Chapter

Clinical Use of Melatonin in the Treatment of Sleep Disorders

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Abstract

Sleep disorders are a group of conditions that affect the circadian rhythm of sleep-wake, leading to social and professional maladaptation. At the moment, there is a wide range of medications aimed at the treatment of sleep disorders, but the results from their use are not always satisfactory. Benzodiazepines, antidepressants, and antihistamines may cause dependence or withdrawal effects. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the pineal gland that affects intraday, seasonal rhythm, and the sleep-wake cycle. Studies of the effects of melatonin have demonstrated its ability to synchronize circadian rhythms, reduce the latency of slow sleep, increase the duration of sleep, and improve its subjective quality. This review highlights the current therapeutic possibilities of using melatonin in various sleep disorders, taking into account the mechanisms of its action. Also, the prospects of using melatonin due to its chronobiological effect in other sleep disorders, such as parasomnia, sleep-dependent respiratory disorders, and hypersomnia, are emphasized. At the moment, melatonin is one of the methods for correcting intraday rhythms and some types of insomnia.

Keywords: sleep, melatonin, sleep disorders, sleep-wake cycle

1. Introduction

Sleep is fundamental to the mental and physical health of a person. Lack of sleep is a significant risk factor for obesity, diabetes, diseases of the cardiovascular system, as well as anxiety and depressive disorders. Sleep disorders have a significant financial burden on the healthcare system and complicate the treatment of major somatic diseases. Sleep disorders are a category of diseases that include hypersomnia, insomnia (accompanied by difficulty falling asleep, maintaining sleep, and early awakening), circadian rhythm disturbance, parasomnia, and sleep-dependent breathing disorders. The consequence of some sleep disorders is a violation of falling asleep and maintaining sleep, drowsiness, and, as a consequence, a decrease in the quality of life. Some sleep disorders can also lead to severe impaired ability to perform every day and professional tasks related to concentration, switching attention, and spatial perception [1].

The development of pharmacological treatment methods has provoked an increase in the frequency of sleep disorders in the last decade, as a result of undesirable effects of this therapy. The most common disease is insomnia, which according to the classification criteria for mental disorders *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* in the general population is found in 4–6%.

The main classes of drugs for the treatment of insomnia are barbiturates, benzodiazepines, benzodiazepine agonists, antidepressants, and anxiolytics. These drugs can cause a large number of side effects associated with excessive daytime sleepiness, decreased concentration, and switching attention and can cause deterioration of short-term memory. In some cases, with prolonged use of these drugs, dependence may form, and with cancelation, a "rebound phenomenon" may occur. In this regard, it becomes relevant to search for new pharmaceuticals that reduce the number and severity of these side effects while maintaining the proper level of effectiveness. One of these drugs, with long-term administration of minimal side effects and sufficient effectiveness in certain sleep disorders, is melatonin. Melatonin is mainly produced by the pineal gland with a peak of activity at night; the concentration fluctuation coincides with the circadian rhythm. Melatonin-based preparations have good tolerance in various age periods, without forming dependency [2–4].

Other effects are inherent to melatonin, namely, regulation of circadian, seasonal rhythms; regulation of the psychoemotional and cognitive sphere; antioxidant, neuroprotective, and geroprotective effect; immunomodulatory; vegetative stabilizing; and oncological and stress-protective effect.

The multiplicity of effects of melatonin is due to the large number of targets on which this hormone has an effect. The most studied mechanism for the implementation of the action of melatonin remains its effect on suprachiasmal nuclei (SCN) of the hypothalamus. Through SCN, the chronobiological effect of melatonin is realized and, of course, its hypnotic effects. Melatonin interacts with two types of G-protein-bound receptors—MT1 and MT2 [5]. MT1-type receptors are distributed in the hippocampus, caudate nucleus, pillow, suprachiasmatic nuclei, paraventricular nucleus, supraoptic nucleus, Meynert nucleus, adjacent nucleus, substantia nigra, mammary bodies, and retina. MT2-type receptors are mainly detected in the hippocampus, SCN, and the retina. Both types of receptors are expressed by neurons and glial cells of the cerebral and cerebellar cortex, in the thalamus, and pineal gland [5, 6].

Melatonin is released into the blood plasma as a rhythmic oscillatory pattern, which is regulated by SCN neurons. Daylight suppresses the release of melatonin through the retinohypothalamic tract, projecting from melanopsin-expressing retinal ganglion cells to SCN neurons. It is known, for example, that night illumination is 2000–2500 Lux within 2 hours, which completely inhibits the secretion of melatonin. On the other hand, traditional home light (50–300 Lux) practically does not have a suppressive effect on the secretion of melatonin [7]. The neural relationship between the structures of the central nervous system, where axons of melanopsin-expressing ganglion cells are projected, primarily with SCN neurons and the sympathetic nervous system, is via the superior cervical sympathetic ganglion, from where the nerve fibers go directly to the pinealocytes and regulate the exocytosis of norepinephrine, which activates melatonin synthesis and its release [8]. As mentioned above, melatonin easily penetrates through biological barrier: it is secreted continuously into the blood plasma and enters various fluids (saliva, urine, cerebrospinal fluid, preovulatory follicle, spermatozoa, amniotic fluid, and human milk). The maximum level of melatonin in blood plasma is at 03.00–04.00 at night. The indicator varies depending on the chronotype and is not determined in the daytime. Melatonin levels have a pronounced intersubject heterogeneity but are steadily repeated in the same person. After birth, the rhythmic production of melatonin during the day reaches very high levels by 3–6 years of life and then decreases by almost 80% to levels in an adult. The melatonin rhythm is generated by the endogenous clock of the hypothalamic SCN neurons, which are affected by the light/dark cycle (zeitgeber). Seasonal effects on the secretion of melatonin are manifested in an increase in nighttime secretion of melatonin, which is associated

with a decrease in plasma of ovarian steroids. On the other hand, urban lighting reduces seasonal differences in the secretion of melatonin, cortisol, and thyrotropin. Winter-type seasonal affective disorders are characterized by recurrent depressive episodes during a short photoperiod.

Melatonin, due to its amphotericity (amphiphilicity), is able to penetrate into the cell, organelles, and nuclear membranes and directly interacts with intracellular molecules, exerting a non–receptor-mediated effect. Along with this, melatonin exerts a receptor-mediated effect on target cells, as a result of the interaction of the hormone with either membrane or nuclear receptors [9]. The main physiological functions of melatonin are due to its hormonal properties; however, the hormone also has an autocrine and paracrine effect, in particular in the retina and gastrointestinal tract [10].

Outside of SCN, MT1 and MT2 receptors are also found in large numbers in the duodenum, colon, cecum and appendix, gallbladder epithelium, parotid gland, pancreas, β-cells of the endocrine system, pancreas, coronary, and cerebral arteries adipose tissue. In addition to membrane receptors for melatonin, there are also nuclear receptors: RORα and RORβ. The prevalence of RORα is highest in T and B lymphocytes, neutrophils, and monocytes, whereas RORβ are found mainly in the brain, pineal gland, retina, and spleen.

The modulating effect on sleep architecture is also realized by melatonin due to membrane receptors MT1 and MT2. The activation of the MT2 receptor contributes to increasing the duration of slow-wave sleep. The activation of the MT 1 receptor has a decrease in the duration of slow-wave sleep [11, 12].

The effects of melatonin, in addition to effects on SCN, on neural networks of passive brain function default mode network (DMN) were also demonstrated. Their activation is accompanied by the appearance of a feeling of fatigue and is characterized by changes typical of sleep in such parts of the cortex as the precuneus located in the rostromedial aspect of the occipital cortex [13, 14]. Because the general effect of melatonin through two membrane receptors does not increase the duration of slow-wave sleep (SWS) [15], the main effect of melatonin is not associated with its homeostatic effect on sleep. Therefore, its effect can be attributed to sleep regulation through the circadian component [16].

The multiple representation of melatonin receptors in the central nervous system, its effect on one of the key components of the regulation of the sleep-wake cycle, leads to the multiplicity of the clinical use of this hormone, especially in pathological conditions accompanied by primary or secondary circadian rhythm disturbances.

2. Melatonin and sleep disorders

2.1 Melatonin and disorders of the sleep-wake cycle

Circadian disturbances of the sleep-wake rhythm are associated with disconnection of the synchronization of the endogenous circadian rhythm and environmental influences. Melatonin signals the onset of darkness, and activation of its production indirectly depends on the activity of intrinsically photosensitive retinal ganglion cells (ipRGC) or true light-sensitive retinal ganglion cells. However, there is also an endogenous melatonin release profile that allows SCN activation regardless of external light, maintaining sleep-wake rhythms and neuroendocrine rhythms in a 24-hour cycle. However, the absence of external-stabilizing effect of zeitgeber (daily light change) can lead to the formation of a non-24-hour sleep-wake cycle. For example, in completely blind subjects, it is quite common (in 50–75% of cases)

to observe a non-24-hour sleep-wake disorder (non-24-hour sleep-wake disorder), the occurrence of which is associated with the inability to synchronize with changes in light [17]. Circadian rhythm disorders can be divided into conditions that may be caused by endogenous or exogenous factors. The first subgroup includes the syndrome of delayed onset of sleep and wake phases (advanced sleep-wake phase disorder), early onset of the sleep phase (delayed sleep-wake phase disorder), irregular sleep-wake rhythm disorder (irregular sleep-wake rhythm disorder), and non-24-hour sleep-wake cycle (non-24-hour sleep-wake disorder). The group with exogenous causes of occurrence includes jet lag disorder, a disorder caused by a shift work schedule (shift work disorder) or a result of behavioral features of going to bed and violation of the work and rest regime in the format of about 24-hour circadian rhythm. The circadian rhythm is regulated by melatonin, while the production of melatonin itself is regulated by external influences, the most important of which is the effect of light, which activates the retinal ganglion cells containing the light-sensitive pigment melanopsin. External influences with excessive activation of signal systems implemented through SCN excitation are caused by the lifestyle of modern people, the use of electronic devices. Such excessive activation can lead to difficulty in initiating sleep, reducing its duration [18]. A decrease in melatonin secretion serves as one of the main mechanisms for the occurrence of such a disorder as delayed sleep phases [19]. There is a positive modulating effect of melatonin on the circadian rhythm of sleep-wakefulness and sleep efficiency both in pathology and in healthy subjects [20].

In separate studies in patients with delayed onset of sleep and wake phases in combination with attention deficit hyperactivity disorder, therapy was performed at a dose of 10 mg, lasting for 4 or more years. The therapeutic effect of melatonin was shown in reducing the start time of sleep and increasing the time of wakefulness in these patients. The use of melatonin in a dose of 3 mg for the treatment of disorders of the sleep-wake cycle in children did not show any effects on the process of puberty in the long-term period. However, it should be noted that these studies are isolated and do not carry a sufficiently high level of evidence [21]. However, even this long-term use of melatonin was not accompanied by any significant or serious adverse events.

Table 1 presents data on the efficacy of melatonin and its agonists in various forms of sleep-wake disorder [21].

According to the recommendations for the treatment of these conditions, melatonin and its agonists have a sufficient level of evidence when applied to the diagnosis of delayed onset of sleep and wake phases and irregular sleep-wake

Type of disorder (syndrome)	Efficiency	Level of evidence
Delayed onset of the phases of sleep and wakefulness	Recommended for adults with or without depression Recommended for children and adolescents without or with concomitant psychiatric pathology	Low
	Recommended for children and adolescents without or with concomitant psychiatric pathology	Moderate
Non-24-hour sleep-wake cycle	Recommended for blind adults	Low
Irregular rhythm of sleep-wakefulness	Not recommended for seniors with dementia. Recommended for children and adolescents with neurological pathology	Moderate

Table 1.
The use of melatonin and its agonists in various types of disorders of the sleep-wake cycle.

rhythm syndrome. Concerning the recommendations on the dose of melatonin, no consensus has been formed, since in studies on the basis of which recommendations are formed with the use of a wide variety of doses of melatonin, from 0.3 to 10 mg. For the non-24-hour sleep-wake cycle syndrome alone, in 2014, the US Food and Drug Administration (FDA) approved a melatonin agonist (tasimelteon) as a therapy.

However, individual studies have demonstrated a high therapeutic effect in the treatment of completely blind patients with N24HSWD immediate-release melatonin preparations. Taking a 0.5–10 mg of melatonin helped accelerate the synchronization of the endogenous sleep-wake rhythm with a 24-hour rhythm, according to the profile of the production of melatonin and cortisol. Also, separate studies demonstrate that drugs with modified melatonin release can also be effective in stabilizing circadian rhythms in completely blind patients with N24HSWD [22].

The so-called sleep-wake cycle disturbance states, namely, "jetlag," which occurs when changing time zones during an eastbound flight, can be corrected quite well with exogenous melatonin. In separate studies, various doses of melatonin (from 0.5 to 10 mg) used at bedtime, 3 days before the transmeridian flight and 5 days after it, were used to treat jetlag [23, 24]. The effectiveness of melatonin in most studies was already shown during the first 3 days after the completed flight, but subsequently, patients who did not take melatonin showed the same sleep-wake cycle characteristics as the group of people taking it. The main effect of melatonin in the first 3 days after the transmeridian flight was an increase in the duration and quality of night sleep, based both on subjective sensations and on the data of objective methods for recording sleep patterns (polysomnography and actigraphy) [25, 26].

At the same time, melatonin had a positive effect on latency and duration of sleep. Melatonin agonists have also shown their effectiveness in accelerating adaptation to a new time zone. Melatonin agonists (ramelteon and tasimelteon) are approved by the FDA for the treatment of time zone change syndrome ("jet lag"). As a pharmacological method of treating these types of disorders, the use of agomelatine, long-acting melatonin, and tasimelteon was approved by the European Medicines Agency. Most studies have evaluated the effects of melatonin on jet lag when changing time zones eastward, but there are also few studies showing its effectiveness in treating jet lag with a transmeridian flight (12 time zones) westward [27, 28]. A definitive statement regarding the most effective dose of melatonin in jet lag treatment cannot be made; however, separate studies have shown a greater efficacy of a 5 mg immediate-release melatonin dose relative to the group of patients taking 2 mg delayed-release melatonin [24].

Melatonin, as a dietary supplement, is used widely enough but is not an approved treatment for these types of disorders. The reason for this, as a rule, is the lack of sufficient evidence in the form of clinical trials conducted at the appropriate level to evaluate the clinical effects.

2.2 Melatonin in the treatment of insomnia

Insomnia is a pathological condition caused by a variety of endogenous and exogenous factors. Insomnia is characterized primarily by the difficulty of initiating and maintaining sleep, which results in low-quality daily activity. People suffering from chronic insomnia are usually more prone to psychiatric disorders, primarily anxiety-depressive disorders, and cardiovascular diseases [29]. With age, the prevalence of insomnia increases; one of the reasons for this is an involutional decrease in the level of secretion of melatonin [30], a decrease in its concentration with SCN [6]. According to epidemiological studies, 6% of adults in industrialized countries

suffer from a chronic form of insomnia [30]. In addition to night manifestations, accompanied by an increase in sleep latency, a decrease in sleep time, low sleep efficiency, and an increase in wakefulness during sleep, daytime manifestations of this disease are also formed, namely, fatigue, decreased short-term memory, decreased mood, headaches, and gastrointestinal disturbances intestinal tract [31].

The architecture of sleep begins to change already in adulthood, while initially a decrease in the duration of slow sleep is observed. The main goals of treating insomnia are to improve the quality of sleep and its duration and also to improve daily activity. As polysomnographic markers used to objectify the effectiveness of therapy insomnia, wake time after sleep onset (WASO), sleep onset latency (SOL), the number of awakenings, and sleep effectiveness. Despite this, polysomnography is an optional research method. Its use is advisable in cases of suspected secondary genesis of insomnia, as well as to exclude other sleep disorders.

According to the questionnaire, patients with insomnia have higher values (more than 7 points) when questioning on the Insomnia Severity Index (ISI) scale. According to the Pittsburgh Sleep Quality Index (PSQI), there may be more than 5 points. The Beck Depression Questionnaire demonstrates at least the presence of minimal signs of a depressive state, reaching values of 10 or more points. To assess the long-term effects of therapy, keeping a sleep diary is one of the objective methods (recommendation level IIB, based on expert consensus).

According to the recommendations of the American Academy of Sleep Medicine (AASM) from 2008, the use of benzodiazepines and a melatonin receptor agonist (ramelteon) is recommended as a therapy for primary insomnia (psychophysiological, idiopathic, and paradoxical forms). At the same time, there are no clear recommendations regarding the order of initiation of therapy with one of the groups of these drugs. The simultaneous use of melatonin and benzodiazepines is acceptable, to reduce the severity of side effects of the latter. It has been shown that agonists of melatonin receptors have a positive effect on the subjective quality of night sleep and their positive therapeutic effect is objectively confirmed by a polysomnographic study. At the same time, the main criteria for the effectiveness of the treatment of insomnia are achieved, namely, a decrease in WASO and SOL by at least 30 minutes, a decrease in the frequency of awakenings, an increase in sleep duration of more than 6 hours, and an increase in sleep efficiency (ratio of sleep time to recording time) to 80% or more [32, 33]. However, given the short half-life of melatonin and melatonin receptor agonists (e.g., ramelteon), the main clinical effects of these drugs are aimed at the treatment of presomic disorders [33]. In this case, immediate-release melatonin has no other effects on the structure of night sleep, except as a decrease in sleep latency. At the same time, there are observations demonstrating, but not explaining, the reason for the increase in the efficiency of activation of MT1 receptors with SCN, which increases their sensitivity to melatonin, which may be the basis of the therapeutic effect in relation to presominal disorders [34].

One of the mechanisms for implementing the hypnotic effect of melatonin can be realized through hormonal stabilization of the limbic system, which is involved in adaptogenic behavior [7, 9].

According to the recommendations of the European Sleep Research Society (ESRS) from 2017, based on a meta-analysis of 109 studies with a total number of patients 13,969 for the period from 2005 to 2016, melatonin and melatonin receptor agonists have shown unequivocal efficacy in the treatment of insomnia (weak recommendation – low-quality evidence). According to the results of individual studies, polysomnographic criteria for the effectiveness of insomnia therapy were achieved, namely, a decrease in sleep latency and an increase in the total sleep time and sleep efficiency [35, 36]. In a number of studies, even a decrease in the number

of nocturnal awakenings was noted, which demonstrated effectiveness in relation to intrasomnic disorders. According to these studies, no dependence of the clinical effect on the dose of melatonin used was revealed. A common opinion formed as a result of the analysis of research data is a high safety profile for melatonin.

Melatonin is approved in Europe for the treatment of primary insomnia in adults over the age of 55, with a level of evidence of 1B (level of evidence based on the results of several randomized, placebo-controlled trials) [37].

Studies are demonstrating the effectiveness and perspective use of new forms of melatonin delivery [38]. Modified release tablet formulations with melatonin (MLT) are clinically more useful in initiating and maintaining sleep in elderly insomniacs than those designed for immediate release. The release of MLT from formulation F(nf)2 (nanofiber mats incorporated into 3-layered tablets containing lactose monohydrate both in the upper and lower layers) was found to be in closer alignment with these effects than the other delivery systems [39].

Among healthy children, sleep problems are observed in 20–40% [40] and, among children with impaired development of the nervous system, up to 80% [41, 42]. In pediatric practice, sleep disturbance is most often found among children with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), as well as in anxiety or depressive states [43]. Numerous clinical studies have shown the effectiveness of melatonin in the treatment of falling asleep in patients of various age groups, including children with ASD [44] or adolescents suffering from depression [45]. The physiological concentration of melatonin is crucial for the development of cognitive and behavioral functions [46]. A number of studies have demonstrated a causal relationship between a decrease in melatonin levels and the onset of ASD. Forty percent of children with ASD experienced an increase in serotonin while a decrease in melatonin. An increase in the intermediate metabolite of N-acetylserotonin (NAS) was also observed in 47% of patients [47]. One of the reasons for a decrease in the level of melatonin and an increase in the concentration of its precursor may be due to a violation of the activity of hydroxyindole-O-methyltransferase [46].

Despite the lack of clinical recommendations, the use of delayed-release melatonin is recommended for children with difficulty maintaining sleep, while immediate-release melatonin is recommended for children with difficulty falling asleep [41, 48]. According to individual recommendations (level of evidence C), melatonin should be used as a sleep inducer at a dose of 1–3 mg 30 minutes before bedtime. To obtain chronobiological effects, a melatonin drug should be taken with immediate release 3–4 hours before bedtime at a dose of 0.2–0.5 mg; the maximum dose for children is 3 mg and for adolescents 5 mg [49].

Despite the fact that in a number of studies melatonin has been shown to be effective in treating insomnia in patients with attention ADHD, its effect on cognitive function and behavior in this population of children has not been found [50].

Melatonin has also been shown to be effective in patients with secondary iatrogenic insomnia receiving beta blockers for hypertension [51] as well as in children with attention deficit hyperactivity disorder (level of IA recommendations based on the results of randomized, placebo-controlled clinical trials) [52, 53].

The use of melatonin in pediatric practice is associated with a minimal number of side effects. However, there are reports of undesirable phenomena of mild severity, namely, an increase in the clinical manifestations of nocturnal enuresis, morning drowsiness, and extremely rare insomnia [54].

Thus, according to the main clinical recommendations in the treatment of insomnia, melatonin has a positive effect both on the subjective quality of night sleep and on its objective characteristics. The drug has a high level of evidence of its effectiveness in the long-term therapy of insomnia in patients older than

55 years, associated mainly with the difficulty of falling asleep and the poor quality of night sleep. Ensuring physiological control of the sleep-wake cycle in children with pathology of the development of the nervous system and patients older than 55 years with insomnia is the goal of replacement therapy with melatonin, since in both groups there is a decrease in the secretion of endogenous melatonin during the night [55, 56].

2.3 Melatonin and parasomnia

Parasomnias are undesirable physical or psychological phenomena that usually form at certain stages of sleep, causing a number of clinical manifestations, including the formation of secondary insomnia. Quite often, parasomnia, especially accompanied by motor manifestations, can lead to injuries of varying severity and the formation of psychological problems or social maladaptation [21, 57]. The most striking in its clinical manifestation is REM behavior disorder (RBD). In the treatment of this form of parasomnia, clonazepam is most successfully used. But, the use of this drug is associated with numerous side effects typical of benzodiazepines, especially if the elderly patient has sleep-related breathing disorders (SRBD). An alternative pharmacological method is the use of melatonin. Melatonin also causes a decrease in the frequency and severity of motor activity during an RBD episode, which leads to a decrease in the frequency and severity of injuries. According to the results of a few studies, the use of melatonin at a dose of 3–15 mg led to a significant reduction in paradoxical sleep without atony, as well as the severity of motor manifestations of behavior disorder in the REM phase [58]. One of the options for therapeutic treatment may be taking the drug melatonin for 5–7 days at a minimum dose of 3 mg, followed by an increase in the dose of the drug every 5–7 days to a maximum of 12 mg at night [59, 60]. Little information is available regarding the efficacy of prolonged forms of melatonin or agonists in patients with RBD. There were also no comparisons of the clinical efficacy of clonazepam and melatonin.

Indeed, a number of studies demonstrate a more effective therapeutic effect with the combination of clonazepam and melatonin [61]. The potentiation of the effects of melatonin and clonazepam in the context of RBD therapy has no definitive explanation. It is believed that clonazepam reduces the phase activity inherent in paradoxical sleep, but at the same time, motor activity and minimal disturbance of behavior may remain, according to a polysomnographic survey [62]. The effect of melatonin in combination with clonazepam is due to the modulating effect of the structure of paradoxical sleep, reducing the number of transitions to other stages [59]. An alternative hypothesis explaining the effectiveness of melatonin in RBD may be its effect on increasing the effect of GABA on the GABA receptors of motor neurons of the anterior horns of the spinal cord, which leads to more intense muscle atony. Efficiency may also be related to the fact that melatonin helps to reduce the concentration of calmodulin, which affects the structure of the cytoskeleton and nicotinic acetylcholine receptors of skeletal muscles, which also leads to a progressive decrease in muscle tone [61]. The presence of a favorable safety profile makes the use of melatonin more attractive relative to clonazepam, especially in the elderly [61]. Therefore, in some few clinical trials, melatonin is used as a first-line therapy for RBD, especially in the presence of cognitive impairment, Parkinsonism, or SRBD. In the presence of minimal effectiveness of melatonin or a decrease in its effectiveness during therapy, clonazepam should be additionally prescribed. According to AASM recommendations, melatonin has a “B” level of evidence regarding its effectiveness. Doses of the drug in the studies on the basis of which these recommendations were made ranged from 8 to 12 mg; therefore, there are no clear recommendations regarding the dose of administration [63].

There is also another class of parasomnia in the treatment of which the effectiveness of melatonin was studied. These are parasomnia associated with slow eye movement, which is defined as undesirable motor and psychophysiological manifestations that occur at the time of awakening from a slow-wave sleep. Parasomnia associated with slow eye movement is defined as undesirable motor and psychophysiological manifestations that occur at the time of awakening from a slow-wave sleep [64]. In cases of severe clinical manifestations of these forms of parasomnia, benzodiazepines (clonazepam) or antidepressants (imipramine or clomipramine) may be used. When walking in a dream, the drugs of choice are benzodiazepines or selective serotonin reuptake inhibitors (SSRIs), such as paroxetine and imipramine [64]. The use of melatonin did not reveal a reliable therapeutic effect on the clinical manifestations of these forms of parasomnia. There are only a few studies on the use of melatonin as a first-line therapy for nightly fears in children; the first-line drug is melatonin or L-5-hydroxytryptophan [65]. The absence of a significant clinical effect is associated with the absence of a homeostatic effect on sleep in melatonin.

2.4 Melatonin in the treatment of complications of sleep-dependent respiratory disorders

Sleep-dependent respiratory disorders are represented by several types of pathological conditions: Obstructive sleep apnea (OSA), central sleep apnea, sleep-related hypoventilation, and sleep-related hypoxemia disorder. Most studies are devoted to the study of melatonin metabolism in OSA. A number of studies have demonstrated impaired melatonin secretion in OSA. At the same time, it is believed that the decrease in secretion is secondary. There is also data on the relationship between the concentration of melatonin at night and the duration of night sleep, as well as body weight [66–68]. Some studies have shown a relationship between the severity of OSA and the degree of decrease in melatonin [69]. Approximately 25% of patients with OSA have an altered circadian rhythm of melatonin secretion. In patients with OSA with a maintained rhythm of secretion, peak melatonin levels at night are significantly lower than in healthy people. The 3-month treatment period with continuous positive airway pressure (CPAP) can help restore the physiological rhythm of melatonin in patients with OSA with an impaired secretion profile [70]. One of the uses of melatonin is its use as a drug that reduces the complications associated with respiratory failure during sleep. Numerous studies on biological models demonstrate the positive effect of melatonin on the unfolding pathophysiological cascade of changes in the body in the presence of sleep-dependent respiratory disorders. For example, melatonin inhibits an increase in glucose, the concentration of which increases during periods of apnea [71]. Melatonin modulation of the activity of adenosine monophosphate-activated protein kinase reduces the progression of cardiac muscle hypertrophy. Melatonin also inhibits the expression of inflammatory cytokines, such as tumor necrosis factor alpha, interleukin-6, and cyclooxygenase-2 [72]. It also helps to reduce the severity of Ca^{2+} caused by impaired myocardial contractile function, thus reducing the manifestations of endothelial dysfunction.

The use of melatonin as a prophylactic helps to prevent cardiac remodeling due to hypoxia arising from obstructive apnea [73]. Effects on the cardiovascular system are also realized due to the ability of melatonin and melatonin receptor agonists to inhibit bradykinin B2 receptors, as well as dimerization of angiotensin-converting enzyme I, improving therapeutic control of blood pressure [74]. Another way of realizing the effects of melatonin is the stabilizing effect on angiotensin II receptors and ACE-B2R dimers, which increases the production of nitric oxide by endothelial cells, increasing tissue perfusion. The activation of the MT1 receptor promotes

vasoconstriction and MT2 receptor vasodilation. Thus, melatonin can act as a therapeutic agent in the treatment of cardiovascular diseases and hypertension resulting from comorbid diseases in sleep-dependent respiratory disorders. These effects of melatonin in carotid-dependent respiratory disorders were found as a result of a few studies; therefore, they do not have a sufficient recommended level.

2.5 Melatonin in the treatment of hypersomnia

Hypersomnia, such as type I and type II narcolepsy, and idiopathic hypersomnia, are diseases of which the main clinical syndrome is excessive daytime sleepiness. At the same time, drowsiness, being one of the obligate syndromes of diseases, can be modulated by sleep disturbances, observed in these patients, associated with disturbances in sleep structure, and the stability of being in a slow-wave sleep. Currently, drugs approved by FDA, for example, include methylphenidate, modafinil, oxybate, and pitolisant. Methylphenidate, being an analogue of amphetamine, blocks the transport of dopamine and norepinephrine, increasing their concentration. This drug has a fairly large number of side effects. Modaphenyl is better tolerated but may cause psychological dependence on administration [75]. Oxybate and pitolisant are well tolerated. Pitolisant is currently undergoing an expansion of indications up to 6 years of age in the treatment of types 1 and 2 narcolepsy.

Melatonin can affect the severity of hypersomnia in these patients indirectly due to the effect on the architecture of night sleep. A positive impact on the architecture of night sleep is realized by increasing the representation of paradoxical sleep. The positive effects of melatonin administration in patients with hypersomnia in Parkinson's disease have been described, slowing down the decrease in the loss of dopamine-producing neurons and contributing to the suppression of dopamine transport [76]. Presumably, one of the causes of excessive daytime sleepiness in Parkinson's disease is the decrease in the concentration of melatonin [77]. The use of melatonin in patients with neurodegenerative diseases is promising, since a number of interesting effects of melatonin exposure were obtained on biological models. For example, melatonin, freely penetrating the blood-brain barrier, activates brain-derived neurotrophic factor and cyclooxygenase-10, suppressing plasma tumor necrosis factor (TNF-alpha) and IL-10 levels. In experiments, a decrease in the number of apoptotic cells induced by phenylhydrazine was demonstrated. These studies confirm the role of melatonin in neuroprotection and protection against apoptosis in oxidative damage to neurons [78]. According to domestic guidelines for the treatment of nonmotor manifestations of Parkinson's disease, melatonin is recommended for use as a therapy for excessive daytime sleepiness [79].

3. Conclusion

A decrease in the secretion of melatonin is often observed with aging and diseases of various etiologies. Inadequate sleep hygiene, namely, excessive night illumination or night work, are the most common causes of suppression of pineal melatonin production, which has a chronobiological effect on the body. A decrease in the production of melatonin in some cases can be caused by neurodegeneration, accompanied by a change in the functioning of SCN, disrupting the operation of the circadic oscillator. The most common manifestations of epiphyseal deficiency of this hormone are various functional psychopathological disorders in the form of insomnia, anxiety, or depressive disorders. The role of melatonin is currently being actively discussed in the treatment of insomnia and the sleep-wake cycle disorder. A few clinical studies demonstrate the effects in the treatment of the main

manifestations of such forms of sleep disorders as hypersomnia and parasomnia. A positive effect is noted in the correction of the pathophysiological cascade arising as a result of hypoxia against the background of sleep-dependent respiratory disorders. Thus, the numerous clinical effects of melatonin demonstrate its universal modulating effect on physiological processes in the body and some common features of the pathogenesis of pathological conditions such as insomnia and circadian rhythm disturbances.

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Conflict of interest

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