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# Features of Circadian Rhythms in Patients with Cerebrovascular Diseases

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Additional information is available at the end of the chapter

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## Abstract

The chapter describes in detail the pathogenetic role of desynchronization in the development of cerebrovascular diseases (CVD). The data of domestic and foreign literature on the study of desynchronization are presented. The role of melatonin in the regulation of circadian rhythms (CR) is shown. Pathological changes in CR affect sleep disturbance, emotional and cognitive disorders. It is demonstrated the need of the further study of the prevalence and structure of desynchronization in patients with CVD. The search of the most significant factors of desynchronization development in patients with vascular diseases is of great scientific and practical significance. The importance of creating and introducing diagnostic and therapeutic algorithms for chronodiagnostics and chronotherapy of CVD into everyday practical activities. The effectiveness of melatonin for the normalization of sleep and CR in patients with insomnia, acute stroke, depressive disorders is shown. Complex therapy of the patients with CVD taking into account chronobiological disorders allows to eliminate the adverse effect of sleep disorders and CR on the regulation of the cardiovascular system and improve the efficiency of rehabilitation.

**Keywords:** circadian rhythms, desynchronization, chronobiology, SCN, melatonin, cerebrovascular disease, stroke, sleep disorders, cognitive disorders, phototherapy, chronodiagnostic, chronotherapy

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## 1. Introduction

Physiological processes in living systems undergo rhythmic fluctuations, called biological rhythms. Among the great variety of biological rhythms in maintaining the health and functioning of the organism, circadian rhythms (CR) with a period of oscillations of about 24 hours are particularly important. Evolutionally formed synchronization of the CR as an indicator of

internal and external synergism, indicates a health status [1]. In the case of discrepancy of the CR, there is desynchronization – a form of circadian pathology, a nonspecific manifestation of pathological conditions characterized by changes in the structure of the rhythm: an increase (decrease) in amplitude; inversion of acrophases; change the duration of the period [2]. The manifestation of many diseases, such as myocardial infarction, stroke, sudden death, etc., is closely associated with certain periods of the day [3–5]. The diurnal rhythms of biochemical processes and physiological functions are synchronized in time, or synchronous. Thus, the number of heart rate (HR) and respiration rate are correlated as 4:1 (72:18, 80:20), that ensures optimal oxygen supply to tissues and is consistent with the rhythms of metabolism. There are several theories about the nature of endogenous factors. In 1976, the chronohypothesis was developed. According to it there is a site in the DNA structure – “chronon,” controlling biorhythms. According to the multi-oscillator model of biorhythms, there are many drivers of rhythm-pacemakers in the body [6].

External factors of general synchronization include geophysical factors: photoperiods (day-night), fluctuations in the geomagnetic field of the Earth, changes in the temperature of the environment, etc. For a modern person, the change in the phylogenetically formed stereotype under the influence of social factors is very important [7].

In the process of evolution, complex mechanisms of nervous and humoral regulation of biorhythms, their optimal synchronization were developed. The launching of circadian oscillations and their interconnection is carried out by the activity of the central nervous mechanism performing the pacemaker function, which is realized through the humoral regulating link [2]. Light is the main factor that determines the activity of suprachiasmatic nuclei (SCN) as a biological clock. The information on the light mode is fed into the SCN from the retina of the eye. They also receive signals from other parts of the brain (afferent inputs) and send impulses to various brain structures (efferent inputs) [8].

Through the efferent pathways, the SCN are involved in the regulation of the rhythmic activity of the endocrine system, blood circulation, eating behavior and other functions. Another structure important for the rhythmic organization of functions is the epiphysis – neuroendocrine transducer, an organ that transmits information about the illumination of the environment from the nervous system to the endocrine. Biologically active substance-melatonin is synthesized in epiphysis cells [9].

There are different methods for detecting biorhythmological personality: measuring body temperature, blood pressure, heart rate, breathing, sleep-wake cycle, metabolic rate during the day, determining the level of melatonin in the blood or its metabolites in saliva or urine [10]. The prevalence of sleep and wakefulness disturbances in patients with cardiovascular diseases (CVD) is very high. After a stroke, patients often experience sleep disorders such as insomnia, daytime sleepiness, fatigue, behavioral disturbances in the sleep phase with rapid eye movements and the restless legs syndrome, obstructive sleep apnea syndrome [11–16].

To detect sleep disorders, semi-quantitative scales and questionnaires, polysomnography are used [10]. Examination of Daily blood pressure and Holter monitoring of ECG allow to establish violations of daily dynamics of blood pressure and heart rate. Holter monitoring of ECG

enables to evaluate the circadian index (CI), which is an informative method for assessing circadian diurnal fluctuations in the heart rhythm [17].

The study of CR in patients with CVD has a great practical interest, since CRs are highly sensitive to various types of external influences and their disturbances can be the first symptoms of beginning abnormalities in the vital activity of the organism. There is a lot of data on the existence of chronobiological patterns in the development of stroke and myocardial infarction [11–16, 18–26].

The great scientific and practical interest is the study of the chronotropic activity of melatonin, the leading biochemical marker of CR. There is clear CR of melatonin production in the epiphysis and suppression of its secretion in the light [8].

The role of melatonin in the regulation of diurnal fluctuations of blood pressure is proved [27]. It has anti-inflammatory and antioxidant, as well as possible epigenetic activity [28, 29]. A number of studies have shown the effectiveness of melatonin for normalizing sleep and circadian rhythms in patients with insomnia, acute stroke, depressive disorders, arterial hypertension, etc. [29–35]. Chronotropic or rhythm-organizing activity of melatonin determines the origin of two leading, official indications for its use: treatment of sleep disorders and desynchronosis [29, 31, 36].

The analysis of published data shows the high scientific and practical relevance of further study of chronobiological disorders in patients with diseases of the cardiovascular system. It allows to reveal the pathogenetic relationship of comorbidity of disorders and to substantiate complex approaches to therapy [37–39].

## **2. Morphofunctional, molecular, genetic and biochemical basis of circadian rhythm regulation**

### **2.1. Morphofunctional features of suprachiasmatic nuclei and their connections with epiphysis**

**Circadian rhythms (CR)** are physiological and behavioral cycles, which are provided by the internal oscillator and remain in the absence of an external “regulator”. The ability to maintain a 24-hour rhythm is a fundamental characteristic of a circadian system that allows the body to adapt to environmental conditions [1].

*Circadian system operates due to four key components:*

1. Photosensitive retinal neurons and retinohypothalamic tract through which light signals come from the environment;
2. Internal circadian oscillator, generating rhythms and synchronizing them with the environment;
3. Signal paths transmitting information from the central regulator to peripheral rhythm generators;
4. Peripheral rhythm generators – clock-genes and proteins in peripheral cells [10].

The central circadian oscillator is the suprachiasmatic nuclei of the hypothalamus (SCN), which are heterogeneous in structure and neurochemical organization and are subdivided into the rostral and caudal divisions [8, 9].

Most of the SCN neurons are GABA and secrete different peptide neurotransmitters. GABA provides a link between the neuronal populations of the ventral and dorsal sections of the SCN. It participates in stabilizing the activity of the SCN and maintaining high-frequency oscillations of neurons in the CR. Many of the individual SCN neurons exhibit electrical and molecular rhythms in isolation, but the rhythms are weaker and less stable [8–10].

It is found, that light stimuli trigger the intra- and intercellular cascade of gene expression first in the center of the SCN, whence elements of peripheral parts are involved in the process through the GABA-ergic signaling pathways. Specific neuropeptides, gap junctions, astrocytes and GABA-ergic signaling realize interrelation between the SCN neurons. Vasoactive intestinal peptide (VIP) and arginine-vasopressin (AV), involved in the regulation of rhythms, are most studied. Studies show that VIP maintains and synchronizes rhythms of the SCN, while AV participates in maintaining high amplitude of the output signal from the SCN and in re-input pulse modulation [8–10].

Rhythmicity and synchronism of the nuclei operation in the diurnal regime is maintained in this way. The physiological role of the SCN, which reduces to the generation of circadian signals and the subordination of the activity of neighboring brain structures and peripheral organs, is entirely determined by the nature of their afferent and efferent connections [8].

Among the afferent projections of the SCN, the retinohypothalamic tract, which provides the nucleus with information about the state of photoperiodic processes, is of particular importance. It transmits to the SCN the main stream of optical impulses and is represented by collaterals of retinal ganglion cells. Its damage affects the dynamics of the CR in the form of a phase shift [8].

Another significant afferent input for SCN is the ascending axons of the neurons of the seam nuclei projecting here. The existence of direct raphohypothalamic tracts explains the high content of serotonin in the SCN. The electrical stimulation of the seam nuclei clearly inhibits the rhythmic of the hypothalamic neurons. In experiments on isolated SCN neurons, agonists and antagonists of serotonin receptors when applied locally, simulating the effect of light, were shown to be able to shift the phase of CR cells [8, 9].

The SCN forms neural connections with the nuclei of the stem, responsible for the regulation of sleep and wakefulness processes [10]. The SCN have direct connections with supraventricular and preoptic regions, dorsomedial divisions of the hypothalamus, arcuate and paraventricular nuclei. The direct and inverse relations of the SCN with the various elements of the limbic system and the motor centers have great functional significance. In particular, some nuclei of the amygdala and septa are projected onto the SCN [40].

A special place in the temporal organization of adequate adaptive behavior and the genesis of affective disorders is attributed to the interaction of the SCN with the **epiphysis and emotiogenic limbic structures**. Epiphysis is an important relay station and the leading link in the realization of circadian signals in relation to different functional indicators [8, 9].

The SCN almost entirely determines dependence of brain activity on the state of external illumination. During the day, light entering the retina activates its photosensitive ganglion cells, the information from which is transmitted through the retinohypothalamic tract and further into the SCN. Signals from the SCN are transmitted to the paraventricular nucleus of the hypothalamus, and further, through the intermediolateral column of the spinal cord, reach the upper cervical ganglion. Sympathetic postganglionic noradrenergic fibers innervate melatonin-secreting cells in the epiphysis. Norepinephrine acts on postsynaptic beta-1 and alpha-1-adrenergic receptors in the cells of the epiphysis, which trigger the synthesis of **melatonin**. There is a clear daily periodicity: the production of melatonin begins with the onset of darkness, reaches a maximum at midnight and stops in the light. In the light phase of the day, this process is replaced by an increased synthesis of **serotonin** [7, 8, 41].

There are reciprocal relationships between the SCN and the epiphysis, and melatonin is able to make certain corrections to circadian dysrhythmia, including inhibiting the discharges of SCN neurons. Under the influence of melatonin, the CR phase shift is also described in humans, which allowed recommending it for the correction of latitudinal desynchronization [29, 41].

By obeying the signals of the SCN, the epiphysis through melatonin can directly interfere with the functional activity of the limbic structures of the brain. Hyperactivity of the latter causes the development of dysrhythmia, accompanied by an increased level of anxiety. With steady stressing, the anxiety transforms into a depressive state. The SCN due to its direct efferent projections into the subcortical limbic nuclei, and indirectly (via melatonin) limits hippocampal excitability. Probably, this is one of the ways to realize anti-anxiety properties of the epiphyseal hormone. Thus, the disturbance of the interaction of SCN with the epiphysis is one of the pathogenetic factors of anxiety and depression [42, 43].

In addition to managing the CR of the psychoemotional state, along with other circadian fluctuations, the SCN provide regulation of the basal cycle of calm-activity. It is known, the patients with depression are characterized by night sleep disturbance and phase structure of sleep disorder. One of the probable causes is legitimately sought in violation of the normal activity of the central pacemaker. It has been established that the SCN lesion in animals along with other CR disturbance significantly disturbs the sleep [42, 43]. Insomnia in humans is often combined with neurodegenerative pathology (Alzheimer's disease (AD), etc.), which is usually accompanied by the SCN lesion. On the other hand, a rhythmic change in the states of sleep and wakefulness is quite an autonomous process and persists in people deprived of external time sensors, which emphasizes the dependence of sleep on the activity of the leading pacemaker [44–48].

According to modern concepts, the periodic nature of the sleep-wake cycle is determined by the co-operation of the brainstem formations in the ascending awakening system of the brain and the hypnogenic pathways, the impulse from which, following to the forebrain, along with other structures, involves ventrolateral preoptic nuclei. The latter provide alternating excitation of activating and inactivating (hypnogenic) mechanisms with rhythmic change of sleep and wakefulness states during 24 hours, demonstrating a switching function. The weakness of the rhythm-organizing properties of the SCN can be determined by the pathological reorganization of intranuclear processes at the molecular level. An important reason for this is often the changes in the circadian oscillations of the clock genes [49, 50].

## 2.2. Molecular mechanisms of circadian oscillations

The molecular basis for the CR regulation is provided by the hour genes, whose work is carried out on the principle of loops of positive and negative feedback. The BMAL1 and CLOCK proteins accumulated during the day form the BMAL1/CLOCK complex. The BMAL1/CLOCK dimer activates the transcription of the PER genes (PER1, PER2, PER3) and CRY (CRY1, CRY2). Synthesized PER and CRY proteins also form a PER/CRY dimer acting on the principle of negative feedback. PER/CRY moves to the cell nucleus and inhibits the activity of the BMAL1/CLOCK complex, which leads to a decrease in the expression of PER and CRY proteins. During the night, the PER/CRY complex is destroyed, and the 24-hour cycle begins anew [49, 50].

Another clock gene involved in the regulation of this cycle is REV-ERB-alpha. The BMAL1/CLOCK complex activates the transcription of the gene, which leads to the accumulation in the cell of the protein REVERB-alpha. The REVERB-alpha protein in turn inhibits the transcription of the BMAL1 gene and presumably the CLOCK and CRY1 genes [51].

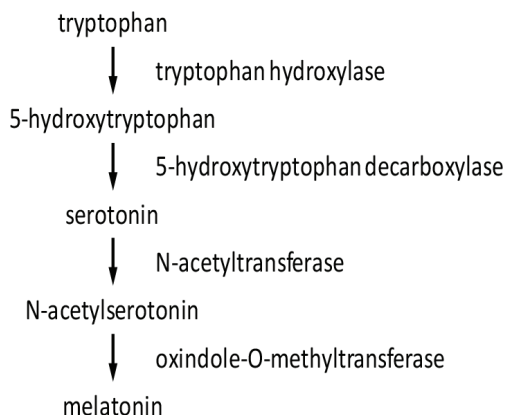
## 2.3. Melatonin involvement in the circadian rhythms regulation

The leading regulator of biological rhythms is the epiphyseal hormone melatonin (N-acetyl-5-methoxytryptamine) acting on circadian systems via MT1- and MT2-melatonin receptors in the hypothalamus SCN [1, 28, 29].

The melatonin donor is the amino acid tryptophan, which participates in the synthesis of the neurotransmitter serotonin, which under the influence of the enzyme N-acetyltransferase turns into melatonin (**Figure 1**) [29].

Melatonin is an indole derivative of serotonin and is produced at night with the participation of N-acetyltransferase and hydroxyindole-O-methyltransferase enzymes [29].

Extrapineal sources of melatonin synthesis are enterochromaffin cells of the gastrointestinal tract (EC-cells), the main depot cells of serotonin (contain up to 95% of all endogenous serotonin). The



**Figure 1.** Melatonin synthesis scheme.

synthesis of this hormone has been found in many neuroendocrine cells of the airways, lungs, in the cortical layer of the kidneys and along the boundary between the cortical and medullary layer of the adrenal glands, under the hepatic capsule, in the paraganglia, ovaries, endometrium, prostate gland, placenta, gallbladder and inner ear. In recent year's studies, melatonin synthesis is found: in blood cells – mast cells, lymphocytes – natural killers, thrombocytes, eosinophilic leukocytes, in the thymus, pancreas, cerebellum, retina. Functionally, many melatonin-producing cells belong to the so-called diffuse neuroendocrine system – a universal system for adapting and maintaining the body's homeostasis. Thus, two links of melatonin-producing cells are distinguished: central (includes the pineal gland and cells of the visual system), in which the rhythm of melatonin secretion coincides with the rhythm of light-darkness, and peripheral – all other cells where the secretion of the hormone does not depend on illumination [1, 2, 29].

Melatonin is transported by serum albumin, after liberation from albumin it binds to specific receptors on the membrane of target cells, penetrates into the nucleus and performs its action there. The biological half-life of melatonin is 45 minutes. This makes it difficult to collect material for research purposes. Melatonin is rapidly hydrolyzed in the liver and excreted in the urine (80–90%), the main metabolites are 6-hydroxymelatonin-sulfate (6-SOMT) and 6-hydroxyglycuronide. The concentration of melatonin metabolites in saliva and/or urine correlates well with the total level of melatonin in the blood during the sampling period [1, 10, 30].

It has been found that the effect of melatonin is realized through MTNR1A (MT<sub>1</sub>) receptors, which are expressed mainly on the cells of the anterior lobe of the pituitary gland, the hypothalamus SCN and in many peripheral organs; as well as MTNR1B (MT<sub>2</sub>) receptors, expressed in some parts of the brain, in the retina and in the lungs. The nuclear receptors of melatonin of the subfamily RZR/ROR of retinoid receptors have recently been discovered. Many immunostimulatory and antitumor effects of melatonin are mediated through them [52].

During the first years of life, peak concentrations of melatonin increase and reach a maximum by 2–4 years, after which they begin to decrease and reach the plateau by the time of puberty. The secretion of melatonin continues to decrease yearly after the end of puberty [10]. Both basal and peak concentrations of melatonin decrease with age, the daily curve of melatonin secretion is smoothed and the peak of night secretion decreases [10, 52–54].

The daily fluctuations in the melatonin level in the blood (melatonin curve) looks like the following. Its concentration is minimal by day (1–3 pg./ml), it starts to increase 2 h before the usual time for going to sleep (if there is no bright light). After turning the light off in the bedroom, the concentration of melatonin increases rapidly (up to 100–300 pg./ml). In the pre-hour hours, a recession usually begins, which ends after awakening. For each person, the melatonin curve is stable from night to night, while in different people of the same gender and age the curves differ significantly, so one can speak of an individual curve [10, 52].

In a number of experiments on animals, the *antioxidant properties* of melatonin have been demonstrated. The mechanism of antioxidant action is manifested in the fact that melatonin has a pronounced ability to bind free radicals, including those formed during peroxidation of hydroxyl radical lipids, and exogenous carcinogens, and it also activates glutathione peroxidase, a factor protecting the body from free radical damage. The main functions of the melatonin antioxidant action are aimed at protecting DNA [10, 29, 52, 55]. To a lesser extent on the protection of



proteins and lipids. Its addition to the ration of rats resulted in an increase in life expectancy and testosterone levels in males [52, 56]. In the study of V.A. Lesnikov and W. Pierpaoli transplantation of the pineal gland from young to older individuals increased their lifespan by 42% and, conversely, transplantation of the epiphysis of older individuals reduced it by 29% [57]. Against the background of the use of melatonin in aging mice, not only the duration of life but also the volume of thymus, adrenals and testes increased, which was accompanied by an increase in the level of testosterone and thyroid hormones in the blood. Thus, a decrease in melatonin synthesis probably plays an important role in aging processes [53].

Reducing melatonin concentrations in the elderly is probably one of the main factors in the development of age-related neurodegenerative diseases. A retrospective analysis of 6-year-old data in patients with depression revealed a disruption in the regulation of the synthesis and metabolism of catecholamines, neurotransmitters, melatonin and immunological proteins [42]. It has also been shown that melatonin supports the optimal mitochondrial membrane potential and preserves mitochondrial functions. In addition, mitochondrial biogenesis and its dynamics are also regulated by melatonin. Mitochondrial dynamics demonstrates an oscillatory pattern that corresponds to the CR of the secretion of melatonin in the pinealocytes and, possibly, in other cells [28, 52, 55]. A number of recent scientific studies have identified the neuroprotective effect of melatonin, which is manifested by affecting the proliferation and differentiation of neural stem cells, increasing the content of myelin and oligodendrocytes [58, 59].

In other studies, melatonin demonstrated a *neuroprotective effect* in neurodegenerative diseases. Melatonin reduces the toxicity of beta-amyloid and prevents the death of cells in experimental AD models, and also reduces oxidative stress in PD models [44–46, 48].

In addition, the experiment demonstrated the effect of melatonin *on the proliferation and differentiation of stem nerve cells*. Depending on the dose of melatonin introduced into the mice cortex, the proliferation rate of oligodendrocytes, the percentage of the main myelin protein, as compared with the control group, increased. Thus, melatonin may have a potential therapeutic effect for some neurological diseases associated with oligodendrocyte pathology and myelinopathy [59].

In recently published papers it is reported that melatonin synchronizes not only central but also peripheral biorhythms, which allows to synchronize biological functions by means of CR with respect to periodic changes in the environment and, therefore, facilitates adaptation of the individual to the external environment [28, 52].

The large number and diversity of the main effects of melatonin opens up important prospects for measuring the level of melatonin as a biomarker for the purpose of clinical, preventive and therapeutic use [10, 32].

### 3. Violation of CR and cerebrovascular diseases (CVD)

#### 3.1. Desynchronosis as a risk factor for stroke

The presence of chronobiological disorders in patients with CVD is noted by many researchers [11–26, 60–86].



In a comparative analysis of autonomic control of the rhythms of the cardiovascular system (CVS) in young and elderly healthy people in Ukraine, it was shown that circadian regulation of blood pressure and heart rate is impaired in elderly people. [25].

There are reports that chronobiological disorders are detected in patients with arterial hypertension [70–72], diabetes mellitus [73–75], cardiac ischemia [11, 12, 14, 61, 66], dementia [67–70], etc. Nowadays there is a lot of data on the existence of chronobiological patterns in the development of stroke and myocardial infarction (MI) [11, 12, 14].

It is known that Ischemic stroke (IS) develops more often in the early morning hours [10]. This may be due to an increase in the activity of the coagulating system of blood at this time [71], as well as with a violation of the daily regulation of blood pressure and heart rhythm in these patients [72, 73]. In epidemiological studies, increased frequency of sudden cardiac death, MI and transient myocardial ischemia, pulmonary embolism and critical ischemia of the lower extremities, as well as rupture of the aortic aneurysm at dawn.

The second small peak of incidence is noted in the early evening [74]. European researchers point to an increased incidence of stroke and MI in winter [75].

In the epidemiological study conducted in Hawaii, it was found that the MI in local population of the Caucasoid race occurs most often between 04:00 and 12:00, and in Japanese visitors – from 12:00 to 16:00, which corresponds to the morning hours in Japan [76]. Similar daily dynamics of MI and stroke development early in the morning and between 12:00 and 18:00 was noted in a prospective study conducted in India involving 158 elderly patients [77]. Such a pattern of development of MI and stroke in the morning can be associated with an increase in platelet aggregation capacity in the morning hours with a peak at 09:00 [71–73]. Also in the early morning, endothelial cells reduce the synthesis of tissue activator plasminogen, nitric oxide and prostacyclin, the tone of the myocytes of the vascular wall is reduced, which promotes thrombosis [71].

In addition, there is a seasonal and cyclical decompensation of the CNS. As a rule, exacerbations occur in the spring and autumn. There is evidence that hemorrhagic stroke (HS) often manifests in winter and spring, and IS in summer and autumn [78]. Daylight saving time transgresses the CR and shifts the picture of the diurnal variation at the beginning of the stroke, but the effect on the IS frequency is unknown.

Effects of 2004–2013 daylight saving time (DST) transitions on IS hospitalizations and in-hospital mortality were studied nationwide in Finland. Hospitalizations during the week following DST transition (study group,  $n = 3033$ ) were compared to expected hospitalizations (control group,  $n = 11,801$ ), calculated as the mean occurrence during 2 weeks prior to and 2 weeks after the index week. DST transitions appear to be associated with an increase in IS hospitalizations during the first 2 days after transitions. Susceptibility to effects of DST transitions on occurrence of ischemic stroke may be modulated by gender, age and malignant comorbidities [79].

Disorders of CR are associated with an increased risk of IS. A monitoring of blood pressure for 5 days after a previous IS or HS, conducted in 50 patients (India), indicates a decrease in natural circadian fluctuations with an increase in blood pressure during the night [77].

According to the Stockholm population cohort study, 48-hour heart rate monitoring in 678 practically healthy people aged 55–75 years allowed to reveal a statistically significant risk of MI development in patients with reduced nighttime heart rate variability. Some authors point to a direct relationship between the frequency and severity of MI and the severity of violations of daily BP regulation. They divide patients into groups of “dippers” and “non-dippers”. It was established that the activity of the central link of the sympathetic nervous system was increased in patients with “non-dipper”, i.e., those who do not have a decrease in blood pressure during night sleep or less than 10% of the daytime sleep. These people are less active in endothelium-dependent vasodilation, and a possible cause of high pressure is the damage to the baroreceptor reaction. As a result, “non-dippers” are characterized by increased sympathetic activity during sleep and, as a consequence, have a high risk of general and cardiovascular mortality [80].

The dependence between the amount of brain damage and the degree of decrease in nighttime blood pressure (BP) is established: the greater the amount of brain damage, the less it decreases at night. Thus, in patients with lacunar stroke, in contrast to patients with non-lacunar stroke, a greater BP reduction is detected during monitoring at night. This may indicate the safety of the mechanisms of regulation of circadian rhythms of pressure in the case of lacunar stroke [81].

The results of the large clinical trial in Japan with a 24-hour outpatient BP measurement in 515 patients and parallel magnetic resonance imaging (MRI) of the brain showed that increasing the pulse pressure during sleep and mean BP on waking, especially in the elders, are independent predictors of MI in elderly hypertensives. In this case, the effect of pulse pressure and the mean value of BP on stroke risk differs in separate phases of the sleep-wake cycle. Thus, an increase in the pulse pressure for every 10 mmHg. in a sleep independently increases the risk of stroke by 43% ( $p = 0.001$ ), while the average BP index during sleep is not so significant. At the same time, the mean BP increase for every 10 mmHg. on waking, independently increases the risk of stroke by 48% ( $p < 0.001$ ), and the level of pulse pressure upon awakening is not a significant factor [82]. The study of night-time heart rate variability may have prognostic value for the stroke prevention.

Our study with the inclusion of 226 patients with cardiovascular diseases (CVD) has shown a high incidence of sleep disorders and desynchronosis in these patients. A comparative analysis of the nature of sleep disorders in patients with cardiological disease (myocardial ischemia, essential hypertension) and CVD showed that sleep disorders due to anxiety-depressive disorders prevail in patients with CVD in the structure of detected sleep disorders, and after a stroke – sleep disturbances due to desynchronosis. This may indicate deeper violations of the adaptive mechanisms regulated by nonspecific brain systems, which leads to disturbances in the sympathetic and parasympathetic links in the vegetative status.

Patients with MI also showed sleep disorders, which may indicate the role of cardio-cerebral interactions in the regulation of sleep mechanisms.

Patients with CVD showed a decrease in the level of 6-SOMT, among which predominate the patients with MI [83,84]. The presence of cognitive disorders, sleep disorders and chronobiological

disorders (daily regulation of heart rhythm and BP) was related with a low level of 6-SOMT in daily urine examined [85, 86].

The study of sleep characteristics in patients with CVD revealed high frequency of occurrence of sleep disorders and desynchronization in these patients and their positive correlation with the development of behavioral and affective disorders ( $r = 0.57$ ,  $p = 0.002$ ), as well as their effect on the daily profile of the cardiac rhythm and BP ( $r = 0.46$ ,  $p = 0.008$ ). Therefore, timely diagnostic and complex psycho-pharmacological correction of sleep disorders and desynchronization in patients with CVD will improve the psychological and emotional status of patients, normalize daily profile of heart rhythm and BP. A positive correlation between desynchronization and stroke was proved ( $r = 0.39$ ,  $p = 0.013$ ). This suggests that desynchronization is a risk factor for stroke in patients with CVD [25].

### 3.2. Stroke and sleep disorders

According to the polysomnographic study sleep disorders in stroke reach 100% of the cases and are manifested as insomnia, disturbance of the “sleep-wake” cycle and respiratory distress in sleep as the type of “sleep apnea” syndrome [87]. It was found that sleep disorder is one of the etiological factors of stroke, also increases the risk of recurrent stroke and prevents recovery after it [18–25, 62, 87–95].

Large population studies (more than 3000 patients) indicate that a reduction in sleep duration (less than 6 hours) is associated with an increased risk of hypertension, especially among women compared to men, and is stronger in premenopausal women than in postmenopausal women. The revealed relationship does not depend on the socioeconomic status, traditional cardiovascular risk factors and psychiatric comorbidity, and is stronger in premenopausal women. Consequently, a decrease in the duration of sleep increases the risk of developing hypertension, which can lead to the cardiovascular pathology (CVP) development in women [62].

In the Danish cohort population study over 12 years, which included 20,432 men and women aged 20–65 years, a high incidence of CVP was found in people with insufficient duration and quality of sleep [15]. In the Australian study, among 218,155 people 45 years of age or older, it was found that sleep duration of less than 6 hours and more than 9 hours is associated with a high risk of diabetes, stroke, hypertension and coronary heart disease (CHD). A prospective study of 1986 patients aged 55–69 years (Great Britain) showed that IS is more likely to develop in patients with disturbed sleep at night, and MI is associated with increased daytime sleepiness [25].

In 2016, scientists from the University Clinic of Essen published a meta-analysis of 29 scientific papers evaluating sleep disorders that may be associated with stroke. A total of 2,343 patients with IS, HS or transient ischemic attack (TIA) participated in the studies. Sleep disorders in these patients were divided into 2 groups: (1) disturbance of breathing during sleep (obstructive sleep apnea); (2) sleep and wakefulness disorders, which reduces the duration of sleep. It was revealed that sleep disturbance was observed in 72% of patients with IS, in 63% of patients with HS and in 38% of patients with TIA. A lot of patients had a sleep disorder before stroke. This allows to believe that sleep disorders increase the risk of stroke [22].

The authors also proved that not only insomnia, but hypersomnia and restless leg syndrome increase the risk of stroke. To date, specific mechanisms for increasing cardiovascular risk in restless legs syndrome have been described: (1) periodic movements of limbs in a dream, accompanied by a significant increase in the heart rate and BP; (2) fragmentation of sleep and lack of sleep, invoking changes in the regulation of nervous and vascular systems, metabolism, oxidative, inflammatory processes; (3) iron deficiency, which creates new risks for CVP [90–92].

In general, the exact mechanisms by which sleep disorders can lead to stroke are not disclosed. Nevertheless, it is shown that sleep has an important restorative function of the brain and affects the processes of neuroplasticity. Sleep disorders can persist after a stroke, and without appropriate correction may obstruct the after stroke rehabilitation.

### *3.2.1. Characteristics of sleep disorders in patients with stroke*

Insomnia in stroke patients is characterized by a change in the duration of sleep, frequent nocturnal awakenings, lack of satisfaction at night sleep, and the appearance of “heaviness” in the head [22, 87]. According to the polysomnographic study, there is an increase in stages 1 and 2, a decrease in phases 3 and 4 of the slow-sleep phase (SSP), and often a reduction in the phase of fast sleep (FSP) [10, 13].

Sleep-wakefulness disorders in patients with stroke are caused by damage of the hypothalamic structures associated with the “internal clock”, or their connections. Clinically manifested by disturbance of night sleep, pathological daytime drowsiness or a combination of both. This is more common in multiple lacunar stroke. In patients with severe cognitive impairment after stroke, the inversion of the sleep-wake cycle with sleeplessness at night and daytime drowsiness is often observed. As a rule, these conditions are accompanied by behavioral disorders. At the same time the patient is nervous, cannot understand where he is, tries to get out of bed, go, resists the actions of medical staff. These conditions cause the difficulties in rehabilitation of these patients in the hospital [22, 87].

Studies of recent years have shown that obstructive sleep apnea (OSAS) is an independent modifiable risk factor for stroke. To date, it has been established that respiratory events associated with OSAS are involved in cyclical episodes of hypoxemia and hypertension, increased platelet aggregation, reduced fibrinolysis, endothelial dysfunction, increased intracranial pressure, decreased cerebral blood flow and local cerebral ischemia. In the acute period of IS the incidence of OSAS is 36% [93]. Respiratory disturbances in sleep in patients with stroke, cause the worst efficiency of the rehabilitation process. It is shown that the presence of OSAS is accompanied by greater functional insufficiency and a longer period of hospitalization of patients [94–100].

In general, for all stages and forms of stroke, changes in both the mechanisms of sleep generation and the mechanisms of its maintenance are typical. The cause of these violations are not only the damage and death of brain tissue of a local nature, but also disorders of general and local hemodynamics, the appearance of edema and displacement of the brain substance, the ingress of blood into the cerebrospinal fluidways, and as a result – the irritation of various structures located in the brainstem [18].

It is believed that the greatest impact on sleep is the nature, size, localization of the process and the stage of the disease.

### *3.2.2. Features of sleep disorders depending on the type, localization of the focus, stage of stroke and development time of the stroke*

HS in comparison with IS leads to the most severe disorders of night sleep. Characterized by a deep reduction in the duration of sleep, frequent and prolonged awakening, an increase in the representation of the first stage. However, with a favorable outcome of the disease, the degree of recovery of the structure of sleep is faster than in IS. In IS there is a focus of necrotic decay of brain tissue, while with hemorrhage, damage occurs as a result of the stratification of brain structures with blood. Therefore, the restoration of both the clinical picture and night sleep is better and for a shorter period in HS [22, 101].

*The size of the focus of stroke* plays a significant role in the formation of sleep disorders. A large focus leads to a common swelling of the hemisphere, sometimes even the opposite, the emergence of processes of compression of the brain stem. Hence the most severe disorders of sleep are observed in large foci of stroke. In the available studies it was shown that the maximum proximity of the focus to the median structures and the liquor-bearing pathways (medial arrangement) leads to more severe sleep disorders. Not only quantitative but also qualitative changes in the structure of sleep are noted. Thus, the medial focus with the capture of thalamic structures is characterized by the disappearance on the side of the lesion of "sleepy spindles" (electroencephalographic signs of stage II of sleep). The lateral processes are accompanied by less severe sleep disorders [19].

**The localization of the lesion** in the hemispheres or in the brain stem causes specific changes in the structure of sleep. Greater disorders observed in the *right hemispheric processes*: decreases the duration of d-sleep and FSP, lengthen the waking period and stage I, the duration of falling asleep; the number of awakenings increases. The reason for such sleep disorders in right hemisphere patients is the damage of the deep mechanisms of the relationship between the right hemisphere and the hypnogenic structures of the brain. In addition to sleep disorders, these patients notice marked changes in vegetative regulation, which is manifested by tachycardia, various types of cardiac arrhythmia, high BP numbers. The *left hemisphere* is most closely associated with the activating systems of the brain. There is an opinion that this is the cause of frequent impairment of consciousness in left hemispheric strokes [19].

When a process occurs in the area of the pons, the duration of the FSP dramatically decreases, and its latent period increases. Bulbar symptoms are accompanied by a decrease in the duration of d-sleep.

*The acute stage of stroke (week 1)* is characterized by a number of clinical and polysomnographic features. In this period, there are difficult to control hemodynamic, general cerebral and local neurological processes. Depending on the direction of the disease, a different picture is observed in polysomnography. Severe disturbances of consciousness (sopor, coma), as a rule, are accompanied by a diffuse slow wave activity, which excludes the possibility of isolating individual stages of sleep. The emergence of separate stages and sleep phenomena against

a background of diffuse cerebral electrical activity is a prognostically favorable sign. With conserved consciousness in the most acute period, polyphase and inversion of the “sleep-wakefulness” cycle due to circadian disorders are often enough. In the first case, patients fall asleep several times during the day; in the second – the cycle “sleep-wakefulness” shifts, there are daytime sleep and night wakefulness. In the presence of general cerebral symptoms, frequent awakenings, a decrease in d-sleep and the absence of FSP are observed [19].

The structure of sleep in patients with stroke also differs depending **on the time of its onset**. A characteristic feature for a stroke that occurred during sleep is a high FSP presence, which, along with the “vegetative storm” in this phase, can be one of the causes of stroke at night. According to statistics, in patients with a “morning stroke” in comparison with “daytime” and “night”, the shortest FSP time is noted [19].

Investigation of the night sleep structure in patients with stroke showed the premorbid sleep problems (frequent awakening, long sleep, dissatisfaction with sleep, early awakening), which are associated with worse parameters of sleep quality after stroke [18, 101]. Thus, the initial feature of the regulation of the “sleep-wake” cycle influences the formation of structural changes in sleep after stroke.

### *3.2.3. Sleep disorders and recovery from stroke*

The quality of sleep can serve as a prognostic criterion for the possibility of recovering patients with stroke. So, changes in the structure of sleep in the acute period of stroke have an important prognostic value. If a normal pattern of sleep does not return within 7–10 days after a stroke, the prognosis is considered unfavorable [10]. A multicenter-observational and correlation study involving 280 patients with mild and moderate severity of stroke showed initially high rates of affective and cognitive impairment (26.9%) and sleep disorders (567%) in patients in the early recovery period of stroke. In patients with sleep disorders, regardless of the severity of the stroke, recovery of the neurological deficit, cognitive functions proceeded more slowly compared to patients without sleep disorders, primarily with regard to improving the Berg balance scale. It was found that sleep disturbance after stroke has a negative effect on functional recovery, especially on improving the balance in the group of moderate stroke [102].

Restoring and maintain a natural biorhythm sleep-wakefulness with the use of physical and medicinal methods for the stroke prevention and treatment are recommended.

Currently, in the correction of sleep in patients with stroke, the leading place is the drug therapy. The strategy of pharmacotherapy of sleep disorders in patients with stroke is reduced not to achieving a one-time hypnogenic effect, but to normalizing the adaptive-compensatory potential of the central nervous system. Based on such positions the advantages of melatonin as a hypnotic are estimated. As a natural chronobiotic, melatonin synchronizes CR, provides normalization of desynchronized CNS activity. Therefore, the correction of sleep disturbances with melatonin (as opposed to “classical” hypnotic drugs) becomes not only as the result of a hypnogenic effect, but due to normalizing the activity of various brain structures that support the processes of complex central regulation. Exogenous melatonin, taken in the evening,



stabilizes the work of the SCN and marks the starting point for determining the subjective dark time of the day [29, 31, 32].

A number of clinical studies have shown the positive effect of melatonin on daytime sleepiness, a reduction in the period of falling asleep and the number of nocturnal awakenings, the restoration of disturbed sleep initiation in patients with stroke [33–37].

In one of the major studies to correct the disturbances of the sleep-wake cycle, patients with stroke were prescribed a melatonin (Melaxen, Unipharm, Inc., USA) in a dose of 3 mg at bedtime for 10 nights. Against the background of taking Melaxen, there was an increase in the time of night sleep and a decrease in the number of sleep episodes during the day. That is, there was a normalization of the distribution of the sleep time in the 24-hour sleep-wake cycle [35].

When studying the condition of the CNS in 60 patients in the acute period of stroke, it was found that the inclusion in the scheme of complex therapy of Melaxen at a dose of 6 mg per day contributed to a faster and more complete recovery of motor disorders, improvement of the cranial nerves function. In addition, while Melaxen's administration, a rapid normalization of a number of electrophysiological parameters during the recording of an electroencephalogram was observed: changes in activity in the EEG delta and theta bands, which were accompanied by a change in the BIS and ITA indices [104].

We evaluated the effectiveness of chronotherapy (Melaxen) on the dynamics of sleep disorders, cognitive and emotional disorders, neurotrophic brain factor (BDNF), the level of melatonin secretion (6-SOMT) in patients in the early recovery period of cerebral stroke. 112 patients were examined in the early recovery period of the stroke (mean age  $58.0 \pm 9.74$  years). The main groups of patients, along with the standard treatment regimen, received phototherapy and Melaxen 3 mg per day for 3 months. The effectiveness of the therapy was assessed by the dynamics of sleep disorders, psychoemotional status, the concentration of the neurotrophic brain factor BDNF, the level of 6-SOMT in the urine. The study demonstrated a high effectiveness of chronotherapy (Melaxen, phototherapy) in the rehabilitation of patients in the early recovery period of stroke. The presence of cognitive disorders, sleep disorders and emotional disorders correlated with a low level of 6-SOMT in urine in the patients.

Complex therapy with Melaxen, revealed a significant increase in the level of excretion of 6-SOMT in patients by the end of the 3-month follow-up period. An increase in the concentration of BDNF after 3 months of therapy and throughout the observation period may indicate activation of the synthesis of growth regulators and differentiation of the nervous tissue (**neurotrophic effect**). Increased concentrations of BDNF, 6-SOMT in the urine correlated with improved sleep, cognitive and emotional status, motor disorders and quality of life of patients.

In another our study, with 132 outpatients (59 men and 73 women) aged  $61.4 \pm 4.7$  years in the early recovery period of ischemic stroke (IS), OSAS was detected in 52 (39.4%) cases. Light and medium OSAS was diagnosed in 49 cases, in 3 patients – severe OSAS, which required selection of CPAP therapy. Patients with OSAS of mild and moderate severity (49 persons) were divided into 2 groups, comparable by sex, age and neurological manifestations.



All patients received drug therapy according to the standards of specialized medical care; positional therapy, exercise therapy, mechanotherapy, psychotherapy. Patients of the main group (25 people, mean age  $59.5 \pm 4.8$  years), along with the treatment described above, received melatonin 3 mg per day for 30–40 minutes before sleep for 3 months and used intraoral repositioning applicators. Patients in the control group (24 patients, mean age  $62.3 \pm 4.2$  years) were prescribed only standard therapy. Already a month after the start of therapy, the patients of the main group had a positive dynamic: decrease in daytime sleepiness, snoring, and an expression of morning fatigue. After 3 months, the sleep characteristics of the patients in the main group were statistically significant ( $p < 0.05$ ), differed from the control group by a shorter sleep time ( $8.8 \pm 3.2$  vs.  $20.9 \pm 16.7$  minutes), an extended total sleep duration ( $431, 0 \pm 34.7$  vs.  $386.9 \pm 90.4$  minutes), greater representation of the 4th stage of slow sleep ( $12.6 \pm 3.5\%$  vs.  $8.1 \pm 6.7\%$ ) and a lower total waking time ( $8, 0 \pm 4.2$  vs.  $37.5 \pm 12.8$  minutes). After 6 months of therapy, positive changes in the polysomnography index remained, a reduction in the frequency of obstructive events in the patients of the main group as compared with the control.

Simultaneously with the normalization of sleep, the positive dynamic of clinical and neurological indicators was demonstrated. By the 3rd month. Therapy, the cumulative cognitive parameters of the MoCA test, the psychoemotional functions and the quality of life of the patients in the main group were statistically significantly improved, in contrast to the controls.

Detailed study of night sleep in patients with stroke is not only of scientific interest, but also has serious practical significance in matters of prognosis, secondary prevention, as well as medical and rehabilitation measures.

The use of a standardized criterion for assessing the dynamics of the CR of the heart rate extends the diagnostic capabilities, reveals new pathogenetic links of the CVD, optimizes the treatment regimen for patients with CVP. Identification of CR abnormalities in the management of BP and heart rhythm in combination with sleep disturbances allows to include melatonin drugs in therapy.

Thus, the detection of sleep disorders and desynchronization in patients with CVD requires that medical, psychological and social aspects is included in complex therapy.

It is advisable to use the following chronotherapeutic approaches:

1. Change of daily regime according to a chronotype of the patient and reduction of a mode of work and rest in conformity with natural photoperiods;
2. Use of physiologically appropriate diet;
3. Optimization of the motor activity regime with the recommendation of walking outdoors and moderate insolation;
4. Inclusion of photo- and color therapy in the complex of rehabilitation;
5. The Chronopharmacological approach in Drug Administration.
6. Melatonin administration at a dose of 3 mg per day. For 30–40 minutes before bedtime.

#### 4. CR disorders in patients with DVB and development of cognitive disorders

At present, there is enough evidence on the association of early and progressive CR disorders, changes in quality and sleep architecture with an increased risk of developing cognitive impairment (CI) [67–70, 103–112].

When analyzing 12,926 documents from the PubMed, EMBase, ISI WebofScience and PsycINFO databases published before October 28, 2016, among 246,786 patients in 25,847, an average of 9.49 years was observed in dementia. The prognostic role of sleep disturbances, their subtypes (insomnia, OSAS, excessive sleepiness during the day, sleep disorders, and nonspecific sleeping problems) in the development of dementia were evaluated. Compared to those without sleep disorders, patients with sleep disorders had a higher risk of developing dementia. Subgroup analysis showed that insomnia increases the risk of developing AD, but not vascular dementia (VD). In contrast, OSAS was associated with a higher risk of early onset of SI, incl. AD and VD [105].

The relationship between the sleep architecture and the potential risk of developing CI in the community is considered on the basis of Framingham Heart Study (FHS). For 19 years' study (the average follow-up period was  $12 \pm 5$  years), there were 321 patients participating in Sleep Heart Health Study between 1995 and 1998, over the age of 60 at the time of sleep assessment. 32 cases of dementia were traced; 24 cases were due to AD. After adjusting for age and sex, a low percentage of FSP and greater latency of REM sleep were associated with a higher risk of dementia. Each percentage reduction in FSP was associated with an increasing the risk of dementia by approximately 9% ( $p < 0.05$ ). The relationship between the percentage of FSP and dementia was similar for the following adjustments for multiple covariates, including vascular risk factors, depressive symptoms, and drug use. The stages of slow wave sleep were not associated with the risk of dementia [106].

Among 96 patients in the acute period of IS, 79% of patients had heterogeneous post-stroke CI. In 21% of patients they had a dysmnestic character. The concentration of 6-SOMT was lower in patients with IS compared with the control. In the study of chronotypes, it was found that the majority of patients had an early variant, while the social jetlag value was 40 minutes. This indicator decreased with increasing age of patients. In most patients, IS developed in the morning, these patients had the lowest content of 6-SOMT in daily urine and the lowest values for MMSE. Potentially this is associated with a decrease in the protective activity of the melatonin. There was a correlation between chronobiological parameters and cognitive status. Thus, the expression of the "social jetlag" was associated with the semantic coding of memory, reflecting the function of the hippocampus. Patients with a late version of the chronotype were characterized by higher rates of delayed reproduction and semantic verbal fluency. With an increase in the social jostlag, the concentration of 6-SOMT in urine, probably compensatory, increased. The use of melaxen accelerated the recovery of CR, which had a positive effect on the rehabilitation of patients. It has been suggested that in elderly and senile patients, a high concentration of 6-SOMT in the acute period of IS was a marker of dysregulatory cognitive impairment, whereas its low content in the presence of a cognitive deficit may indicate a mixed, hippocampal type of CI [86].

Possible prospects for the use of melatonin in elderly patients with CI are due to its antioxidant, neuroprotective and nootropic effects. The positive effect of exogenous forms of melatonin on sleep in elderly patients is confirmed by the results of two placebo-controlled studies in which more than 500 patients over the age of 55, with primary insomnia [1107].

Using 6 mg of melatonin once a day before bedtime for 10 days in patients with moderate CI (MCI) led to significant improvement in memory and regression of depressive symptoms simultaneously with normalization of the sleep-wake cycle [103]. H. Jean-Louis et al. [108], Peck et al. [109], observed 26 patients with MCI syndrome received similar results. While 1 mg melatonin administration just before sleep for 4 weeks, there was a significant decrease in forgetfulness in the auditory memory modality and improvement in night sleep compared with placebo. By Cardinali et al. there was made the retrospective analysis of the effect of melatonin therapy on cognitive functions, night sleep and wakefulness in 96 patients with MCI (61 patients received melatonin in doses of 3–9 mg once daily for 9–18 months). It has been proven that melatonin therapy contributes to significant cognitive improvement and regression of depressive symptoms [110].

The high efficiency of the combination of memantine and melatonin in the correction of MCI was shown in the experiment [111].

There is a discussion about the importance of light therapy in correcting of CI. Most of the studies demonstrate the stabilization of CR sleep-wakefulness and a reduction in the time of sleep in dementia with melatonin and light therapy [112].

The prevalence and correction of sleep disorders in patients with CVD need further study in randomized clinical trials in large groups of patients for understanding their impact and establishing cause-effect relationships in the development of CI. These investigations results will help to develop a treatment strategy.

## 5. Conclusion

Thus, literature data show that stroke has a peculiar organization in time. The vegetative dysrhythmia and failure in the work of the Central control of biorhythms regulation play a key role in these processes.

The night sleep structure investigation is essential part in patients with stroke and patients with cardiovascular disease risk factors. The CR violation leads to the syndrome of desynchronosis—mismatched dynamics of different indicators of the internal environment. This is a potential basis for the cerebrovascular and cardiovascular pathology.

Therefore, including the restoration of the CR with the chronotherapeutics methods is need for the vascular diseases prevention and treatment. Distribution of daily cases of stroke depends on individual properties of CR hemostasis and cerebral hemodynamics, and the specific of the night sleep structure of the of patients. In this regard, there must be a differentiated approach in the treatment of “day” and “night” strokes. The main aspect of reducing the probability of primary and secondary cardiovascular “accidents” development should be the timely detection of sleep disorders and desynchronosis, as one of the leading risk factors.

The use of the personalized chronotherapeutics approaches allows to neutralize the negative impact of desynchronization.

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## Conflicts of interest

The authors declare no conflicts of interest regarding the content of the manuscript.

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