.
160. Qi, G., et al., *Nobiletin protects against insulin resistance and disorders of lipid metabolism by reprogramming of circadian clock in hepatocytes.* Biochim Biophys Acta, 2018. **1863**(6): p. 549-562.
161. Solt, L.A., et al., *Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists.* Nature, 2012. **485**(7396): p. 62-8.
162. Banerjee, S., et al., *Pharmacological targeting of the mammalian clock regulates sleep architecture and emotional behaviour.* Nat Commun, 2014. **5**: p. 5759.

163. Amador, A., et al., *Pharmacological Targeting the REV-ERBs in Sleep/Wake Regulation.* PLoS One, 2016. **11**(9): p. e0162452.

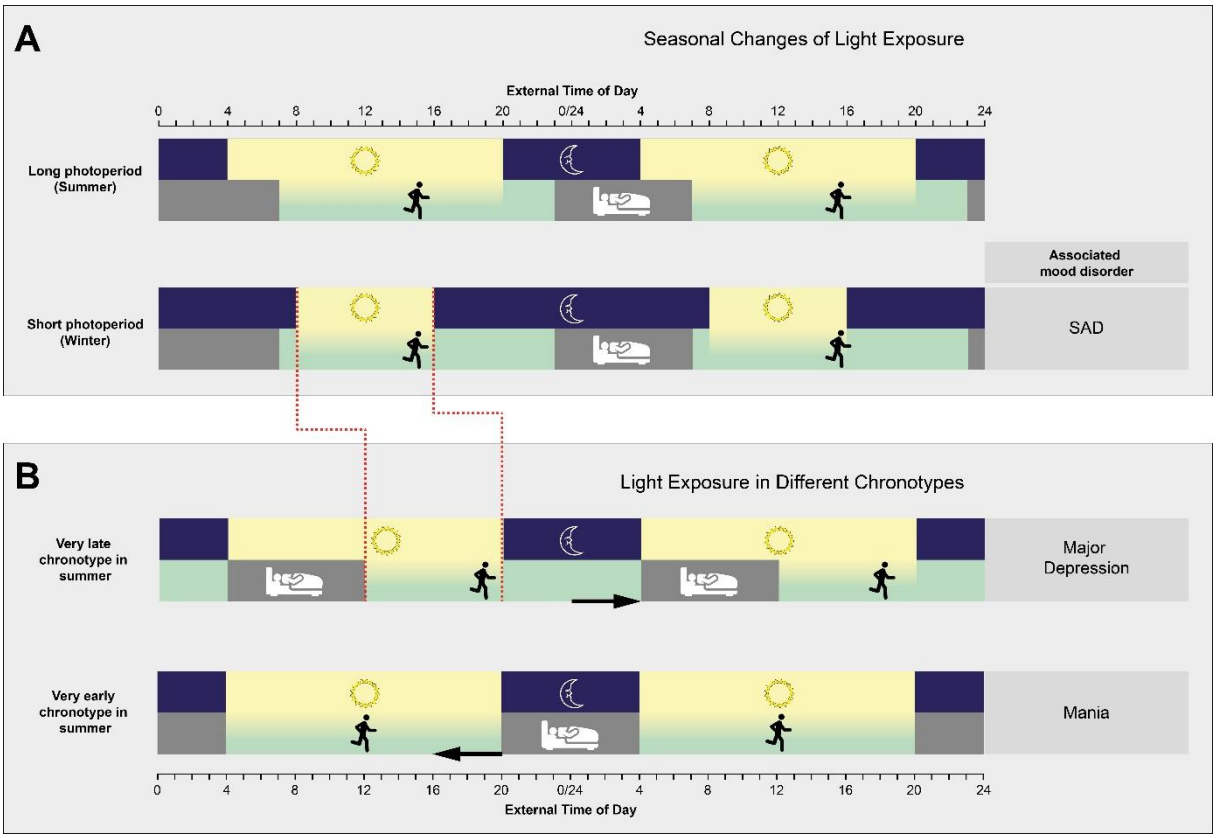


**Figure 1:** Light exposure during summer and winter months as well as in late and early chronotypes and associations with mood disorders. (A) Natural light exposure of summer and winter is compared to sleep-wake behavior of a human with an average chronotype. In summer, long photoperiods ensure relatively long exposure to natural light during the activity phase. Contrarily, short photoperiods in winter have the effect that humans are exposed to only short periods of natural light during their activity phase. This condition facilitates the development of SAD during winter. (B) Humans with very late chronotypes are so delayed (arrow) that they miss a lot of daylight and may only receive as much natural light in summer like a person with a normal chronotype receives in winter (the orange dashed line demonstrates similar lengths of light exposure in winter of a normal chronotype and in summer of a late chronotype). In contrast, humans with an extreme early chronotype get a lot of daylight during their activity phase. The chronic lack of light may explain why usually late chronotype strongly correlates with MDD, and not early chronotypes. The lighting conditions approximate seasonal conditions in central Europe. Icons were taken from https://www.flaticon.com/.

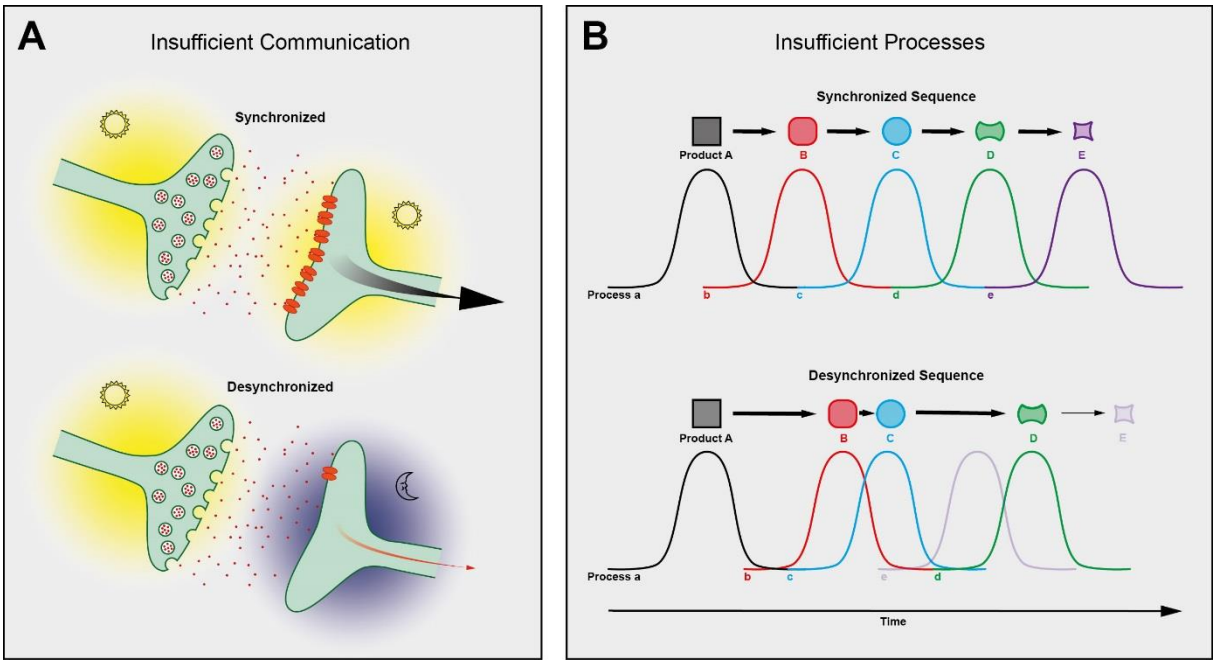


**Figure 2:** Possible complications induced by internal desynchronization. (A) Internal desynchronization may promote insufficient communication among different tissues. As an example, two neurons of different brain areas are shown. The release of most neurotransmitters is under control of circadian clocks. Similarly, the expression of their receptors is often adjusted accordingly. Consequently, under synchronized conditions, at times of high neurotransmitter release the receptor is most prevalent ensuring optimal communication among the brain areas. In contrast, when brain areas are not synchronized, the release of a neurotransmitter may be ineffective as the receptor is not yet fully expressed or the peak of expression is already over. (B) Internal desynchronization might affect the flow of various physiological processes in the body. Shown is a hypothetical sequence of processes a-e leading to product E. The processes may occur within one cell type/tissue or in different tissues. The circadian clock determines the timing of processes a-e and ensures the fluent synthesis of product E. In case circadian clocks are not synchronized and, therefore, the sequence of processes a-e is disturbed, the production of intermediate products B-D may be affected. In the worst case, when the timing of subsequent processes is extremely misaligned, the synthesis of product E is strongly impaired.

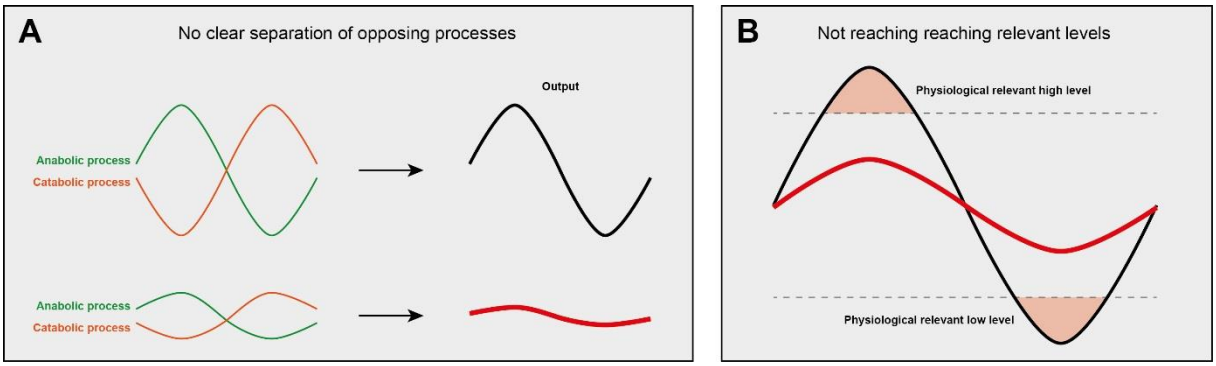


**Figure 3:** Consequences of decrease of circadian rhythm amplitude. (A) Circadian clocks ensure the proper timing and separation of opposing processes in the body, like the activation and inhibition of anabolic and catabolic pathways. Consequently, the output of the two processes shows strong circadian rhythms. In conditions of low amplitude rhythms, the separation of opposing processes is not very pronounced with the consequence that both processes take place simultaneously over the course of the day. Therefore, their output shows strongly impaired rhythmicity. (B) Many physiological processes require a certain level of activators/inhibitors in order to be induced or interrupted. When circadian rhythms amplitude is low, these levels may not be reached and the process cannot take place.