Review Article

Chronobiology, excessive daytime sleepiness and depression: Is there a link?

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Abstract

The complaint of excessive daytime sleepiness (EDS), commonly encountered in clinical practice, may arise from a variety of psychiatric disorders, most importantly depression. Even though EDS frequently leads depressed patients to seek medical assistance, it is commonly under-evaluated and under-diagnosed. Therefore, a comprehensive understanding and management of EDS is essential in the clinical assessment of depression. Within a theoretical framework, a chronobiological approach may shed new light on the complex interaction of EDS and depression. In this review, studies on EDS and depression are summarized and discussed within the context of circadian and sleep regulatory mechanisms. Furthermore, potential chronobiological therapeutic strategies are proposed to address some of the unmet needs in the treatment of EDS and depression.
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1. Introduction

Excessive daytime sleepiness (EDS) is a tendency to fall asleep despite volitional attempts to remain alert. Chronic sleep loss and/or poor sleep quality are the major underlying reasons for EDS. They occur in numerous sleep disorders, such as obstructive sleep apnea and narcolepsy, as well as in psychiatric disorders, particularly depression. Approximately 80% of depressive states are associated with comorbid insomnia, related or not to EDS [1]. Depressed patients exhibit a plethora of complaints related to daytime energy levels. However, even though sleep quality and quantity are very often substantially decreased in depression, patients do not necessarily have a higher propensity to fall asleep during the day, but rather experience a subjective state of sleepiness [1,2]. This state of sleepiness in depression differs from EDS as typically encountered in narcolepsy and obstructive sleep apnea (OSA). In the former, subjects experience EDS as "sleep attacks," namely short and recurrent periods of sleep in the daytime, regardless of the prior amount or quality of night sleep. In OSA, there is a higher propensity to fall asleep during the daytime, possibly due to sleep fragmentation and/or hypoxemia related to chronic intermittent respiratory events [3].

There is ample evidence for an association between daytime sleepiness and moderate to severe depression [4,5]. Given that insomnia, particularly when associated with impaired daytime function, plays a key role in the onset of depression [6], it is of significant clinical importance to unravel the link between EDS and depression. Furthermore, knowledge on the inter-relation between EDS and mood disorders may have ramifications for the treatment of depression [7,8].

Apart from the sleep perspective, circadian rhythms play a key role in the association between depression and EDS. Depression is strongly intertwined with bio-

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logical rhythms on a wide range of dimensions, which includes neurobiological systems that underlie both the pathophysiology of depression, such as the serotonergic system, as well as the clinical aspects of depression [9]. This rhythmicity can manifest itself as an intra-episodic symptomatic expression – such as diurnal variation of mood and early morning awakening – or as an inter-episodic expression – such as seasonal recurrence of clinical depression or reappearance after therapeutic management. Disorders of the human circadian system per se can result in circadian misalignment, leading to sleep disturbances (namely, insomnia and/or EDS), reduced attention and impaired daytime alertness, lack of energy, lower performance, negative mood and gastrointestinal disorders. Interestingly, these symptoms also occur in depression, which further extends the idea that depression and circadian rhythms are intimately connected. Among depressive disorders, major depression, bipolar depression and seasonal affective disorder are defined as being both episodic and recurrent, thus possibly reflecting a chronobiological disorder [10]. Together with the rhythmicity of clinical symptoms, the aforementioned disorders have been associated with alterations of the rhythm of several physiological variables. These include sleep–wake cycle disruption and pathophysiological changes in the secretion of an array of hormones, including cortisol, TSH, GH and melatonin, among others [11–14].

The application of chronobiological and sleep regulatory concepts in the treatment of depressive disorders has led to effective therapeutic strategies, among which bright light therapy and sleep deprivation can be highlighted [9,11]. Furthermore, there is evidence that the circadian system is implicated in pharmacological treatment mechanisms, such as lithium therapy for bipolar depression [15]. Lithium can modify the phase-angle between circadian temperature rhythm and rest–activity cycle and lengthens the period of circadian rhythms by increasing the circadian period of firing rate rhythms of SCN neurons in a concentration-dependent manner [16,17]. Therefore, the stabilization of circadian rhythms may be a key action of clinically effective mood-stabilizing treatments.

In this review, studies on EDS and depression will be summarized and discussed within the framework of current sleep and chronobiology perspectives. A brief outlook of the probable chronobiological underpinnings will be given in order to provide insights on this inter-relationship and possibilities of chronobiological therapies.

2. EDS and depression

EDS is a common complaint in clinical practice [18]. On the societal level, the negative impacts of sleepiness are likewise significant. For instance, in the USA, a sizable proportion of adults (43%) report that they are so sleepy during the day that it interferes with their daily activities, with one out of five individuals experiencing this level of daytime sleepiness at least a few days per week or more [19]. On the individual level, EDS not only reduces personal efficiency of labour, but also leads to difficulties with concentration, memory and mood impairment, which further negatively impact performance and well being [2,18,20].

EDS is commonly viewed as a cardinal sign of disturbed or inadequate sleep, and can be directly linked to depression [4,5]. In a recent study conducted with a random sample of 16,500 individuals in the USA, 8.7% displayed EDS [21]. Strikingly, EDS was more strongly associated with depression (OR = 3.12) than with obesity or other metabolic factors and sleep-related breathing disorders. Indeed, depressive disorders are often associated with disrupted sleep. While the majority of depressed patients with sleep disruption suffer from insomnia, a considerable number of them report hypersomnia with concomitant daytime sleepiness [22]. This subset of patients is often diagnosed with bipolar depression or depression with DSM-IV-TR atypical features which include irritability, increased appetite and sleepiness [23].

Recently, we observed a significant association ($r = 0.80$) between EDS and suicidal ideation in depressed patients [24]. This unequivocal result was striking, considering that no specific relation of EDS with suicidal ideation had been previously described. An explanation for this finding may be that patients with severe depressive disorder rank daytime sleepiness in line with other major depressive symptoms [25–27]. If these findings are confirmed in a larger sample size, EDS should, therefore, be considered in the assessment of suicidal risk in depression.

Despite the significant evidence linking EDS to depression, the mechanisms underlying this relationship remain uncertain to date. One important line of research builds upon findings from several large-scale epidemiological studies, which have demonstrated that approximately 20% of depressed patients exhibit a frequently undiagnosed sleep-disordered breathing, mostly obstructive sleep apnea [28,29]. This goes in line with a large number of reports which have gathered data linking metabolic syndrome and, most importantly, obesity and diabetes or insulin resistance, together with elevated inflammatory markers, to both sleep-disordered breathing and depression [30–36].

3. Depression and circadian rhythms

Diurnal variations of mood and sleep disturbances belong to the core of classical symptoms that have linked depression to the circadian system [37]. Typical mood variation consists of a substantially improved mood in the evening in contrast to worsening in the

morning after sleep [38]. The improved state in the evening includes other spheres, such as psychomotor activity and cognitive performance [39,40]. The existence of this type of daily variation is a predictor for positive response to certain types of treatment, such as sleep deprivation [41]. However, this pattern does not occur in all subtypes of depression and the opposite has also been described, particularly for bipolar depression and atypical depression [10]. In a given patient, different patterns of diurnal mood variation can occur during a single depressive episode.

Shortening of REM sleep latency and an abnormal distribution of REM sleep throughout the night may typically occur in depression [42–44]. In atypical depression, hypersomnia is frequent, with increased night sleep duration up to 12 h, combined or not with EDS [24]. Since both REM sleep and sleep duration are under strong circadian control, these sleep alterations may reflect disturbances in the circadian system of depressed patients. There is a considerable body of evidence suggesting that daytime sleep may occur in depressed patients more frequently than commonly thought, possibly as a consequence of a dampened circadian rhythm of sleep propensity. In normal subjects, daytime napping can result in nocturnal sleep changes similar to those seen in depressed patients [1,21]. Thus, the nocturnal sleep disturbance in depression may actually reflect the occurrence of daytime naps with slow-wave sleep or slow-wave EEG activity [44].

Seasonal Affective Disorder (SAD) illustrates how an alteration between the external light–dark cycle (i.e., photoperiod) and circadian rhythms may elicit a depressive disorder. Most SAD patients become depressed in the winter time because of the later dawn, which leads their circadian rhythms to delay with respect to both clock time and to the sleep–wake cycle [45]. Changes in the latter sleep–wake are apparent, with most patients presenting hypersomnia in conjunction with EDS.

Abnormalities in the circadian rhythm are also observed in non-seasonal depressed patients, including variations in the circadian phase and amplitude of core body temperature [9,38] and the endogenous melatonin rhythm [51,14]. Though overall studies have yielded conflicting results, chronobiological studies in which sleep timing and/or total amount of sleep were re-scheduled in patients provide evidence for the implication of circadian rhythms in depression [46,47]. However, it is still unclear whether these observations represent functional changes of the circadian system itself or are due to the influence of other factors downstream.

One critical aspect in major depression is the hyperactivity of hypothalamus–pituitary–adrenal (HPA) axis which reflects a stress response and/or abnormality of the circadian rhythm of cortisol [48]. Usually, the acrophase of the cortisol rhythm occurs early in the morning prior to awakening, while the nadir is registered at night,

a short time after initiating sleep [12]. However, in depressive states, HPA hyperactivity leads to sustained high levels of cortisol resulting in insomnia and a hyper-arousal state [13]. Furthermore, depressive patients often present high levels of thyrotropin-releasing hormone (TRH), and a reduction of the normal nocturnal elevation of serum thyrotropin has been suggested as a marker of an abnormal circadian rhythm of this hormone in depressive states [49]. As a consequence, hypothyroidism may be an additional factor for high levels of subjective sleepiness during daytime.

In addition to circadian and endocrine changes in depression, recent imaging studies have shed new light on the neurobiological basis of depression. The increased magnitude of ultradian (i.e., within-day) mood variability in depressed patients compared with non-depressed subjects [52] may be related to regional cerebral metabolic changes in the evening relative to morning and may reflect functional changes in components of the ventral and dorsal emotion neural systems [53]. Diurnal variation in mood may be related to different patterns of diurnal changes in the regional cerebral metabolic rate of glucose (rCMRglc) in depressed and healthy subjects. Morning-to-evening changes in rCMRglc differ with regard to the brain systems that promote wakefulness. In healthy adults, relative rCMRglc increases during the evening compared to the morning in wake-promoting brainstem and hypothalamic regions [54]. This pattern may reflect an input from the circadian timing system to promote wakefulness in face of the increasing sleep pressure. Considering that circadian rhythms can be attenuated in depression, diurnal variations in rCMRglc in brainstem and hypothalamic areas may be, therefore, blunted in depressed compared to healthy individuals [55].

4. Sleepiness, mood and chronobiology: bridging the gap

From a conceptual point of view, EDS can be considered to result from the biological need for sleep as characterized by a complex interaction between circadian and homeostatic processes [8]. Briefly, the master pacemaker driving circadian rhythms, the suprachiasmatic nuclei (SCN), is synchronized to the external light–dark cycle through retinal light input (light being the main synchronizer or "zeitgeber") [56]. A specialized non-visual retinohypothalamic tract provides direct neuronal connection to the SCN from novel photoreceptors in the retinal ganglion cells that measure illuminance [57,58]. Although the SCN is the so-called master clock, circadian oscillators have been found in practically every cell [59]. Therefore, the SCN would act in a manner to organize an internal temporal conjunction of several peripheral oscillators. The homeostatic component is dependent on the duration of prior wakefulness and is dissipated during sleep, reinitiating its build-up during

the following wake period [60]. The two-process model of sleep regulation has unified these two components to understand the timing and architecture of sleep [61]. This model can also be utilized to describe possible disturbances in either process during depression. The clinical sleep disturbance with early morning awakening could arise from an impaired build-up of S during waking (diminished sleep pressure) or an earlier timing of process C. Other possible abnormalities could lie in the decline of S during sleep or altered circadian period, phase, or amplitude [37].

Considering that mood is such a complex phenomenon, modulated by a plethora of factors extending from hormones to social situations, insight into its regulation is a rather difficult task. Surprisingly, though, mood is also determined by circadian and homeostatic factors [62,63]. Several hypotheses have been proposed to explain the mechanisms that underlie the relationship of sleep, sleep disorders and depression. According to the internal coincidence hypothesis, an abnormal relationship between the circadian system and the sleep–wake cycle occurs in which the phase-angle between an advanced circadian pacemaker and the sleep–wake cycle is depressogenic [64]. In other words, depressive patients sleep at the wrong biological clock-time. Thus, such patients commonly develop insomnia that may be associated with EDS. On the other hand, the S-deficiency model proposes a deficient build-up of process S (i.e., sleep need) in depression, with process C remaining unaffected [60]. A third hypothesis suggests that disturbed neurochemical interaction mechanisms underlie abnormalities in the ultradian rhythm of REM sleep in depressed patients [37].

Two important protocols have been developed in order to dissect out the relative contributions of circadian and sleep homeostatic processes in humans, namely the constant routine and the forced desynchrony protocols [65]. In the first procedure, the amplitude and phase of many circadian rhythms can be elucidated without the masking effects of motor activity, meals and light conditions. In the second protocol, subjects live on artificially very long or very short days, so that the circadian system is no longer entrained to the imposed sleep–wake cycle, enabling the measurement of an individual's circadian period. The desynchronized subjects sleep at different circadian phases of the entire 24-h cycle, and subsequent analyses can differentiate the relative contribution of the sleep homeostat or the biological clock to a given variable [66]. Usually – but not always – both factors contribute substantially to subjective measures, such as mood, sleepiness and neurobehavioral performance [67,68]. However, only few studies have used these techniques in a controlled manner to unmask the contribution of the circadian clock in depression. These protocols can certainly contribute to a more accurate understanding of the circadian disruptions that occur

in depression, and, thus, can be of substantial value in future research [9]. Table 1 gives an overview of constant routine and forced desynchrony studies in depressed patients [69–72,67,73].

5. Further hypotheses: sleepiness, neurotransmitters and hyperarousal

Sleepiness may be deemed as a physiological state or urge, that promotes the onset of sleep, and which is reversed or satiated (although not always) by the attainment of adequate sleep. The neurobiological substrates of sleepiness are not understood completely. Sleepiness may reflect the waning of processes maintaining wakefulness or it may result from distinct neural systems acting to promote sleep [74]. In other words, these neurological substrates interact in a complex fashion to generate sleep and wakefulness. For instance, according to the "flip–flop" model of sleep and wakefulness [75], monoaminergic nuclei, including the locus coeruleus, the serotonergic dorsal and median raphé nuclei and the histaminergic tuberomammilary neurons, promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep promoting neurons of the ventrolateral preoptic nucleus. During sleep, the latter inhibits monoaminergic-mediated arousal regions through GABAergic and galaninergic projections. Orexin-containing neurons seem to play an important stabilizing role in the proposed "flip–flop" mechanism. On the other hand, the accumulation of a sleep-promoting substance that enhances the activity of sleep-promoting cells and reduces the activity of wake-promoting neurons may be a potential mechanism for homeostatic sleep regulation [75]. However, it remains to be determined how these and other brain structures act and interact to generate EDS in various disorders.

Circadian rhythms involve the same neurotransmitters that have been postulated to be important for depression, such as serotonin, thus leading to a situation in which changes in one system have repercussions on the other [9]. Serotonin plays an important part in sleep regulation, and prefrontal cortical serotonin has been linked to mood. All these inter-relationships have been conceptualized in a dual model whereby circadian rhythms and serotonin [76] together are involved in a system vulnerable to depression through genetic, hormonal and light exposure factors [9,11,37,62,77].

From a pathophysiological standpoint, sleep disturbance in depressed patients with a chief complaint of daytime sleepiness appears to be associated with a centrally driven hyperarousal, whereas idiopathic sleepiness is usually associated with a centrally driven hypoarousal. This hypothesis has been supported by recent work in which both groups exhibited differences in night time sleep and daytime alertness [78]. The main postulation was that these disorders are related to the altered arou-

Table 1

Constant routine (CR) and forced desynchrony (FD) protocols with depressed patients

	Type of Study	Subjects	Depression diagnosis	Protocol procedure	Circadian marker	Phase/amplitude/phase angle changes in depressed
Dahl et al. (1993) [69]	CR	6 SD[a] 6 CT[b]	SAD	27-h CR	DLMO[c] CBT[d]	DLMO & CBT phase-delay
Buysse et al. (1995) [70]	CR	26 UP 17 CT	DSM-IV unipolar depression[e]	36-h CR	CBT melatonin cortisol	No differences
Wirz-Justice et al. (1995) [71]	CR	11 SD 8 CT	SAD	40-h CR	CBT melatonin	No differences
Avery et al. (1997) [72]	CR	6 SD 6 CT	SAD	27-h CR	CBT cortisol	CBT & cortisol phase-delay
Koorengevel et al. (2002) [67]	FD	7 SD 7 CT	SAD	120-h FD (six 20-h days)	CBT melatonin	CBT amplitude ↓
Koorengevel et al. (2003) [73]	FD	7 SD 7 CT	SAD	120-h FD (six 20-h days)	CBT melatonin	CBT amplitude ↓

[a] Seasonal depressed.
[b] Control subjects.
[c] Dim light melatonin onset.
[d] Core body temperature.
[e] Unipolar depression.

sal state and not sleep per se. This was further supported by the fact that idiopathic sleepiness is usually associated with dysfunction of the autonomic nervous system such as orthostatic hypotension and hypoactivity of the corticotropin-releasing hormone neuronal system (that is directly linked to arousal), whereas psychiatric hypersomnia is most frequently related to depression and anxiety, conditions deemed to be associated with hyperarousal [79]. However, more research on physiological parameters, such as metabolic rate and temperature, is required to test the hypothesis that sleepiness in depression, and idiopathic sleepiness are disorders of arousal.

6. Diagnosis of EDS

Although daytime sleepiness is highly prevalent, it is frequently under-diagnosed. To tackle this problem, the diagnosis of EDS should start with a precise definition and clinical history. EDS can result from the interaction of three following factors that account for increased sleepiness: physiological (due to the interplay of circadian and homeostatic components, as detailed above), manifest and introspective sleepiness [80]. Manifest sleepiness refers to the behavioural correlate of the physiological need for sleep. Reduced performance and alertness in a sleepy individual, involuntary sleepiness despite volitional attempts to remain awake and low performance in cognitive and behavioural tests can be some of the main hallmarks of "manifest sleepiness" in non-medicated depression. Manifest sleepiness is modulated by individual motivation and environmental factors. Introspective sleepiness consists of the individual ability to characterize internal subjective state [80]. In healthy subjects, there is an adequate perception of sleepiness after

sustained sleep deprivation. Nevertheless, in chronic sleep deficit due to clinical disorders such as depression, the perception of sleepiness may be dramatically reduced, thus leading to an underestimation of sleepiness [6].

Depressed patients may present subjective complaints of tiredness or fatigue instead of more specific symptoms of sleepiness. In order to discriminate between tiredness and sleepiness, questions regarding the need to take naps, dozing in passive situations, or how long it is needed to initiate sleep at usual bedtime can help to distinguish real sleepiness from less specific complaints [1,20,81]. Problems concerning performance or neuro-cognitive function are often completely ignored. Performance alone may not always be the best indicator of sleepiness, as motivation may temporarily override a performance decrement. Compensatory strategies may also be invoked, such as avoiding increased errors by adopting a slower pace [82]. Likewise, individuals might also accept lower levels of achievement. An accurate evaluation of EDS usually requires several assessment methods [22]. A wide array of tools has been developed to assess sleepiness in a more objective fashion, although all of them have their shortcomings. Initially, introspective behavioural scales and performance tests were utilized to assess sleepiness. Subjective scales try to analyze the perception of alertness/sleepiness. However, a serious limitation to this approach is that patients must have an insight into their problem and be able to distinguish sleepiness from other factors affecting performance, which may not be the case. On the other hand, scales, such as the Stanford Sleepiness Scale and the Karolinska Sleepiness Scale, can convey an appropriate assessment of the *momentary* degree of alertness/sleepiness [83,84]. Furthermore, they are quite useful in tracking symptoms over time, although they

do not provide a *global* perspective of sleepiness. The Epworth Sleepiness Scale offers a better method for assessing overall sleepiness, since it reports on sleepiness over a one-month period, including both active and passive situations of possible behavioural sleepiness [85]. Visual analogue scales require the subject to provide a response along a linear 100 mm line, ranging from very sleepy to very alert [6]. The main advantage of these scales is that they can be utilized often and sequentially to track subtle changes in the feeling of sleepiness over a given time period. Performance tests, such as the PVT, have been frequently utilized to measure sustained attention [86]. However, questionnaires utilized in the assessment of subjective sleepiness (e.g., Epworth or Stanford scales) do not always correlate with objective quantifications. Objective tests of daytime sleepiness rely on measurement of physiological parameters, the most extensively used test being the multiple sleep latency test (MSLT). The MSLT is performed after an overnight polysomnogram in order to assess sleep during the prior night (which controls for nocturnal sleep disruption that could account for daytime symptoms, such as obstructive sleep apnea) [87]. Accordingly, mean sleep latency >10 min is deemed normal, the 5–10 min range as a grey zone and <5 min as severe daytime sleepiness.

Waking EEG changes may also provide insight into the state of sleepiness in depression. For instance, in a 40-h constant routine study looking at the EEG and subjective sleepiness in seasonal affective disorder (SAD), we observed that the progressive build-up of sleepiness was considerably reduced in SAD patients [88]. The time course of waking EEG theta–alpha activity showed a rapid increase during the first 10 h, which then remained constant, in contrast to control subjects who showed a slower continuous exponential increase in the course of the 40-h episode of sustained wakefulness. Given that this pattern was independent of clinical state or season, SAD patients may have a trait deficiency in the homeostatic build-up of sleep pressure.

7. Chronobiological treatments for sleepiness and depression

A chronobiological approach may address some of the unmet needs in the treatment of depression, such as diminishing the latency of onset of antidepressant action, reducing residual symptoms and preventing relapse in the long-term. Circadian rhythm and sleep research have led to promising non-pharmacological therapies [9,11,89]. Sleep deprivation therapy exerts a rapid and dramatic, albeit usually short-lasting, improvement of mood in the majority of patients with major depressive disorder. Light therapy has been applied to a wide range of mood disorders as stand-alone therapy or as an adjunct to antidepressant pharmacotherapy [90]. Light acts as a synchronizing agent for disturbed circadian rhythms, while sleep deprivation challenges the sleep–wake homeostat [91,92]. Table 2 summarizes the main chronobiological therapies employed for depressive disorders.

Total sleep deprivation (TSD) for one whole night improves depressive symptoms in 40–60% of treatments [37,92]. The degree of clinical change spans a continuum from complete remission to worsening. Sleep deprivation (SD) response shows up in the SD night or on the following day. After recovery sleep, 50–80% of first day responders suffer a complete or partial relapse; nevertheless, improvement can last for weeks. Sleep seems to lead to the relapse, although this may not necessarily be the case. Treatment effects may be stabilized by antidepressant drugs, lithium, shifting of sleep time or light therapy [93]. Current opinion is that partial sleep deprivation (PSD) in the second half of the night is equally effective as TSD. Sleep deprivation may hasten the onset of antidepressant medication action and repeated trials of SD can also be an efficient treatment strategy in drug refractory depression [37,91,92]. Given that insomnia associated or not with EDS is such a prominent feature of depression, further investigations may consider track-

Table 2
Chronobiological therapies of depressive disorders

	Therapeutic duration	Duration of response
Total sleep deprivation (TSD)	Hours	1 day
Partial sleep deprivation (PSD) in the second half of the night	Hours	1 day
Repeated TSD or PSD	Hours	Days/weeks
Repeated TSD or PSD with antidepressant therapy	Hours	Weeks/months
Sleep–wake cycle phase advance	3 days	Up to 2 weeks
TSD followed by sleep phase advance	Hours	Up to 2 weeks
Single or repeated TSD or PSD followed by light therapy	Hours	Weeks/months
Single or repeated TSD or PSD followed by phase advance and light therapy	Hours	Weeks/months
Single or repeated TSD or PSD combined with lithium or serotonin selective receptor inhibitors	Hours	Months
Light therapy (winter seasonal MDD)	Days	Weeks/months
Light therapy (non-seasonal MDD)	Weeks	Weeks/months
Light therapy combined with serotonin selective reuptake inhibitors (non-seasonal MDD)	Up to 2 weeks	Weeks/months

*Modified by Wirz-Justice et al. (2005) [81].
MDD, major depressive disorder.

ing EDS as a concomitant outcome measure of sleep deprivation therapy for depression.

Light per se exerts powerful non-visual effects on a wide range of biological functions including the modulation of human alertness levels. Factors such as the dose (illuminance levels), exposure duration, timing and wavelength of light have important repercussions on the alerting response to light in humans and can lead to a substantial decrement in sleepiness [94]. Bright light therapy is characterized by a fast onset of antidepressant action and by additive properties to antidepressant medication [95]. Bright light therapy, beginning in the morning after partial sleep deprivation, has been demonstrated to prevent depressive relapse after recovery sleep in sleep deprivation responders [95]. Although until now bright light therapy has been regarded as a first-line treatment only for seasonal affective disorder (SAD) [96], recent studies on non-seasonal depression and the Cochrane meta-analysis on light therapies for this type of depression have provided evidence for the efficacy of bright light as an adjuvant to antidepressant pharmacotherapy [94,97,95,98]. Taking into account the insufficient remission rate of depression solely with pharmacotherapy and the favourable risk-to-benefit ratio of light therapy, it can offer a promising non-pharmacological biologically oriented treatment approach [90].

The combination of treatment strategies that manipulate circadian rhythms has lead to some very promising results. A strategy to block relapse in successful sleep deprivation responders includes therapeutic interventions combining sleep deprivation, phase advance and light therapy. For instance, one combination encompasses total sleep deprivation plus phase advance [44]. The underlying assumption is that, after a successful sleep deprivation, the avoidance of recovery sleep during a hypothesized critical early morning time period may prevent sleep deprivation associated relapses, with a concomitant improvement in both mood and subjective sleepiness [99].

On the pharmacological domain, the use of modafinil, a wake-promoting agent, has been recently suggested as a well-tolerated adjuvant in the treatment of EDS and depression, with a substantial improvement in both mood and sleepiness [100]. Furthermore, it is a particularly attractive alternative to other stimulants because of its low abuse potential. However, in a double-blind placebo control study, no significant improvements for daytime sleepiness, depression scores or overall clinical state were found [101]. Thus, caution should be kept in mind when using modafinil in depression.

Regarding antidepressants, some of the therapeutic properties of selective serotonin (5-HT) reuptake–inhibiting (SSRI) drugs can be related to the 5-HT_{2C} receptor subtype, and it is interesting to observe that 5-HT_{2C}

receptor agonists in the rat SCN mimic the effects of light [50]. Serotonergic drugs may thus improve entrainment.

Recently, a novel antidepressant drug, agomelatine, a melatonin agonist and 5-HT_{2c} antagonist, targeted both the circadian system and mood. Agomelatine [102] has identical physiological actions to melatonin [103] when administered in the evening to advance circadian phase and to promote a rapid sleep onset without after-effects on the following day. Indeed, unlike other antidepressants, notably SSRIs, agomelatine does not lead to insomnia, fragmentation of slow-wave sleep and nightmares, but rather improves the quality of sleep, with possible increases in both slow-wave sleep, and to a lower extent, REM sleep in depressed patients [104]. The interesting aspect of this treatment is that its core action aims at the circadian system, and it has been shown to be especially useful for synchronizing circadian rhythms of body temperature, cortisol and thyroid-stimulating hormone secretion [102]. Considering this, agomelatine can be indicated for the management of depression associated with EDS.

Recently, orexin-antagonists Ox1 and Ox2 receptors are being tested in the treatment of insomnia. Orexins are hypothalamic peptides that may play an important role in maintaining wakefulness in mammals. When administered during the active period of the circadian cycle, a dual antagonist of both orexin OX1 and OX2 receptors was shown to increase subjective and objective EEG sleep in humans [105]. Although this study targeted narcolepsy, these results may open new perspectives for investigating the role of endogenous orexins in sleep–wake regulation. Given the central role played by orexins in regulating sleep–wake cycles, it has been suggested that several sleep disorders may be associated with maladaptive orexinergic tone [105]. Whether orexin-antagonists can be utilized for other types of sleep disturbances, such as insomnia in depressed patients, however, remains to be answered.

8. Conclusions

EDS is a complaint frequently encountered in depression. Notwithstanding the significant evidence that links EDS to depression, the underlying mechanisms of this relationship remain uncertain. Considering that depression is intertwined with circadian rhythms on a wide array of dimensions, a chronobiological approach may shed new light on the complex interaction of EDS and depression and offer promising therapeutic strategies.

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