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Personalized Psychiatry and Neurology

Review

The Role of MicroRNAs as Crucial Regulators of Sleep /Wakefulness in Neurological and Mental Disorders (Systematic Review)

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Abstract: Sleep quality disorders in patients with neurological diseases are a common comorbid pathology that leads to mutual aggravation syndromes, accelerating the progression and severity of neurological conditions. Sleep problems speed up the progression of neurological diseases. In turn, these diseases further reduce sleep quality, this creates a "vicious cycle". The prediction and early diagnosis of sleep quality disorders in patients with neurological profiles require the development of new sensitive and specific biomarkers. Among them, microRNA patterns are the most promising. This report will present the results of preclinical and clinical studies on changes in microRNA expression and their association with sleep quality disorders in experimental animals and humans with various neurological diseases and mental disorders. Additionally, a new personalized approach to assessing the risk of sleep quality disorders in patients with neurological and psychiatric profiles will be presented. This approach evaluates the risk of sleep disorders (low, medium, or high) based on the most thoroughly studied microRNA patterns.

Keywords: *sleep disorder, neurodegenerative disease, mental disorder, epigenetic biomarker, microRNA.*

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1. INTRODUCTION

Sleep disorders are a group of conditions characterized by disruption of the normal circadian rhythm, which negatively impacts psychological well-being and physical health [1]. The International Classification of Sleep Disorders (ICSD), third edition, includes: insomnias; sleep-disordered breathing; central hypersomnia; circadian rhythm sleep-wake disorders; parasomnias; sleep movement disorders; sleep disorder, unspecified; and somatic and neurological disorders associated with sleep [2].

Modifiable and non-modifiable risk factors for sleep disturbances (insomnia) are identified (Table 1) [3].

Non-modifiable risk factors include genetic factors, including polymorphisms in circadian rhythm genes; genes associated with insomnia, bipolar disorder, schizophrenia, etc. Modifiable risk factors, in addition to environmental factors (insolation, noise, xenobiotics), also include the nature of a person's work activity [4]. In recent years, epigenetic risk factors have been studied, among which small non-coding ribonucleic acids (microRNAs or miRs) are of the greatest interest [5].

MicroRNAs are a group of non-coding RNAs, 18–25 nucleotides in length, that regulate gene expression at the post-transcriptional level. The diversity of their mechanisms of action and the complexity of their interaction networks can regulate various biological processes, such as cell division, cell differentiation, apoptosis, angiogenesis, and oncogenesis [6]. MicroRNAs can also influence the development of sleep disorders [7]. Dysregulation of microRNA synthesis causes cellular inflammation and stress, and conversely, increased stress causes dysregulation of microRNA synthesis, creating a vicious cycle leading to nerve cell apoptosis and neurodegeneration in people with sleep disturbances [8].

Table 1. Modifiable and non-modifiable factors of sleep quality disturbances.

Modifiable factors	Non-modifiable factors
Poor sleep hygiene	Sex
Sun exposure	Age
Nature of work (night shift work, flexible work schedules, business trips with time zone changes)	Polymorphisms of genes controlling the circadian rhythm of sleep and wakefulness (*CLOCK, PER 3, PPARGC1A*, etc.)
Caffeine and caffeinated beverage abuse	Polymorphisms of genes associated with insomnia, bipolar disorder, and schizophrenia (*ROR1, PLCB1*, etc.)
Alcohol abuse	
Abuse of psychostimulants prescribed for medicinal purposes	Polymorphisms of genes associated with restless legs syndrome (*MEIS1*, etc.)
Use of other psychostimulants of organic and synthetic origin (mushrooms, amphetamines)	Polymorphisms of genes associated with obstructive sleep apnea (*PHOX2B*, etc.)
Dietary habits (spicy foods containing capsaicin)	
Internet addiction	
Noise pollution	
Epigenetic factors (circulating microRNAs)	

Late identification and untimely correction of modifiable risk factors for sleep quality disorders can lead to the development and progression of chronic insomnia and comorbid neurodegenerative diseases (e.g., Parkinson's disease, Alzheimer's disease, multiple sclerosis, etc.); cardiovascular diseases (hypertension, chronic heart failure, etc.), mental disorders (BD, depression, schizophrenia), endocrine diseases (type 2 diabetes mellitus, metabolic syndrome) [9] [10].

The aim of this review is to summarize and systematize the results of preclinical and clinical studies of the role of microRNAs as epigenetic biomarkers of the development and progression of pathological conditions that play a key role in sleep quality disorders and comorbid neurological diseases and mental disorders.

2. MATERIALS AND METHODS

Russian-language and English-language publications were analyzed in the Google Scholar PubMed, OxfordPress, Clinical Keys, Scopus, and e-Library databases. Inclusion criteria: full-text versions in Russian or English, publication type (original article, systematic review, meta-analysis, Cochrane review). The search was conducted using the following keywords and phrases: sleep quality, epigenetic factors of sleep disorders, chronic insomnia, and microRNA. Publications published from 2018 to 2024 were analyzed, including original preclinical studies on experimental animal models, clinical trials involving patients with sleep disorders and neurological diseases. This review was prepared taking into account the international PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1). A total of 124 publications were analyzed, from which duplicate publications and publications with negative results were excluded. A total of 27 publications meeting the objectives and search criteria were included in this review. MicroRNA studies were conducted using samples from brain, blood (plasma, serum), hematopoietic stem cells, and the immortalized HELA cell line. MicroRNAs were identified as epigenetic biomarkers of sleep disturbances, neurodegenerative diseases, and new therapeutic strategies for sleep disturbances in neurodegenerative diseases.

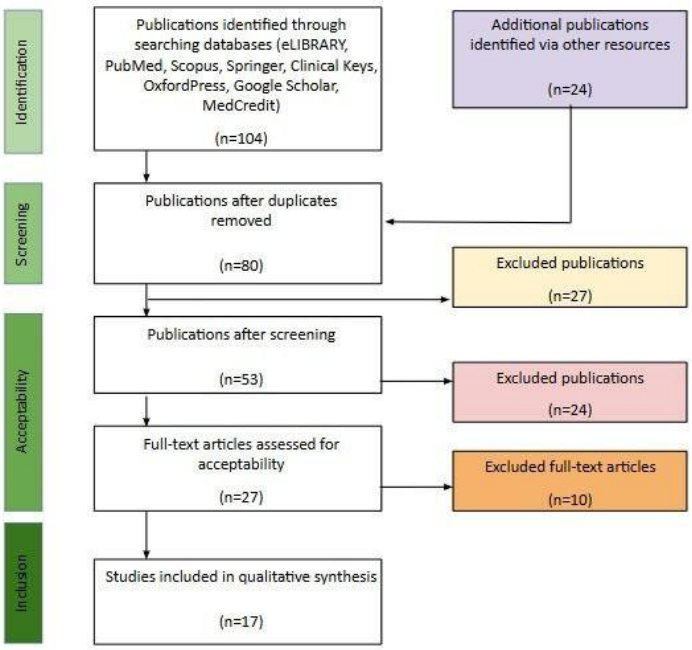

Figure 1. PRISMA 2020 flow diagram of the study selection process.

3. RESULTS

3.1 Preclinical studies

This review analyzed 17 publications on experimental studies performed on various animal models: drosophila [11], zebrafish [12], mice [11], [13], [14], rats [15], [16], [17], [11], sheep [18], and pigs [19]. Brain neurons from experimental animals [19], [20], [16], [17], [5], [12], [11], [18], spinal ganglia neurons [15], and embryonic fibroblast cells [14] were used as tissue samples in which the expression levels of microRNAs associated with sleep quality and circadian rhythm disorders were studied. Seven clinical studies of microRNAs were also analyzed using blood samples (serum, plasma) [15], [21], [22], saliva [5], hematopoietic stem cells (HSCs) [11], as well as three studies performed using HELA cell lines (an "immortal" cell line created specifically for scientific research) [5], [18], [23].

Melatonin (MT) is a pleiotropic regulatory hormone synthesized in the pineal gland at night, modulating ineffective sleep, disrupted circadian rhythms, and immune imbalance. MT is a potent antioxidant, acting on mitochondria, and has anti-inflammatory and pluripotent anticancer properties [26].

Qiu J. et al. (2019) demonstrated that miR-7 overexpression in the porcine pineal gland suppresses MT synthesis and secretion in vitro and in vivo experiments [19]. Overexpression of miR-7 inhibits the expression of AANAAT (arylalkylamine N-acetyltransferase, a pineal gland enzyme that regulates MT synthesis) and blood MT levels [27].

Rolls et al. (2024), studying mouse HSCs, found that sleep deprivation downregulated miR-19b expression, a negative regulator of suppressor of cytokine signaling (SOCS) genes that inhibit HSC migration and homing. Accordingly, HSCs from sleep-deprived mice exhibited higher levels of SOCS gene expression, lower migratory capacity in vitro, and reduced bone marrow homing capacity in vivo. Restoration of sleep after sleep deprivation restored HSC potential to normal. This study provides insight into the cellular and molecular mechanisms underlying the effects of sleep deprivation on HSCs and highlights the potentially important role of donor sleep in the success of HSC transplantation in the treatment of neurodegenerative diseases [11].

Table 2. Preclinical studies of the role of microRNAs in sleep disorders.

MicroRNA	Study design	Tissue	Pathological mechanism of sleep disorder	Reference
miR-7	Experimental study (pigs)	Pineal gland tissue (pinocytes)	Overexpression of miR-7 inhibits the production of AA-NAAT, a key enzyme involved in melatonin synthesis	[19]
miR-19b	Experimental study (rats)	Hematopoietic stem cells	Overexpression of miR-19b is associated with reduced sleep duration	[11]
miR-19b	Experimental study (rats)	Lumbar ganglion cells (neurons). Blood (plasma)	Overexpression of miR-19b is associated with circadian rhythm disturbances in patients with widespread pain syndrome and post-traumatic stress disorder	[15]
miR-25-3p	Experimental study (male mice)	Saliva	Overexpression of miR-25-3p is associated with impaired sleep quality in restless legs syndrome	[13]
miR-30c-5p	Experimental study (male mice)	Saliva	Overexpression of miR-30c-5p is associated with delayed sleep phase syndrome (presomnia)	[13]
miR-124	Experimental study (drosophila with recombinant alleles UAS-DsRed-mir-124)	Neurons	Hypo-expression of miR-124 is associated with sleep quality disturbances due to abnormal motor activity in Drosophila, leading to loss of sensitivity to the morning/evening cycle	[20]
miR-124 miR-182	Experimental study (rats)	Neurons (medial temporal lobe)	Hypo-expression of miR-124 and miR-182 is associated with decreased sleep duration, sleep disorders, and cognitive impairment (memory decline)	[17]
miR-125a	Experimental study (rats)	Neurons	Hypo-expression of miR 125a is associated with a decrease in the duration of	[16]

		(medial temporal lobe, hypothalamus, prefrontal, occipital, and somatosensory cortex)	NREM sleep during the light phase, an increase in NREM sleep during the dark phase, and a decrease in the duration of sleep during the light phase	
miR 132	Experimental study (rats)	Neurons (medial temporal lobe)	Hypo-expression of miR-132 is associated with reduced REM-sleep duration and impaired memory consolidation in the hippocampus.	[17]
miR-132	Experimental study (rats)	Neurons (medial temporal lobe, prefrontal, and somatosensory cortex)	Hypo-expression of miR-132 in the prefrontal and somatosensory cortex is associated with reduced sleep duration Overexpression of miR-132 in the hippocampus is associated with reduced sleep duration	[5]
miR-137, miR-637, miR-654-5p, miR -665	Experimental study (zebrafish)	Brain tissue (hypothalamus, pineal gland)	Hypo-expression of miR-137, miR-637, miR-654-5p and miR-665 results in increased hypocretin synthesis, increased wakefulness and decreased sleep duration	[12]
miR-138	Experimental study (rats)	Neurons (hippocampus, hypothalamus, prefrontal cortex, occipital cortex, and somatosensory cortex)	Hypo-expression of miR-138 in the hypothalamus, prefrontal, occipital, and somatosensory cortex and overexpression in the hippocampus are associated with reduced sleep duration and shortened NREM sleep	[11]
miR -142-3p	Experimental study (rats)	Neurons (suprachiasmatic nucleus of the hypothalamus and immortalized cell lines obtained after knocking down the mPerLuc1 gene)	Overexpression of miR-142-3p is associated with impaired sleep quality and inhibition of the expression of circadian genes *clock* and *bmall*	[24]

miR-146	Experimental study (mice)	Saliva	Overexpression of miR 146 is associated with impaired sleep quality	[25]
miR-199a-5p miR-449a	Experimental study (wild-type mice and mice with a modified clock gene)	Embryonic fibroblast cells. Neurons (suprachiasmatic nuclei of the hypothalamus)	Overexpression of miR-199a-5p and miR-449a is associated with impaired quality of life due to the inhibition of the circadian rhythm gene *per2*	[14]
miR-263a, miR-984 miR-986	Experimental study (drosophila)	Neurons (brain)	Overexpression of miR-263a, miR-984, and miR-986 is associated with reduced daytime and nighttime sleep	[11]
miR-483	Experimental study (rats, rams)	Neurons (pineal gland pinocytes, olfactory tract region, retina)	Overexpression of miR-483 is associated with impaired sleep quality due to the inhibition of AANAAT, a key enzyme involved in the synthesis of melatonin	[18]

Linnstaedt S. D. et al. (2020) found that miR-19b may be a key regulator of circadian transcripts *CLOCK* and *RORα* (genes that control the circadian rhythm of sleep and wakefulness), and that miR-19b overexpression may play an important role in the development of sleep quality disturbances in the context of post-traumatic widespread pain and post-traumatic stress disorder (PTSD) [15]. Hypo-expression of miR-19b was found in patients with idiopathic REM (rapid eye movement) sleep disorder several years before the primary diagnosis of Parkinson's disease or LBD [5].

Yoshida Y. et al. (2023), studying the levels of microRNA expression in the saliva of male mice, also identified an association of miR-30c-5p overexpression with delayed sleep syndrome (presomnia) [25]. The association of miR-124 expression levels and sleep deprivation was studied by Ma Q. et al. (2020) in a study of Drosophila brain neurons with recombinant *UAS-DsRed-mir-124* alleles. It was found that abnormal motor activity in drosophila is associated with miR-124 hypoexpression and leads to a loss of sensitivity to the morning/evening cycle in drosophila [20].

Lyons, L.C. et al. (2023) demonstrated an association between miR-125 hypo-expression and impaired sleep quality. Intraventricular administration of a miR-125a inhibitor resulted in a decrease in NREM-sleep duration during the light phase, an increase in NREM-sleep during the dark phase, and a reduction in sleep duration during the light phase [16].

Meister B. et al. (cited in [28]) demonstrated that intraventricular injection of premiR-132 reduced the duration of NREM and REM sleep in mice.

Davis C.J. et al. (2020) reported that sleep deprivation in rats affects miR-132 expression in a region-specific manner, which in turn increases in the hippocampus but decreases in neurons of the somatosensory and prefrontal cortex after sleep deprivation. It was shown that REM sleep deprivation for a period of 3 to 6 hours impairs memory consolidation, while REM sleep deprivation for a period of 0 to 3 hours had no effect on sleep quality [5]. The association of miR-137, miR-637, miR-654-5p, and miR-665 expression

with hypocretin synthesis and sleep duration impairment was demonstrated by Holm A. et al. (2022). The authors found that hypo-expression of these microRNAs leads to increased hypocretin synthesis, increased wakefulness, and decreased sleep duration in zebrafish [12].

A systematic review by Ahangarpour A. et al. (2024), which analyzed 20 studies published between 1998 and 2021, convincingly demonstrated that miR-138 hypo-expression reduces both sleep duration and NREM sleep in rats subjected to sleep deprivation [11]. Chinnapaiyan S. et al. (2020), studying the expression levels of miR-142-3p in the suprachiasmatic nucleus of the hypothalamus of rats (immortalized cell lines obtained after knocking in the mPerLuc1 gene), found that miR-142-3p overexpression is associated with impaired sleep quality and inhibition of the expression of the circadian genes *clock* and *bmall* [24].

The association of miR-199a-5p and miR-449a with the expression level of the *per2* gene was studied by Wang Y. et al. (2018) in fibroblast cells and neurons of the suprachiasmatic nucleus of the hypothalamus in wild-type mice and mice with a modified clock gene. It is known that CLOCK/ARNTL1 heterodimers can bind to the E-box in the regulatory sequence and activate miR-449a expression. MiR-449a, which acts as a negative regulator of the *per2* gene, affects its 3'-untranslated region. Per2 expression levels are reduced by overexpression of miR-199a-5p and miR-449a. Conversely, PER2 protein levels are increased by inhibition of miR-449a using microRNA antagonists [14].

Yoshida Y. et al. (2023) reported that miR-146 overexpression is associated with reduced sleep duration in mice with restless legs syndrome [25].

Tamplin O. J. et al. (cited in [11]) found that overexpression of miR-263a, miR-984, and miR-986 in Drosophila is associated with reduced sleep duration. The authors also showed that overexpression of the studied microRNAs is associated with both nocturnal and daytime sleep disorders.

An association between miR-483 and sleep impairment was demonstrated in an experimental study by Kim J. Y. et al. (2023). The authors attributed this phenomenon to overexpression of miR-483 and its indirect inhibition of the key enzyme AANAAT, involved in MT synthesis [18].

3.2. Clinical studies

Linnstaedt S. D. et al. (2020) demonstrated that miR-19b overexpression in African Americans aged 18 to 65 years is associated with circadian rhythm disturbances in the setting of widespread pain syndrome and PTSD [15]. Sagir F. et al. (2021), studying microRNA levels in the peripheral blood of patients with multiple sclerosis, showed a negative correlation between BDNF (brain-derived neurotrophic factor) levels and miR-19b expression levels in peripheral blood [33].

Hicks S. D. et al. (2018), studying the expression levels of miR-24-3p, miR-26a-5p, miR-200b-3p, and miR-203a-3p, demonstrated an association between overexpression of the studied microRNAs and increased sleep latency in 140 children (aged 2 to 6 years) with autism spectrum disorder (ASD) and associated sleep quality impairments (n = 63) [29].

Liang Y. et al. (2021) in their systematic review of studies of microRNA levels as prognostic biomarkers in Alzheimer's disease found an association between miR-29 (miR-29a, miR-29b, and miR-29c) hypo-expression and the regulation of APP (beta-amyloid precursor protein) and BACE (β-secretase) and impaired sleep quality in patients with AD. The authors attributed this to increased β-cleavage of endogenous APP-like protein (APPL) by β-secretase (dBACE), which disrupts the circadian sleep-wake cycle [30].

Weigend S. et al. (2019) found that miR-30c overexpression was associated with sleep deficit in young adults (mean age 24 ± 3 years), while restorative sleep reduced the expression of the studied microRNAs [22].

Table 3. Clinical studies of the role of microRNAs as epigenetic markers of sleep disorders.

MicroRNA	Study design	Tissue	Pathological mechanism of sleep disorder	Reference
miR-19b	Case-control (patients with widespread pain syndrome and PTSD)	Blood (plasma)	Overexpression of miR-19b, by altering transcript levels of key circadian genes, is associated with circadian rhythm disturbances in the background of widespread pain syndrome and PTSD	[15]
miR-19b	Case-control study (patients with isolated REM-sleep behavior disorder associated with DaT-positive dopaminergic deficit, PD, DLB, and healthy controls)	Blood (serum)	Hypo-expression of miR-19b was associated with isolated REM-sleep behavioral impairment	[21]
miR-24-3p miR-26a-5p miR-200b-3p miR-203a-3p	Case-control (children with ASD and healthy controls)	Saliva	Overexpression of miR-24-3p, miR-26a-5p, miR-200b-3p, and miR-203a-3p was associated with increased sleep latency (difficulty falling asleep)	[5] [29]
miR-29 (miR-29a, miR-29b, miR-29c)	Case-control (AD patients)	Neurons (anterior temporal lobe, cerebellum)	Hypo-expression of miR-29 paralogs (miR-29a, miR-29b, and miR-29c) was associated with impaired sleep quality in patients with AD	[30]
miR-30c	Case-control (healthy individuals with and without sleep deprivation)	Blood (serum)	Overexpression of miR-30c was associated with reduced sleep duration and impaired sleep quality	[22]
miR-125a miR-126 miR-146	Case–control (patients with short sleep duration and healthy individuals)	Blood (plasma)	Hypo-expression of miR-125a, miR-126, and miR-146 is associated with impaired sleep quality and chronic shortening of sleep duration	[31]
miR-619-5p miR-4433b-3p	Case-control study (patients with sleep disorders and healthy controls)	Blood (serum)	Hypo-expression of miR-619-5p and miR-4433b-3p was associated with impaired sleep quality	[32]

Note: AANAAT - arylalkylamine-N-acetyltransferase, miR - microRNA, AD - Alzheimer's disease, BR - bipolar disorder, HSC - hematopoietic stem cell, DLB - dementia with Lewy bodies, MT - melatonin, NREMS - slow wave sleep, REM - rapid eye movement sleep, HCRT - hypocretin (orexin), PTSD - post-traumatic stress disorder, OSA - obstructive sleep apnea syndrome, ASD - autism spectrum disorder.

Table 4. Clinical studies of the role of microRNAs as epigenetic markers of sleep disorders using cell lines.

MicroRNA	Study design	Tissue	MicroRNA expression level	Reference
miR-181	Clinical study (children with ASD)	Stromal cells (adipose tissue) immortalized stromal cells (bone marrow)	Overexpression of miR-181 is associated with impaired sleep quality in patients with ASD	[23]
premiR-182	Case-control study (patients with major depressive disorder and chronic insomnia and healthy volunteers)	HeLa cells. Blood (plasma)	Overexpression of premieR-183 is associated with sleep quality impairment due to circadian rhythm disruption	[5]
miR-219	Case-control (twins with ASD)	Lymphoblasts (bone marrow cell line)	Overexpression of miR-219 is associated with sleep quality impairment in ASD	[18]

Note: ASD – autism spectrum disorder.

Hijmans J.G. et al. (2019) demonstrated that hypo-expression of miR-125a, miR-126, and miR-146 was associated with sleep quality impairment and chronically reduced sleep duration in middle-aged patients (mean age 55 ± 3 years) sleeping less than 7 hours per night [31].

Baek S.J. et al. (2021), studying the role of epigenetic prognostic biomarkers of sleep deficit, found that miR-619-5p and miR-4433b-3p hypo-expression was associated with reduced nocturnal sleep duration and impaired sleep quality [32].

Knarr M. et al. (2019) demonstrated that miR-181 overexpression is associated with impaired sleep quality in patients with ASD due to increased circadian expression of the PER3 protein (a protein expressed by the Per gene, which controls circadian rhythms of sleep and wakefulness), and is also associated with increased adipogenesis [23].

Kinoshita C. et al. demonstrated in their systematic review that premiR-182 overexpression is associated with impaired sleep quality due to abnormal circadian rhythms in patients with depression and chronic insomnia. (2020) [5], analyzing 89 publications from 2007 to 2019.

A recent systematic review by Kim et al. (2023), based on an analysis of 62 studies from 2008 to 2022, found that miR 219 overexpression is associated with impaired sleep quality in twins with ASD [18].

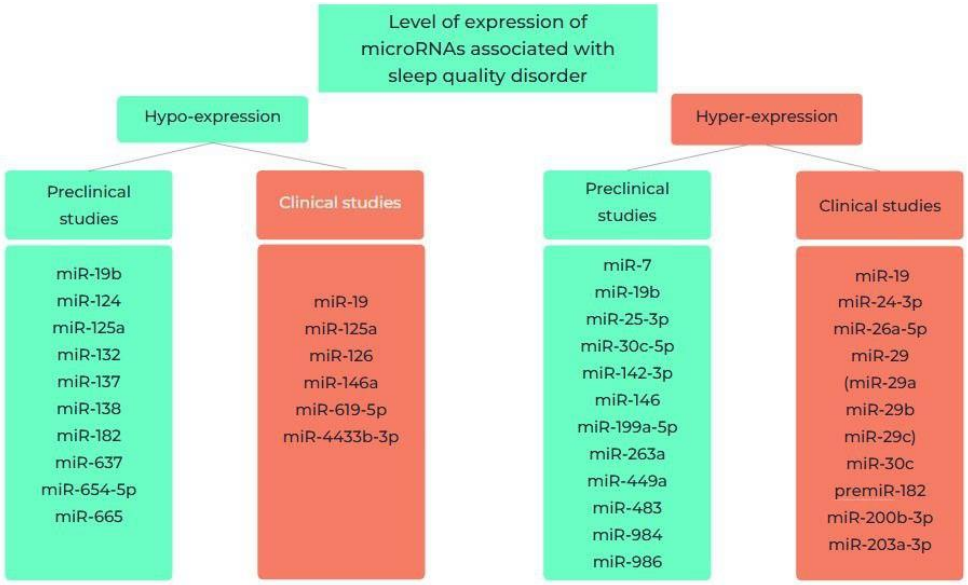

Figure 2. Patterns and levels of microRNAs associated with impaired sleep quality.

Figure 3. Risks of developing sleep quality disorders based on the studied microRNA patterns.

4. DISCUSSION

The systematic review of the role of microRNAs as epigenetic biomarkers of sleep impairment, based on the analyzed and summarized results of 17 experimental studies, 7 clinical trials, and 3 studies conducted using cell lines, demonstrated that the most promising epigenetic biomarkers are miR-19b and miR 146, the role of which has been studied in both preclinical [21], [25] and clinical studies [15], [31]. However, the association of miR-19b and miR 146 expression levels with sleep impairment is contradictory. Thus, in some studies, hypo-expression of miR-19b and miR 146 was associated with sleep impairment, while in others, overexpression of these microRNAs negatively impacted sleep quality. This phenomenon can be explained by a compensatory increase in microRNA expression at the onset of sleep impairment, as well as by different microRNA concentrations depending on the tissue studied. Another well-studied microRNA is miR-125a. The results

of studies on the role of this microRNA are more consistent and indicate that hypo-xpression of miR-125a is associated with impaired sleep quality [31], [16].

MiR-30c is also a potential epigenetic biomarker for impaired sleep quality, as overexpression of this microRNA has been associated with impaired sleep quality and demonstrated in both preclinical [25] and clinical studies [22], but sample sizes were small, and the studies conducted so far are isolated.

Overall, our systematic review allowed us to group previously studied epigenetic biomarkers of impaired sleep quality based on the degree of risk for developing this pathological condition, including low risk, intermediate risk, and high risk (Figure 3). On the other hand, we understand that translation of the obtained results requires additional clinical bridge studies to assess the sensitivity and specificity of the most studied microRNAs associated with sleep quality disorders in the most common neurological diseases and mental disorders.

5. CONCLUSION

MicroRNAs are stable epigenetic biomarkers that can regulate various biological processes, particularly influencing the development and progression of sleep disturbances in neurodegenerative diseases and psychiatric disorders. Growing evidence suggests that sleep disturbances and comorbid conditions alter the levels of certain microRNAs that regulate circadian rhythms of sleep and wakefulness. This systematic review demonstrates the role of microRNAs as epigenetic biomarkers of sleep disturbances in the progression and severity of neurological diseases and psychiatric disorders. These results suggest that clinically significant changes in the expression pattern of microRNAs in patients with sleep disturbances may serve as biomarkers for the development of comorbid neurodegenerative diseases and psychiatric disorders. Furthermore, the regulation of microRNA expression may serve as a potential therapeutic tool for sleep-related disorders in neurological practice. To improve the sensitivity and specificity of blood microRNAs as epigenetic biomarkers of sleep disorders, bridging studies are needed to replicate the results of preclinical and clinical studies obtained worldwide into real-world clinical practice.

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