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CIRCADIAN RHYTHM AND SLEEP DISTURBANCES IN NEURODEGENERATION: BIOMARKERS, DISEASE PROGRESSION, AND INTERVENTIONS

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ABSTRACT

In neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and frontotemporal dementia, sleep disturbances and dysregulation of the sleep–wake cycle constitute a significant clinical problem. These disturbances are not only a manifestation of disease progression but may also contribute to its exacerbation through complex effects on physiological processes. This article analyzes the relationship between neurodegenerative disease progression and sleep disorders, considering molecular, neurophysiological, and digital biomarkers as well as the effectiveness of chronobiological interventions. The review indicates that circadian rhythm disturbances occur in all aforementioned disease entities and are strongly associated with motor and neuropsychological symptoms. Interventions targeting insomnia-such as lifestyle modification, melatonin supplementation, and light therapy-demonstrate moderate efficacy in improving cognitive function. Biomarkers used to assess their effectiveness include changes in EEG, cortisol and melatonin profiles, and the expression of clock genes (PER2, BMAL1).

KEYWORDS

Circadian Rhythm, Sleep Disturbances, Neurodegeneration, Biomarkers, Melatonin, Alzheimer's Disease, Parkinson's Disease, Chronobiological Interventions

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Methodology

This review was developed as a narrative synthesis with elements of a semi-systematic literature review aimed at integrating mechanistic, experimental, and clinical data. A systematic search was performed across PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library. The search covered the period from January 2000 to November 2025. The review included meta-analyses and systematic reviews focusing on behavioral, pharmacological, and technological interventions aimed at improving sleep quality, circadian rhythm biomarkers, and sleep disturbances in neurodegenerative diseases. Inclusion criteria encompassed studies on adult populations with clinically or neuropathologically confirmed neurodegenerative disorders (AD, PD, HD, FTD, LBD). Where possible, data from large cohort studies and meta-analyses were used to summarize quantitative trends.

Introduction

The primary center controlling the circadian rhythm is the suprachiasmatic nucleus (SCN) of the hypothalamus, which regulates the expression of "clock genes," such as BMAL1, PER, and CRY, thereby governing the normal course of physiological processes [1,2]. Efficient synchronization of circadian rhythms is essential for maintaining organismal homeostasis. However, with aging, this synchronization weakens, leading to reduced sleep quality and increased sleep fragmentation [3].

Sleep disturbances are among the early symptoms of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Lewy body dementia (LBD). Circadian rhythm dysregulation-manifesting as nighttime motor activity, excessive daytime sleepiness, REM sleep disturbances, and reduced deep sleep-often precedes cognitive and motor symptoms by many years [4,5]. These phenomena correlate with increased neuroinflammation, β-amyloid and α-synuclein deposition, and dysfunction of glial-mediated brain clearance mechanisms [6–8].

Increasing evidence indicates that sleep disturbances are not only symptoms of neurodegenerative diseases but also actively influence their course and pathogenesis. Chronic sleep disruption exacerbates oxidative stress, mitochondrial dysfunction, microglial activation, and the accumulation of pathological proteins [9]. In many neurodegenerative disorders, structures involved in circadian regulation-such as the pineal gland and SCN-undergo degeneration, further worsening rhythm disturbances [10]. Methods for assessing circadian rhythm-such as actigraphy, melatonin level analysis, polysomnography, sleep EEG, and digital biosensors-enable precise monitoring of sleep abnormalities. Chronobiological interventions, including melatonin and light therapy, offer partial correction of sleep–wake dysfunction.

Circadian Rhythm and Sleep in the Context of Brain Function

A healthy sleep–wake rhythm is essential for homeostasis, physical and mental health, and plays a neuroprotective role. It promotes memory consolidation, clearance of toxic metabolites from the interstitial space, and supports neuroplasticity. Its disturbances-such as reduced NREM sleep, frequent awakenings, or circadian fragmentation-lead to neurotoxin accumulation and accelerate neurodegenerative processes [11]. Activation of the glymphatic system during NREM sleep facilitates β-amyloid clearance [12,13].

The circadian rhythm is based on feedback loops regulating CLOCK, BMAL1, PER, and CRY gene expression. CLOCK and BMAL1 proteins form a transcriptional complex activating PER and CRY expression, whose protein products inhibit their own transcription, generating ~24-hour oscillations [14]. Signals from retinal ganglion cells and peripheral clocks (e.g., in the liver and muscles) are integrated by the SCN, enabling proper cognitive and emotional functioning [15].

Neuroimaging and molecular studies show that early circadian disruptions in AD and PD patients are associated with SCN neuron degeneration, decreased BMAL1 and PER2 expression, and reduced nocturnal melatonin secretion [16,17].

Circadian Rhythm and Sleep Disturbances in Neurodegenerative Diseases

Alzheimer's Disease (AD)

Sleep disturbances in AD may occur years before characteristic cognitive deficits appear [18]. Underlying mechanisms include reduced melatonin receptor density, impaired melatonin secretion, SCN neuron degeneration, and decreased expression of clock genes (BMAL1, PER2) [19,20]. Post-mortem studies show a relationship between sleep disturbances and deposition of phosphorylated tau and β-amyloid [21].A highly characteristic symptom is evening agitation and behavioral dysregulation-known as "sundowning syndrome"-resulting from SCN dysfunction [22]. AD is also associated with NREM sleep reduction, REM sleep deficits, reduced total sleep time, and shortened REM latency [11].

Sleep disturbances contribute to AD pathogenesis: fragmented sleep suppresses glymphatic clearance of β-amyloid, creating a vicious cycle-sleep disruption increases amyloid accumulation, which further worsens sleep [8,12].

Parkinson's Disease (PD)

PD commonly features REM sleep behavior disorder (RBD), in which patients physically act out dreams with intense motor activity. RBD is considered an early marker of α-synucleinopathy, often appearing years before motor symptoms [23,24]. Other mechanisms include atrophy of gray matter structures, thalamic and raphe nucleus abnormalities, dopaminergic dysfunction, and altered cortisol–melatonin rhythms. These changes lead to frequent awakenings, reduced NREM sleep, and circadian activity fragmentation [17,25]. Parasomnias are also frequent.

Lewy Body Dementia (LBD)

Neurodegeneration in LBD affects not only the SCN but also cholinergic and serotonergic brainstem nuclei [26]. RBD is highly characteristic and often co-occurs with attention deficits and hallucinations. Circadian rhythm disturbances in LBD are more severe than in AD, with a marked loss of normal day–night variation and profound REM sleep abnormalities [27].

Huntington's Disease (HD)

At the molecular level, HD involves impaired expression of BMAL1 and PER2 in the SCN and cerebral cortex [28], leading to shortened sleep time, reduced body temperature rhythm amplitude, and unstable sleep–wake cycles [29]. These abnormalities occur both in symptomatic patients and in the presymptomatic stage [30].

Amyotrophic Lateral Sclerosis (ALS)

In ALS, sleep disturbances arise from degeneration of serotonergic pathways and impaired cortisol and melatonin secretion [31]. Patients experience excessive daytime sleepiness, sleep fragmentation, and sleep-related breathing disorders, which influence disease progression [32]. Circadian dysregulation in ALS is likely underestimated.

Biomarkers Related to Circadian Rhythm and Sleep

The identification of molecular, behavioral, neurophysiological, and hormonal markers associated with the sleep–wake cycle is important for diagnosis, monitoring disease progression, and evaluating treatment efficacy.

Key molecular and genetic biomarkers include alterations in clock gene expression. Studies report reduced BMAL1 and PER2 expression in the hippocampus in AD, directly linked to tau accumulation [33]. In PD, decreased CLOCK and CRY1 expression and disrupted rhythmicity of dopaminergic gene transcription have been observed [34]. Peripheral leukocyte expression of circadian genes is also being explored as a biomarker for early AD and PD diagnosis [35].

Melatonin and cortisol are essential hormonal markers of the sleep–wake cycle. Changes include reduced nocturnal melatonin peak, flattened amplitude, and disrupted synchronization with cortisol rhythms in PD and AD [36,37]. Actigraphy studies show correlations between these changes and cognitive/neuropsychiatric symptoms [38].

EEG remains a fundamental tool for monitoring sleep quality. Some EEG patterns are characteristic of specific neurodegenerative diseases. In PD and LBD, REM atonia loss (as in RBD) is a key indicator of α-synucleinopathy [39]. Modern technologies such as actigraphy, smartwatches, and wearable sensors measure parameters including intradaily variability (IV) and interdaily stability (IS), which correlate with dementia severity and may predict disease progression [40,41].

IoT systems and mobile applications enable real-time sleep analysis and contribute to developing digital biomarkers. Integrating data from actigraphy, EEG, and hormonal analyses provides a precise picture of circadian dysregulation across disease stages [42].

Circadian biomarkers may support early detection-even before symptom onset—monitoring therapeutic response, and personalizing treatments based on activity patterns and optimal medication timing. However, standardized biomarker criteria are lacking. Large longitudinal cohorts are needed to advance this field.

Therapeutic Interventions

Research demonstrating the role of sleep disturbances in neurodegeneration highlights the need for interventions targeting circadian regulation and sleep quality to slow disease progression.

Melatonin plays a key role in treating sleep disorders, as its levels are markedly reduced in neurodegenerative diseases. Supplementation can reduce evening agitation, decrease activity rhythm fragmentation in AD, and improve overall sleep quality [43,44]. Effective doses range between 2–10 mg before bedtime. In PD, melatonin alleviates RBD symptoms by reducing motor events during REM sleep [45]. Agonists of melatonin receptors (tasimelteon, ramelteon) are being studied in dementia and PD [46]. Bright light therapy (BLT) - 30-min exposure to 10,000-lux LED light for 4–6 weeks — improves sleep architecture and cognitive function in AD patients [47], with similar effects reported in PD [48]. In dementia, BLT stabilizes circadian rhythms, reduces evening agitation, improves daytime alertness, and normalizes melatonin secretion [49,50]. Evening exposure, however, may delay circadian phase and worsen sleepiness [51].

Chronopharmacology—personalizing medication timing according to circadian patterns-may increase efficacy and reduce side effects. For example, dopaminergic therapy in PD is more effective when administered

according to circadian activity rhythms [52,53].Non-pharmacological approaches include circadian rhythm training (regular sleep schedules, daytime light exposure, structured routines), physical activity, and diets rich in antioxidants and tryptophan to support melatonin and serotonin synthesis and stabilize metabolic rhythms [54]. Physical activity improves mood, circadian stability, and melatonin levels [55]. Wearable technologies allow continuous monitoring of sleep and activity patterns, enabling individualized chronotherapy protocols. AI algorithms can analyze sleep, heart rate, and activity data to optimize treatment strategies [56,57].Future treatment should integrate chronotype, disease stage, and circadian genetics to develop fully personalized schedules for light therapy, sleep regulation, and pharmacotherapy [57].

Methodological Challenges

Research on sleep disturbances in neurodegenerative diseases faces several limitations, including lack of standardized circadian biomarkers, heterogeneity of patient populations, and variation in sleep assessment methods.

Circadian disturbances vary significantly across disease stages. In AD, rhythm disturbances differ between prodromal (MCI), early dementia, and advanced stages [58]. Insufficient staging precision and inadequate control for confounders (medications, depression, vascular dementia) reduce comparability between studies.Most intervention studies are short-term. Translational research combining neurobiology, endocrinology, and chronopsychology is necessary to evaluate long-term effects of circadian interventions on disease progression and cognition [59,60].

Conclusions and Therapeutic Recommendations

Current evidence shows a significant correlation between sleep–wake rhythm disturbances and the progression and pathogenesis of neurodegenerative diseases. These disturbances influence numerous physiological processes - including clock gene expression, cortisol and melatonin secretion, neuroinflammation intensity, and glymphatic clearance efficiency - all of which may contribute to neurodegeneration [12].

Restoring normal sleep architecture through light therapy, melatonin supplementation, and daytime light exposure may slow disease progression and improve cognitive function [17,61].Circadian biomarkers - biochemical (melatonin, cortisol) and digital — hold diagnostic and prognostic potential. Meta-analyses confirm that AD and PD patients exhibit significantly reduced nocturnal melatonin levels and altered cortisol rhythms [62]. Disturbed melatonin–cortisol profiles and reduced amplitude of body temperature rhythms correlate with cognitive and affective symptoms.Wearable-derived digital markers enable long-term, noninvasive monitoring of sleep architecture and may facilitate early disease detection [63].Sleep disturbances frequently precede clinical symptoms of neurodegeneration. In AD, circadian fragmentation correlates with β-amyloid and tau deposition years before cognitive impairment becomes evident [6]. In PD, RBD and excessive daytime sleepiness are established prodromal markers, preceding motor symptoms by 5–15 years.Multidimensional diagnostic models combining molecular, hormonal, and digital biomarkers are a key future direction. Integrating clock gene expression, melatonin profiles, and actigraphy data may enable the identification of patients in prodromal stages [38].

Practical Recommendations for Patients with Neurodegenerative Diseases

- Educate healthcare providers, patients, and caregivers about the impact of sleep quality on disease progression.
- Consider melatonin supplementation in AD and PD (2–5 mg before bedtime).
- Implement sleep hygiene practices, regular physical activity, and a balanced diet.
- Use bright light therapy (BLT) for mood and circadian rhythm disturbances.
- Include routine sleep quality assessment as part of neurological diagnostics, particularly for early detection of AD and PD.

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