REVIEW

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Circadian malfunctions in depression – neurobiological and psychosocial approaches

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Abstract

Depression leads to disturbances in physiological rhythms, which result in disturbances in circadian sleep-wake cycles, hormonal secretion patterns and fluctuations in mood, all of which can be objectively measured. These disturbances, which are associated with depression, can be also used to define depression. Beyond these "transversal" time-related symptoms, there are the "longitudinal" time-related symptoms, since depression evolves over a long period of time, with a profound impact on a person's life and is often associated with long-term psychosocial consequences (Mendlewicz, 2010). The circadian rhythm reflects an approximate 24-hour cycle in the biochemical, physiological and behavioral processes of living entities, which crucially influences human well-being and health. Increasing evidence from clinical and neurobiological research suggests that disrupted temporal organization impairs behavior, cognition, mood, sleep and social activity and may be implicated in mental disorders. It has been proposed that circadian malfunction is a major core feature of mood disorders, depression in particular. In depressed patients, circadian rhythms and homeostatic processes are disrupted, thereby affecting mood, sleep, activity and a variety of biological functions such as hormone secretion and body temperature (Hajak & Landgrebe, 2010). Sleep difficulties are among the most current symptoms in depressed patients. Insomnia is often the reason why depressed patients seek help and relief of sleep disturbance may encourage compliance with antidepressant treatment. Apart from the discomfort that sleep problems produce, they may lead to exhaustion, poor functioning and they are associated with an increase in suicide risk (Wilson *et al.*, 2013).

Keywords: depression, neurobiology, sleep disorders, psychosociology.

The circadian process – generalities

Most human functions demonstrate circadian rhythmicity; that is why alterations in the endogenous machinery regulating biorhythms may lead to both physical and mental disorders [1–3]. In particular, disruptions of endogenous biological rhythms have been strongly associated with mood disorders, especially unipolar depression, for which alterations of circadian rhythms were first described more than 20 years ago [4, 5].

Sleep is a state of physical inactivity accompanied by loss of awareness and a markedly reduced responsiveness to environmental stimuli. Recording the EEG (electroencephalogram) and other physiological variables such as muscle activity and eye movements during sleep (polysomnography) gives information about the different stages of sleep and their pattern of occurrence. This pattern varies from person to person, but usually consists of four or five cycles of quiet sleep alternating with paradoxical and rapid eye movement (REM) sleep. The first part of the night is characterized by periods of deep quiet sleep with more and longer periods of REM sleep in the latter half of the night [3].

The circadian process is that which regulates the daily rhythms of the body and brain. Circadian (24 h) patterns of activity are found in many organs and even in individual cells. The main circadian pacemaker, our "body clock", is found in a group of cells in the suprachiasmatic nucleus (SCN) of the hypothalamus. These cells provide an oscillatory pattern of activity with a cycle time about every 24 h, which drives all of our bodily rhythms, including sleep-wake activity, hormone release, liver function, etc.

Individuals have different preferences for timing their sleep; some like to go sleep early and wake up early in the morning ("larks"), while others go to sleep late and wake up late ("owls") [6]. The sleep-wake cycle is the most obvious circadian rhythm in humans and sleep disturbances represent a prominent feature of depression. Epidemiological studies estimate that 50–90% of patients with diagnosed depression complain about impairment of their sleep quality [7, 8]. Typically, the complaints of depressed patients are about the difficulty in falling asleep, frequent nocturnal awakening and early morning awakening. Insomnia is thereby not only experienced subjectively, but also reflected objectively in altered sleep architecture [9].

These abnormalities consist of impaired sleep continuity and duration, a reduction of slow-wave sleep (SWS), a shortening latency of the initial REM phase, an increase in the proportion of REM sleep in the early part of the night, a prolongation of the first REM period, an increased amount of total REM sleep and an increased number of eye movements during REM periods (REM density) [10]. Longitudinal EEG studies in depressed patients have described a tendency for REM sleep abnormalities to resolve with improvement of the depression and even total normalization has been reported after successful treatment [11, 12].

However, other studies have reported the persistence of REM sleep and SWS abnormalities during remission, even after non-pharmacological treatments [13]. Persistent and/or residual sleep disturbances has thereby been associated with an increased risk of relapse and a persistence of reduced SWS has similarly been associated with more rapid and more frequent recurrence of depression [14].

Seasonal changes in mood, appetite, sleep and daily living function occur physiologically in many individuals. If these variations are of sufficient severity to meet the criteria for a major depressive episode, occur regularly during fall-winter and are generally followed by a remission during the subsequent spring and summer period, they may be regarded as an episode of seasonal affective disorder (SAD). SAD is a disorder with a circannual period and patients with SAD present with apparent chronobiological abnormalities; hence, it is currently assumed that SAD is a disorder of seasonal biological rhythms [15]. Abnormalities of circadian rhythms in sad patients include sleep disturbances, quantitative changes and phase delays in cortisol/melatonin secretion patterns and increases in the minima of the nocturnal body temperature, as well as a phase delay of its 24-hour rhythm [16, 17].

While the importance of human circadian rhythms has been known about for centuries, it has been widely neglected in modern society's way of life. In fact, people living in western industrialized countries increasingly neglect their biological circadian disposition. Working around a 24-hour day, traveling across several time zones, Internet-based intercontinental business and access to 24-hour television are leading to an increasing number of people living their lives against their own biological clocks [18]. *The American National Sleep Foundation* pointed out that between 1998 and 2005 the amount of people sleeping for less than six hours/night increased from 12% to 16%, while those sleeping for over eight hours decreased from 35% to 26% [19]. Obviously, we are marching toward a sleepless and chronopathological society [2].

Increasing evidence suggests that disrupted temporal organization impairs behavior, cognition, affect and emotion; furthermore, disruption of circadian clock genes impairs the sleep-wake cycle and social rhythms. Altogether, these alterations of physiological circadian function may be implicated in particular in mental disorders. Many studies demonstrated interactions between circadian oscillators *via* molecular clocks and the neural circuits subserving higher brain functions and behaviors crucially linked to mental health. In particular, disturbances in sleep and arousal, cognition and mood show close relationships to altered circadian rhythms [20]. A variety of mental disorders have been related to disturbances in the temporal organization of biological functions such as shift-work disorder, SAD, bipolar disorder including mania, major depression, nocturnal eating syndrome, schizophrenia, dementia and others [21].

The circadian model of depression

For more than two decades, evidence has been continuously increasing to suggest that a blunted amplitude of the circadian profile is the main chronobiological abnormality in depression [22]. Scientific debate has addressed several theoretical ways in which disrupted circadian rhythms might lead to depression [23]. On the one hand, alterations in biological clocks at the molecular level could lead to neurobiological dysfunction, which in turn may lead to the depressive state. On the other hand, a primary circadian disturbance of the sleep-wake cycle could lead to insomnia that may facilitate or exacerbate the depressed state. Moreover, unpredictable changes to an individual's circadian profile induced by chronic stress, life events or physical disease may alter the stability of the circadian system [24].

A "zeitgeber" is an exogenous (external) cue that synchronizes an organism's endogenous (internal) timekeeping system (clock) to the earth's 24-hour light/dark cycle. Changes in external time cues acting as zeitgebers may, in addition, further destabilize the thereby altered circadian system. As a result, desynchronization of the rhythmic features of biological and psychological function may cause the mental disease. From this evidence, one can conclude that the widely accepted biopsychosocial model of the pathophysiology of mental illness may be extended to include the important component of circadian rhythm alterations [25].

Depression, therefore, appears to be a circadian rhythm disorder in which biological function following rhythmic internally and externally generated time patterns are disturbed. This may be due to individual genetic disposition and a socially determined circadian profile that is particularly vulnerable to life events which, together with changes in environmental time cues, destabilizes the circadian homeostasis of body and mind (Figure 1).

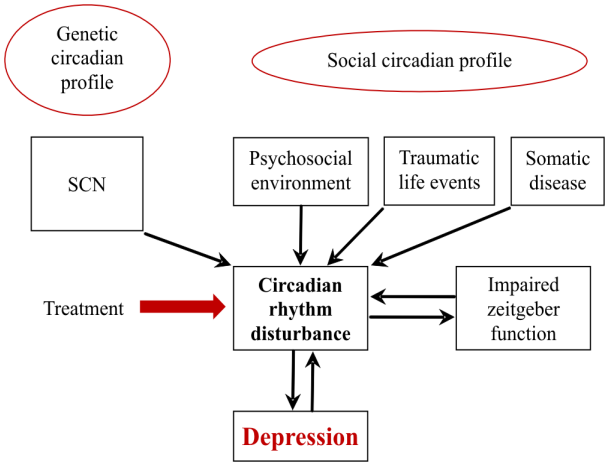

Figure 1 – ***The circadian model of depression [2].***

The clinical finding that depression-related symptoms include sleep-wake disorders with nocturnal insomnia and day-time sleepiness, lack of activity, loss of appetite and diurnal changes of mood has encouraged the idea that abnormalities in circadian rhythms may underlie the development of affective disorders. From the point of view of clinical psychiatrists, quite a number of depressive symptoms have a temporal pattern that parallels the circadian malfunction found in the biological parameters (Figure 2).

Beside symptoms of a disturbed sleep-wake cycle, diurnal variations in depressive symptoms appear to be central to the core of depression. Yet, longitudinal investigation of individual temporal pattern, regularity and relationship to clinical state and clinical improvement has revealed little homogeneity. Morning lows, afternoon slump, evening worsening can all occur during a single depressive episode. Mood variability or the propensity to produce mood swings appears to be the characteristic that most predicts the capacity to respond to treatment [26].

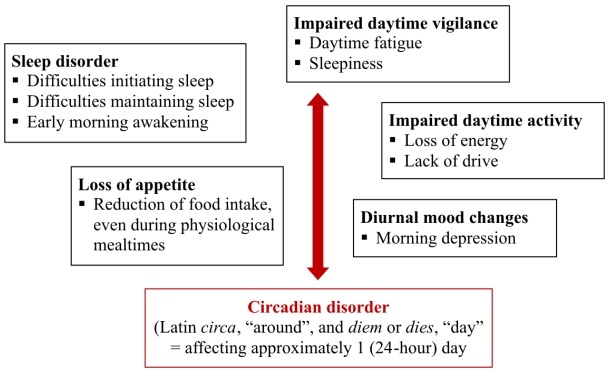

Figure 2 – ***Clinical signs of circadian dysregulation in depression [2].***

Neurobiology of circadian rhythm

In mammals, the master pacemaker controlling the generation and coordination of circadian rhythms is situated in the suprachiasmatic nuclei (SCN), which are two bilaterally paired groups of neurons, containing approximately 10 000 neurons each in the anteroventral hypothalamus situated just above the optic chiasm [27, 28]. Destruction of the SCN, either experimentally in laboratory animals or because of disease in humans, disrupts the ability to express any circadian rhythm [29].

The rhythms generated by the SCN are synchronized to a daily pattern by regularly recurring environmental stimuli ("zeitgebers") [30]. In usually environmental conditions, circadian biological clocks are reset daily to 24-hour astronomical time by the day/night cycle, through the influence of light, the main zeitgeber. Other environmental factors that can serve at zeitgebers are the availability of food, social schedules and social exchanges [31, 32].

Light stimuli arriving at the non-visual photoreceptive retinal ganglion cells are transmitted directly to the SCN by way of the retinohypothalamic tract, in which the putative neurotransmitter is glutamate (Figure 3).

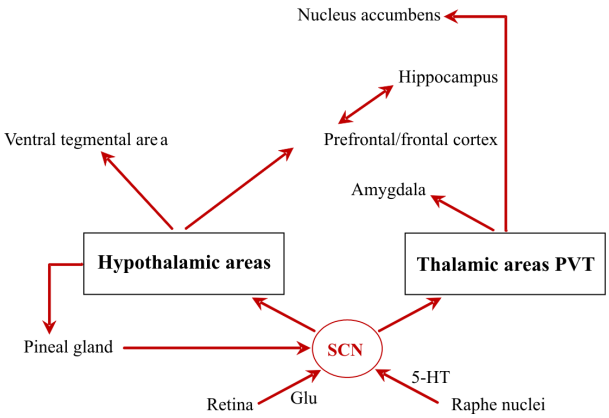

Figure 3 – ***Connections of the suprachiasmatic nuclei ([30] modified).***

Another pathway that indirectly conveys light stimuli to the SCN is the geniculohypothalamic tract. This pathway, in which the principal neurotransmitters are γ-amino butyric acid and neuropeptide Y, runs from the intergeniculate leaflet of the lateral geniculate complex. Moreover, the serotoninergic pathway from the raphe nuclei acts as a synchronizer of the SCN [33, 34]. Indeed, the SCN is one of the important target areas of serotonergic projections [35].

Serotonin (5-HT) is the principal neurotransmitter in the retino-raphe input pathway to the SCN. The serotonergic system in the SCN is involved in the mechanism of entrainment and rhythm modulation through its receptors, which respond to photic and non-photic stimuli and it thus plays a key role in circadian clock resetting. Binding studies have demonstrated the presence of different 5-HT receptors (5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C and 5-HT7) in the SCN with variable levels of expression [36]. In particular, a high concentration of 5-HT2C receptors has been reported [37]. *In situ* hybridization investigations in rats have reported that transcription of 5-HT2C messenger RNA is highest early in the morning, suggesting that 5-HT2C receptors also have a circadian rhythm of expression [38]. It was shown that 5-HT1A receptors, possibly with co-activation of 5-HT7 receptors, are implicated in the non-photic effects of the main clock. By contrast, 5-HT3 and 5-HT2C receptors are involved in photic-like effects and, for the 5-HT2C subtype only, in potentiation of photic resetting [34]. A recent study suggest that 5-HT with a rapid turnover rate plays an important role in the circadian rhythm of sleep–wake cycles [39]. 5-HT deficiency was induced through acute tryptophan depletion in rats by intraperitoneally injecting a tryptophan-degrading enzyme called tryptophan side chain oxidase I (TSOI).

The timing of external zeitgeber stimuli can phase-shift the SCN and this can have an important impact on circadian rhythms. For instance, light during the early part of the night causes a phase delay in the SCN, while light in the early morning causes a phase advance. Other zeitgebers, such as social activity and work schedules can also, either directly or indirectly, affect the SCN, as they influence the timing of food intake, physical exercise, light exposure and sleep. In the absence of external zeitgebers, individual express their endogenous period of circadian rhythms. This period is generally different from the 24-hour period and is called the free-running period [30]. Conditions without zeitgebers are, for instance, constant darkness or constant light in comparison with usually light and darkness alternation and a common example of the occurrence of this is in blind subjects. The free-running inherent rhythm of the SCN is slightly longer than 24 hours.

All of the aforementioned afferent pathways link the SCN to the daily changes in the external environment. In turn, the SCN act as the central pacemaker of the circadian system whereby daily rhythms are regulated according to external environmental changes. It was gradually discovered that the SCN communicates with other brain regions to impart or entrain circadian rhythmicity in physiological and behavioral processes. For example, sleep/wake cycles are modulated by an efferent pathway *via* the paraventricular nucleus of the hypothalamus and *via* a multisynaptic pathway to the pineal gland where melatonin is synthesized at night and suppressed by light during the day.

Melatonin, secreted by the pineal gland, transmits information about the occurrence and duration of darkness. During short winter days, the duration of nocturnal

melatonin secretion increases, whereas it decreases during long summer days [40, 41]. Moreover, melatonin itself has a zeitgeber function; in fact, melatonin, secreted under the hierarchical dependence of the SCN, influences the SCN in return by acting through specific receptors in this area [42]. Preclinical studies have demonstrated that, with respect to other areas in the brain, the SCN have a particularly high concentration of melatonergic MT1 and MT2 receptors, which are temporally expressed in a circadian manner. It has been shown that expression of the MT1 receptor is regulated by both light and the central pacemaker, with a peak level of gene transcription occurring during the middle of the night.

A major development in research has been the discovery that, beside the SCN, various other circadian clocks are present in organisms [43, 44]. We now know that various non-neuronal tissues and non-SCN brain regions (*e.g.*, hypothalamic nuclei, forebrain, olfactory bulb, pineal gland, cortex) contain autonomous oscillators and are capable of generating circadian rhythms when isolated from the organism and cultured *in vitro* [45, 46]. These peripheral oscillators (as opposed to the central SCN clock) relay on feedback loops composed of clock genes and proteins, just as in SCN clock. The diversity of secondary clocks in the brain, their specific sensitives to time-giving cues, as well as their differential coupling to the master SCN clock may allow more plasticity in the ability of the circadian timing system to integrate a wide range of temporal information. Furthermore, this rises the possibilities that pathophysiological alterations of internal timing that are deleterious for health may result from internal desynchronization within the network of cerebral clocks [30].

A novel SCN output pathway to the ventral tegmental area *via* the median preoptic nucleus has been recently described [47]. This projection may function as the circadian regulator of behavioral processes such as arousal and motivation, further linking well-known behavioral observations to reward-related actions and circadian rhythmicity. Another example of a circadian regulator is the hippocampus, pivotal in the neuroplasticity, learning and memory processes, which shows rhythmic gene expression relatively independent of the SCN [48].

Intracellular clock mechanisms and the pathogenesis of depression

The fact that a wide variety of endogenous rhythms are disrupted in individuals with depression has led to speculation that such disturbances are not unique to specific rhythms, but are associated, instead, with a disruption in the activity of the circadian master pacemaker in the SCN. Therefore, it is plausible that alterations of the molecular components of the endogenous clock system play a role in the disturbed circadian rhythms of depressed patients. The cellular machinery behind the circadian timing within the SCN neurons has been largely identified and is believed to be under genetic control.

Genes and coding essential elements of the clock include period (per1, per2, per3), neuronal PAS domain protein-2 (NPAS2), circadian locomotor output cycles kaput (CLOCK), cryptochrome (Cry1, Cry2) and brain and muscle ARNT-like-1 (bmal1) genes. The proteins encoded by these genes are part of a circadian auto-regulatory loop incorporating activators and suppressors of genes, whose activity thereby oscillates with a circadian period, thus generating the endogenous rhythmicity of SCN neurons [49].

Light acts through the retina and direct neural pathways to the SCN to stimulate per1 and per2 gene expression (Figure 4).

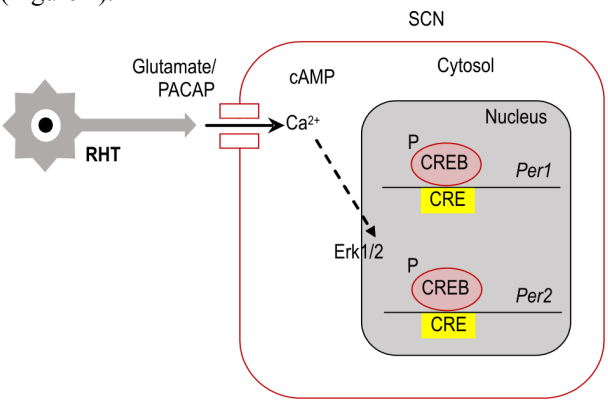

Figure 4 – ***Molecular regulation of the light signal to the suprachiasmatic nuclei [30]. RHT: Retino-hypothalamic tract; PACAP: Pituitary adenylate cyclase-activating peptide; Erk: Mitogen activated protein kinase; CREB: Cyclic AMP response element binding.***

Whereas the genes coding for Clock and Bmal1 are turned on permanently, expression of per genes is rhythmic, being highest in the first part of the day before being suppressed later [50]. Light transmission to the SCN *via* the retino-hypothalamic tract, mainly through glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) leads to activation of the N-methyl-D-aspartic acid (NDMA) and metabotropic glutamate (mGLU), PAC1 and VPAC2 receptors, resulting in membrane depolarization and an influx of Ca^{2+} into targeted SCN neurons [51].

Both animal and human studies have provided preliminary evidence of a role for circadian genes in mood disorders. Mice carrying a mutation in the CLOCK gene display a behavioral profile that is strikingly similar to human mania, including hyperactivity, decreased sleep, reduced depression-like behavior, lower anxiety and an increase in the reward value for cocaine, sucrose and medial forebrain bundle stimulation. Interestingly, many of those mania-like behaviors are reverted by chronic lithium administration and are rescued by expressing a functional CLOCK protein specifically in the ventral tegmental area of CLOCK mutant mice [52].

Studies in humans have become to identify polymorphisms in certain circadian genes that are associated with mood disorders and, in particular, bipolar disorder. The T3111C single nucleotide polymorphism (SNP) of the CLOCK gene has been investigates in both major depression and bipolar disorder. Whereas no differences were found in allelic frequencies between individuals with a history of major depression and healthy controls, the CC genotype has been associated with a greater severity of insomnia during antidepressant treatment, a higher recurrence of bipolar episodes and a reduced need for sleep in bipolar patients [53, 54].

In a family-based sample of bipolar patients, an analysis of 46 SNPs in eight CLOCK genes revealed a significant,

although modest association of Bmal1 and TIM genes with the mood disorder [55]. An independent study using haplotype analysis confirmed the association of bipolar disorder with the Bmal1 gene and detected a new association with the per3 gene [56]. Recent studies suggest that SNPs of per2, NPAS2 and Bmal1 genes are associated with an increased risk for SAD; furthermore, certain allelic combinations of SNPs of these three genes have an additive effect, increasing the risk of developing SAD by 4.43 over other genotypes and 10.67 over the most protective genotype [57].

Based on the above findings, it could be suggested that primary or secondary alterations of the biological clock at the molecular level could lead to disruptions in endogenous circadian rhythms, which in turn may generate the depressed state. Alternatively, it has been proposed that instead of or in addition to molecular abnormalities of the endogenous pacemaker, disturbances in environmental zeitgebers may cause depressive symptoms in biologically predisposed individuals [58].

This social zeitgeber theory specifically postulates that depressive episodes arise at a consequence of life events causing a disturbance of social zeitgebers (*i.e.*, social factors such as the timing of meals, work schedules, social demands, personal relationships) which, in turn, derail an individual's social rhythms. These disruptions can place substantial stress on the body's capacity to maintain stable biological rhythms, particularly sleep-wake, energy, alertness and appetite rhythms. Whereas in most individuals such rhythma will restabilize shortly after the destabilizing events, in predisposed subjects, they may precipitate a major depressive episode [9].

The expression of most rhythms at the behavioral, physiological and biochemical level is regulated by the integration of inputs from the circadian clock and the sleep-wake state of the organism [59]. Thus, the circadian and sleep control centers have evolved together to ensure a timely coordination between the internal and external environment in order to optimize the survival of the species. Therefore, it could be that a primary circadian disturbance of the sleep-wake cycle leads to insomnia that may desynchronize many endogenous rhythms, which then, in turn, may lead to a depressed state [9].

In support of this latter view, evidence has been provided that insomnia is a risk factor for the development of depression, as well as for relapse and recurrence [60]. Most of the circadian abnormalities observed in the depressed state normalize with recovery, therefore it cannot be excluded that they arise as consequence of depression and do not represent the primary determinants of the affective disorder. However, even if so, the presence of disrupted endogenous rhythms might potentially contribute to the maintenance of depressive symptoms and might affect the course and/or the prognosis of the affective episode. Therefore, circadian abnormalities of depressed patients are worthy of clinical and therapeutic consideration [61].

Psychotherapeutic and psychosocial interventions

Successful psychological treatment involves a combination of information about sleep and good sleep habits, behavioral techniques and cognitive therapy, focusing on negative automatic thoughts about sleeping [62].

There is evidence from studies of primary insomnia that cognitive behavioral therapy (CBT) results in improvement that are substantial as those of pharmacotherapy with sedative-hypnotics [63]. The greatest advantage of CBT is that its effectiveness is more durable than that of pharmacotherapy and the benefits persist after therapy is terminated [64]. CBT has also been reported to be efficient in the management of depression [65]. Further research, however, is needing regarding the efficacy of CBT associated with antidepressant therapy for insomniac patients with major depressive disorder [66].

CBT is carried out by trained therapists and aims to change thinking so that not sleeping does not give rise to arousing negative thoughts. These thoughts are common in patients with insomnia; for instance, thinking that they will fail to perform well at work the next day because they are not asleep now [3]. During the rehearsal and planning session, patients are encouraged to set aside a short period (about 15 minutes) in the early evening, after their evening meal, in which they can review the day's activities, write down their achievements and plans and write down positive steps to be taken the next day to resolve problems. No actual work should be done, just planning. Paradoxical intent is sometimes offered as a strategy that patients can try, meaning remaining awake in a comfortable bed in the dark. Concentrating on this can sometimes allow sleep to occur. However, chronic long-term insomnia may not respond to this approach. Care should be taken to identify and treat depressive and anxiety disorders in this group of patients (Figure 5).

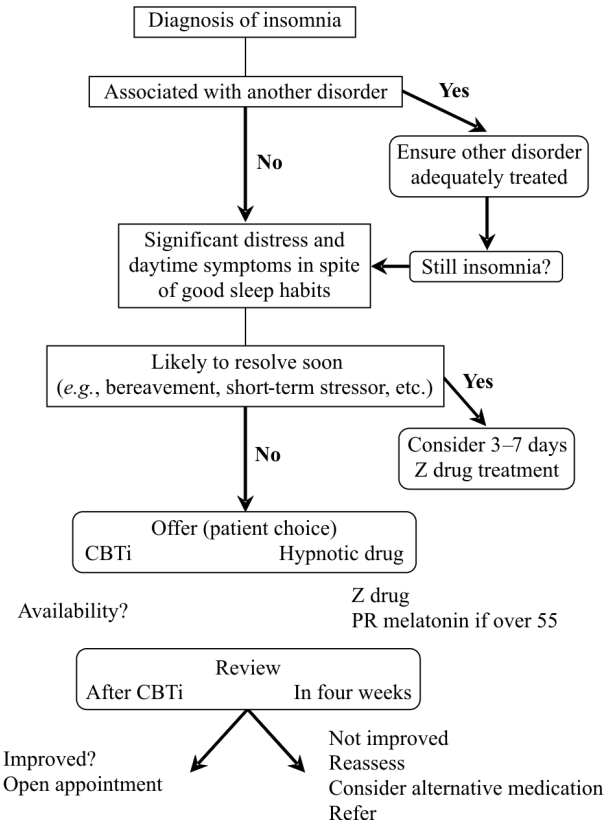

Figure 5 – ***Treatment algorithm from the British Association for Psychopharmacology consensus guidelines for treatment of insomnia (2010).***

Stimulus control seeks to minimize environmental cues that may inhibit sleep or strengthen associations in the mind between being in bed and being awake. Sleep restriction technique aims to increase sleep efficiency (time asleep as a percentage of time in bed). Patients are encouraged to assess how much time on average they have actually slept, say during the past week and then aim to restrict their time in bed to that period. Therefore, if they get only five hours of sleep a night, they choose a preferred getting up time and must then not try to sleep until five hours before that time (their new bedtime). They need to use an effective alarm clock for the preferred waking time and reinforce this with help from family members, if necessary. Thus, sleep efficiency is increased and eventually the time in bed may be increased gradually. This takes a lot of planning; usually, less than five hours in bed is not recommended and the technique can cause increased daytime problems for a while, so it is needed to be carefully supervised by a trained health professional.

Behavioral modification of social rhythms may help in the treatment of depression. Frank *et al.* developed the *Interpersonal and Social Rhythm Therapy* (IPSRT) *Intervention Program*, in order to establish regular social rhythm regularity (having regular bed, wake and meal times, switching to a more regular work schedule and incorporate a regular daily exercise session). IPSRT reduces the risk of recurrence in bipolar patients, regularizes social rhythms, accelerates remission in depressed patients and lowers relapse rates. These effects are comparable with those of intensive pharmacotherapy [67]. Further studies should determine whether IPSRT should be used alone or as an adjunctive treatment in major depression [68].

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All authors have an equal contribution.

References

[1] Mendlewicz J. Time in depression. Medicographia, 2010, 32(2):109–111.

[2] Hajak G, Landgrebe M. Time and depression: when the internal clock does not work. Medicographia, 2010, 32(2):146–151.

[3] Wilson S, Nutt DJ. Sleep disorders. 2nd edition, Oxford Psychiatry Library Series, Oxford University Press, 2013, 4–5, 29–31, 65–66.

[4] Turner J, Drummond LM, Mukhopadhyay S, Ghodse H, White S, Pillay A, Fineberg NA. A prospective study of delayed sleep phase syndrome in patients with severe resistant obsessive-compulsive disorder. World Psychiatry, 2007, 6(2):108–111.

[5] Van Cauter E, Turek FW. Depression: a disorder of time-keeping? Perspect Biol Med, 1996, 29:510–519.

[6] Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms, 2003, 18(1):80–90.

[7] Casper RC, Redmond DE Jr, Katz MM, Schaffer CB, Davis JM, Koslow SH. Somatic symptoms in primary affective disorder. Presence and relationship to the classification of depression. Arch Gen Psychiatry, 1985, 42(11):1098–1104.

[8] Riemann D, Berger M, Voderholzer U. Sleep and depression – results from psychobiological studies: an overview. Biol Psychol, 2001, 57(1–3):67–103.

[9] Monteleone P, Maj M. Circadian rhythm disturbances in depression: implications for treatment and quality of remission. Medicographia, 2009, 31(2):132–139.

[10] Thase ME, Carpenter L, Kupfer DJ, Frank E. Clinical significance of reversed vegetative subtypes of major depression. Psychopharmacol Bull, 1991, 27(1):17–22.

[11] Buysse DJ, Frank E, Lowe KK, Cherry CR, Kupfer DJ. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. Biol Psychiatry, 1997, 41(4):406–418.

[12] Knowles JB, Cairns J, MacLean AW, Delva N, Prowse A, Waldron J, Letemendia FJ. The sleep of remitted bipolar depressives: comparison with sex and age-matched controls. Can J Psychiatry, 1986, 31(4):295–298.

[13] Thase ME, Fasiczka AL, Berman SR, Simons AD, Reynolds CF 3rd. Electroencephalographic sleep profiles before and after cognitive behavior therapy of depression. Arch Gen Psychiatry, 1998, 55(2):138–144.

[14] Kupfer DJ, Frank E, McEachran AB, Grochocincki VJ. Delta sleep ratio. A biological correlate of early recurrence in unipolar affective disorder. Arch Gen Psychiatry, 1990, 47(12): 1100–1105.

[15] Levitan RD. The chronobiology and neurobiology of winter seasonal affective disorder. Dialogues Clin Neurosci, 2007, 9(3):315–324.

[16] Avery DH, Dahl K, Savage MV, Brengelmann GL, Larsen LH, Kenny MA, Eder DN, Vitiello MV, Prinz PN. Circadian temperature and cortisol rhythms during a constant routine are phase-delayed in hypersomnic winter depression. Biol Psychiatry, 1997, 41(11):1109–1123.

[17] Schwartz PJ, Rosenthal NE, Turner EH, Drake CL, Liberty V, Wehr TA. Seasonal variation in core temperature regulation during sleep in patients with winter seasonal affective disorder. Biol Psychiatry, 1997, 42(2):122–131.

[18] Basner M, Fomberstein KM, Razavi FM, Banks S, William JH, Rosa RR, Dinges DF. American time use survey: sleep time and its relationship to waking activities. Sleep, 2007, 30(9): 1085–1095.

[19] ***. National Sleep Foundation, USA. http://www.sleepfoundation.org/.

[20] Benca R, Duncan MJ, Frank E, McClung C, Nelson RJ, Vicentic A. Biological rhythms, higher brain function, and behavior: gaps, opportunities and challenges. Brain Res Rev, 2009, 62(1):57–70.

[21] Lamont EW, Legault-Coutu D, Cermakian N, Boivin DB. The role of circadian clock genes in mental disorders. Dialogues Clin Neurosci, 2007, 9(3):333–342.

[22] Mendlewicz J. Circadian rhythms and depression. Current understanding and new therapeutic perspectives. Wolters Kluwer Health, Paris, 2008, 71–85.

[23] Monteleone P, Maj M. The circadian basis of mood disorders: recent developments and treatment implications. Eur Neuropsychopharmacology, 2008, 18(10):701–711.

[24] Srinivasan V, Pandi-Perumal SR, Trakht I, Spence DW, Hardeland R, Poeggeler B, Cardinali DP. Pathophysiology of depression: role of sleep and the melatonergic system. Psychiatry Res, 2009, 165(3):201–214.

[25] Engel GL. The need for a new medical model: a challenge for biomedicine. Science, 1977, 196(4286):129–136.

[26] Wirz-Justice A. Diurnal variation of depressive symptoms. Dialogues Clin Neurosci, 2008, 10(3):337–343.

[27] Antle MC, Silver R. Orchestrating time: arrangements of the brain circadian clock. Trends Neurosci, 2005, 28(3):145–151.

[28] Herzog ED. Neurons and networks in daily rhythms. Nat Rev Neurosci, 2007, 8(10):790–802.

[29] Cermakian N, Boivin DB. The regulation of central and peripheral circadian clocks in humans. Obes Rev, 2009, 10(Suppl 2):25–36.

[30] Tardito D, Racagni G, Popoli M. Time in the brain: rhythms of intercellular and intracellular processes. Medicographia, 2010, 32(2):152–158.

[31] Van der Zee EA, Boersma GJ, Hut RA. The neurobiology of circadian rhythms. Curr Opin Pulm Med, 2009, 15(6):534–539.

[32] Mrosovsky N. Locomotor activity and non-photic influences on circadian clocks. Biol Rev Camp Philos Soc, 1996, 71(3): 343–372.

[33] Moore RY, Speh JC. Serotonin innervation of the primate suprachiasmatic nucleus. Brain Res, 2004, 1010(1–2):169–173.

[34] Cuesta M, Clesse D, Pévet P, Challet E. New light on the serotonergic paradox in the rat circadian system. J Neurochem, 2009, 110(1):231–243.

[35] Morin LP. Serotonin and the regulation of mammalian circadian rhythmicity. Ann Med, 1999, 31(1):12–33.
[36] Pickard GE, Rea MA. Serotonergic innervation of the hypothalamic suprachiasmatic nucleus and photic regulation of circadian rhythms. Biol Cell, 1997, 89(8):513–523.
[37] Moyer RW, Kennaway DJ. Immunohistochemical localization of serotonin receptors in the rat suprachiasmatic nucleus. Neurosci Lett, 1999, 271(3):147–150.
[38] Holmes MC, French KL, Seckl JR. Dysregulation of diurnal rhythms of serotonin 5-HT2C and corticosteroid receptor gene expression in the hippocampus with food restriction and glucocorticoids. J Neurosci, 1997, 17(11):4056–4065.
[39] Nakamaru-Ogiso E, Miyamoto H, Hamada K, Tsukada K, Takai K. Novel biochemical manipulation of brain serotonin reveals a role of serotonin in the circadian rhythm of sleep-wake cycles. Eur J Neurosci, 2012, 35(11):1762–1770.
[40] Pandi-Perumal SR, Srinivasan V, Maestroni GJ, Cardinali DP, Poeggeler B, Hardeland R. Melatonin: nature's most versatile biological signal? FEBS J, 2006, 273(13):2813–2838.
[41] Stehle JH, von Gall C, Korf HW. Melatonin: a clock-output, a clock-input. J Neuroendocrinol, 2003, 15(4):383–389.
[42] Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. Pharmacol Rep, 2009, 61(3):383–410.
[43] Guilding C, Piggins HD. Challenging the omnipotence of the suprachiasmatic timekeeper: are circadian oscillators present throughout the mammalian brain? Eur J Neurosci, 2007, 25(11): 3195–3216.
[44] Mendoza J, Challet E. Brain clocks: from the suprachiasmatic nuclei to a cerebral network. Neuroscientist, 2009, 15(5):477–488.
[45] Reick M, Garcia JA, Dudley C, McKnight SL. NPAS2: an analog of clock operative in the mammalian forebrain. Science, 2001, 293(5529):506–509.
[46] Abe M, Herzog ED, Yamazaki S, Straume M, Tei H, Sakaki Y, Menaker M, Block GD. Circadian rhythms in isolated brain regions. J Neurosci, 2002, 22(1):350–356.
[47] Luo AH, Aston-Jones G. Circuit projection from suprachiasmatic nucleus to ventral tegmental area: a novel circadian output pathway. Eur J Neurosci, 2009, 29(4):748–760.
[48] Wang LMC, Dragich JM, Kudo T, Odom IH, Welsh DK, O'Dell TJ, Colwell CS. Expression of the circadian clock gene Period2 in the hippocampus: possible implications for synaptic plasticity and learn behavior. ASN Neuro, 2009, 1(3).
[49] Laposky AD, Shelton J, Bass J, Dugovic C, Perrino N, Turek FW. Altered sleep regulation in leptin-deficient mice. Am J Physiol Regul Integr Comp Physiol, 2006, 290(4):R894–R903.
[50] Gillette MU, Mitchell JW. Signaling in the suprachiasmatic nucleus: selectively responsive and integrative. Cell Tissue Res, 2002, 309(1):99–107.
[51] Jakubcakova V, Oster H, Tamanini F, Cadenas C, Leitges M, van der Horst GT, Eichele G. Light entrainment of the mammalian circadian clock by a PRKCA-dependent post-translational mechanism. Neuron, 2007, 54(5):831–843.
[52] Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, Chakravarty S, Peevey J, Oehrlein N, Birnbaum S, Vitaterna MH, Orsulak P, Takahashi JS, Nestler EJ, Carlezon WA Jr, McClung CA. Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci U S A, 2007, 104(15):6406–6411.
[53] Desan PH, Oren DA, Malison R, Price LH, Rosenbaum J, Smoller J, Charney DS, Gelernter J. Genetic polymorphism at the CLOCK gene locus and major depression. Am J Med Genet, 2000, 96(3):418–421.
[54] Serretti A, Benedetti F, Mandelli L, Lorenzi C, Pirovano A, Colombo C, Smeraldi E. Genetic dissection of psychopathological symptoms: insomnia in mood disorders and CLOCK gene polymorphism. Am J Med Genet B Neuropsychiatr Genet, 2003, 121B(1):35–38.
[55] Mansour HA, Wood J, Logue T, Chowdari KV, Dayal M, Kupfer DJ, Monk TH, Devlin B, Nimgaonkar VL. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. Genes Brain Behav, 2006, 5(2):150–157.
[56] Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, McElroy SL, Keck PE Jr, Schork NJ, Kelsoe JR. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet, 2006, 141B(3):234–241.
[57] Partonen T, Treutlein J, Alpman A, Frank J, Johansson C, Depner M, Aron L, Rietschel M, Wellek S, Soronen P, Paunio T, Koch A, Chen P, Lathrop M, Adolfsson R, Persson ML, Kasper S, Schalling M, Peltonen L, Schumann G. Three circadian CLOCK genes Per2, ARNTL and NPAS2 contribute to winter depression. Ann Med, 2007, 39(3):229–238.
[58] Ehlers CL, Frank E, Kupfer DJ. Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. Arch Gen Psychiatry, 1988, 45(10): 948–952.
[59] Turek FW. From circadian rhythms to clock genes in depression. Int Clin Psychopharmacol, 2007, 22(Suppl 2):1–8.
[60] Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. Am J Epidemiol, 1997, 146(2):105–114.
[61] Dombrovski AY, Mulsant BH, Houck PR, Mazumdar S, Lenze EJ, Andreescu C, Cyranowski JM, Reynolds CF 3rd. Residual symptoms and recurrence during maintenance treatment of late-life depression. J Affect Disord, 2007, 103(1–3): 77–82.
[62] Espie CA, MacMahon KM, Kelly HL, Broomfield NM, Douglas NJ, Engleman HM, McKinstry B, Morin CM, Walker A, Wilson P. Randomized clinical effectiveness trial of nurse-administered small-group cognitive behavior therapy for persistent insomnia in general practice. Sleep, 2007, 30(5):574–584.
[63] Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, Buysse DJ. Comparative meta-analysis of pharmacotherapy and behavioral therapy for persistent insomnia. Am J Psychiatry, 2002, 159(1):5–11.
[64] Morin CM. Insomnia treatment: taking a broader perspective on efficacy and cost-effectiveness issues. Sleep Med Rev, 2004, 8(1):3–6.
[65] Feldman G. Cognitive behavioral therapies for depression: overview, new directions and practical recommendations for dissemination. Psychiatr Clin North Am, 2007, 30(1):39–50.
[66] Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. Clin Psychol Rev, 2005, 25(5):559–592.
[67] Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski V, Houck P, Scott J, Thompson W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry, 2005, 62(9):996–1004.
[68] Germain A, Frank E. Chronobiology of the core symptoms of depression. Medicographia, 2008, 30(1):30–34.

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