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SLEEP DEPRIVATION AND CIRCADIAN RHYTHM DISTURBANCES IN NEURODEGENERATIVE DISEASES: MECHANISMS, CLINICAL CONSEQUENCES, AND PREVENTIVE STRATEGIES

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ABSTRACT

Sleep and circadian rhythms play crucial roles in maintaining neural homeostasis, synaptic plasticity, and metabolic clearance within the brain. Increasing evidence indicates that chronic sleep deprivation and circadian misalignment are not merely symptoms of neurodegeneration but active drivers of its onset and progression. This review synthesizes current findings linking disrupted sleep and circadian regulation to neurodegenerative diseases, with emphasis on molecular mechanisms, clinical implications, and therapeutic opportunities. Mechanistically, sleep loss impairs glymphatic and meningeal lymphatic clearance of neurotoxic proteins, compromises blood-brain barrier integrity, and promotes oxidative stress, neuroinflammation, mitochondrial dysfunction, and clock gene dysregulation. These interconnected processes accelerate the aggregation of amyloid-β, tau, α-synuclein, and TDP-43, thereby amplifying neuronal injury. Clinically, sleep and circadian disturbances predict cognitive decline, neuropsychiatric symptoms, biomarker progression, and earlier disease onset across Alzheimer's disease, Parkinson's disease, and related disorders. Preventive and therapeutic strategies, including cognitive-behavioural interventions, light therapy, melatonin supplementation, orexin antagonism, and structured circadian routines, show promising neuroprotective potential. Restoration of sleep architecture enhances glymphatic clearance, reduces neuroinflammation, and stabilizes cognitive function. Recognizing sleep as a modifiable determinant of neurodegeneration reframes it from a passive state into an active therapeutic target, underscoring its pivotal role in preserving brain integrity and delaying neurodegenerative trajectories.

KEYWORDS

Sleep Deprivation, Circadian Rhythm Disruption, Neurodegeneration, Alzheimer's Disease, Parkinson's Disease, Neuroinflammation, Neuroprotection

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1. Introduction

Sleep is a fundamental physiological process essential for brain homeostasis, synaptic plasticity, and cognitive performance. Decades of research have demonstrated that adequate sleep and robust circadian rhythms support neural repair, metabolic regulation, and clearance of neurotoxic waste (e.g. β-amyloid and tau). Disruption of these systems has been increasingly implicated in the pathogenesis of multiple neurodegenerative diseases. Beyond its restorative function, sleep represents an active neurobiological state that regulates synaptic pruning, neuronal network reorganization, and the coordination of glial activity involved in metabolic clearance. The oscillation between sleep and wakefulness therefore maintains the delicate balance between neuroplasticity and proteostatic control, both of which are critical for long-term neuronal survival.

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are characterized by progressive neuronal loss and functional decline. While their etiologies are multifactorial - encompassing genetic, environmental, and lifestyle risk factors - recent evidence suggests that sleep deprivation and circadian misalignment are not merely downstream symptoms but may actively contribute to disease onset and accelerate progression. The interaction between sleep and neurodegeneration is increasingly conceptualized as bidirectional: while neuronal injury in disease-specific regions (e.g., basal forebrain, hypothalamus, brainstem) disrupts sleep-wake regulation, inadequate sleep in turn intensifies neurodegenerative cascades. In experimental models, repeated sleep deprivation in mice produces elevated levels of toxic protein variants, including oligomeric forms of amyloid-β, tau, α-synuclein, and TDP-43 in multiple brain regions after only a few days of disturbance (Rowe et al., 2024). These observations suggest that chronic perturbation of sleep architecture can mimic, and even amplify, the molecular signatures typical of neurodegeneration.

The circadian rhythm, orchestrated by the suprachiasmatic nucleus (SCN) in concert with peripheral clocks, regulates the temporal organization of physiological functions including hormone secretion, synaptic plasticity, immune responses, and metabolism. Perturbations in circadian timing, such as misaligned light-dark cycles or dysfunction of core clock genes, can compromise these processes. The SCN not only synchronizes peripheral oscillators but also integrates environmental cues like light and feeding schedules, allowing the organism to anticipate metabolic and behavioural demands. Disturbance of this coordination results in systemic desynchrony, a state that undermines both metabolic efficiency and neuronal health. For example, in mouse models of AD (APP_SWE/PS1_dE9), alterations in locomotor activity, increased wakefulness, and reduced non-REM sleep appear even in early, "plaque-free" disease stages; these are accompanied by aberrant expression of core clock genes in the SCN, hippocampus, and cortex (Yang et al., 2025). Such findings underscore that circadian dysfunction may precede visible pathology and may represent a preclinical biomarker of neuronal stress.

Clinically, sleep disturbances are among the earliest non-motor features of many neurodegenerative disorders and often precede overt cognitive or motor decline. In Parkinson's disease, disorders such as REM sleep behaviour disorder (RBD), excessive daytime sleepiness, and insomnia may manifest years before the appearance of classic motor symptoms (dos Santos et al., 2015; Videnovic & Golombek, 2013; Zoccolella et al., 2011). The high prevalence of such disturbances in prodromal stages supports the hypothesis that sleep and circadian alterations may serve as early harbingers of neurodegenerative processes. Similarly, in aging human populations at risk for Alzheimer's pathology, increased circadian rhythm fragmentation and shifted circadian phase have been associated with higher burdens of amyloid-β, tau, and cognitive decline (Eckhardt et al., 2025). Together, these findings demonstrate that sleep and circadian health are intimately linked with both the development and the clinical evolution of neurodegenerative diseases.

Mechanistically, sleep deprivation impairs the clearance of misfolded proteins via systems such as the glymphatic and meningeal lymphatic pathways, elevates neuroinflammation and oxidative stress, and can disrupt mitochondrial function. The resulting cascade of cellular stressors feeds back to further destabilize circadian homeostasis, producing a self-reinforcing cycle of dysfunction. Damage to clock gene regulation further exacerbates these perturbations (Bishir et al., 2020; Madamanchi et al., 2025; Yang et al., 2025). This complex interplay suggests that restoring sleep and circadian alignment may not only alleviate symptoms but also modify the underlying disease trajectory.

This review aims to (1) synthesize current knowledge about the molecular, cellular, and systemic mechanisms linking sleep deprivation and circadian rhythm disturbances with neurodegenerative pathology; (2) evaluate the clinical consequences, including prodromal markers, symptom burden, and disease progression; and (3) discuss emerging preventive and therapeutic strategies, with particular attention to translational potential and existing gaps. The overarching goal is to clarify the bidirectional relationship between sleep and neurodegeneration and to highlight sleep restoration as a promising, though underutilized, therapeutic avenue in neurodegenerative disease management.

2. Mechanisms

2.1 Impaired clearance of neurotoxic proteins: the glymphatic-lymphatic interface and blood-brain barrier dysfunction

One of the most extensively discussed mechanisms linking sleep deprivation to neurodegeneration involves the disruption of metabolic clearance pathways responsible for removing neurotoxic waste products such as amyloid-β (Aβ) and tau. During restorative sleep, the glymphatic system - a perivascular network facilitating cerebrospinal fluid (CSF) influx and interstitial solute clearance - exhibits markedly increased activity, effectively promoting the elimination of aggregated proteins and metabolites This clearance is driven by astrocytic aquaporin-4 (AQP4) channels, whose polarization to vascular endfeet is critical for efficient CSF-interstitial fluid exchange. Sleep loss, conversely, impairs this system, resulting in the accumulation of neurotoxic molecules and the gradual saturation of perivascular pathways (Eide et al., 2023).

Human studies have demonstrated that even a single night of total sleep deprivation leads to significant alterations in plasma and CSF concentrations of Aβ40/42 and other biomarkers associated with impaired meningeal lymphatic drainage and CSF efflux to the bloodstream (Ooms et al., 2014). Such transient fluctuations are thought to mirror the chronic accumulation seen in long-term sleep disruption, suggesting that even short episodes of sleep loss may trigger measurable neurochemical consequences. Moreover, alterations in AQP4 distribution observed under circadian misalignment further compromise glymphatic transport

efficiency, implying that not only sleep quantity but also the timing of sleep within the circadian cycle is crucial for optimal clearance.

In parallel, experimental evidence suggests that chronic sleep restriction compromises the integrity of the blood-brain barrier (BBB), increasing vascular permeability and facilitating the entry of inflammatory mediators into the central nervous system (He et al., 2014). BBB breakdown exposes neurons to circulating cytokines and immune cells, amplifying oxidative and inflammatory cascades that perpetuate neural damage. These vascular changes often precede overt neurodegenerative pathology, highlighting BBB dysfunction as an early biomarker of disease progression.

Animal studies have corroborated these findings, showing that repetitive sleep disruption induces widespread accumulation of neurodegeneration-related proteins - including Aβ, tau, α-synuclein, and TDP-43 - across multiple brain regions. Notably, short-term sleep deprivation in mice is sufficient to elevate immunoreactive levels of these toxic species within the cortex, hippocampus, and brainstem (Rowe et al., 2024). The convergence of glymphatic inefficiency and vascular leakage thus creates a dual impairment in brain waste management, leading to chronic neurotoxic stress that accelerates disease-related protein aggregation.

2.2 Oxidative stress, neuroinflammation, and mitochondrial dysfunction

Sleep deprivation and circadian misalignment provoke a state of sustained oxidative stress, reflected by excessive production of reactive oxygen and nitrogen species (ROS/RNS), mitochondrial overload, and impaired antioxidant defence. Such redox imbalance leads to DNA damage, lipid peroxidation, and protein oxidation - events that collectively accelerate neuronal death and synaptic deterioration. The brain, characterized by high oxygen consumption and limited antioxidant capacity, is particularly vulnerable to these oxidative insults.

Concurrently, sleep loss triggers a neuroinflammatory cascade characterized by microglial activation, astrocytic hypertrophy, and upregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6). These processes not only potentiate neuronal injury but also disrupt synaptic remodelling and plasticity, thereby aggravating cognitive dysfunction. Chronic activation of glial cells contributes to maladaptive pruning of synapses, impaired long-term potentiation, and progressive circuit instability. Over time, this persistent inflammatory state resembles the microglial priming observed in neurodegenerative conditions (Owen & Veasey, 2020).

In addition, mitochondrial impairment constitutes a pivotal intersection between oxidative stress and neuroinflammation. Sleep deprivation alters mitochondrial dynamics, reduces ATP generation, and hampers mitophagy - the selective clearance of damaged mitochondria - thus establishing a self-perpetuating cycle of energetic failure and oxidative burden (Sarnataro, 2025). Disrupted circadian regulation of mitochondrial biogenesis and fusion-fission balance further aggravates this dysfunction. Mitochondria, unable to meet neuronal energy demands, release proapoptotic factors and amplify ROS production, promoting cell death cascades. Importantly, evidence suggests that restoring circadian rhythm stability can normalize mitochondrial gene expression and partially rescue oxidative balance, reinforcing the interdependence of sleep, cellular energetics, and neuronal survival.

2.3 Disruption of proteostatic systems: autophagy and proteasomal degradation

The maintenance of neuronal proteostasis relies on two major degradation pathways: the autophagy-lysosome system and the ubiquitin-proteasome system. Sleep loss has been shown to inhibit both, resulting in reduced clearance of misfolded or aggregated proteins. Defective autophagy, in particular, promotes the intracellular accumulation of tau, Aβ, α-synuclein, and TDP-43 - proteins central to the pathology of AD, PD, and ALS (Morrone et al., 2023).

Beyond mere inhibition of autophagic flux, sleep deprivation also disrupts the temporal coordination of proteolytic activity that normally follows circadian rhythms. Lysosomal enzyme expression peaks during sleep, aligning cellular clearance with periods of reduced neuronal firing and metabolic demand. When this synchronization is lost, autophagic degradation becomes inefficient, and the accumulation of toxic intermediates further impairs lysosomal function. Over time, such proteostatic collapse diminishes neuronal resilience, rendering cells more susceptible to oxidative and metabolic insults.

Experimental data suggest that sleep and circadian integrity enhance autophagic flux, while circadian disruption suppresses transcription of autophagy related genes and lysosomal enzymes (‘Impact of Sleep on Autophagy and Neurodegenerative Disease’, 2022). Impaired proteasomal degradation similarly leads to an

imbalance in ubiquitinated proteins and defective removal of damaged organelles, contributing to cytoskeletal destabilization and impaired axonal transport. Consequently, persistent sleep deprivation fosters a cellular environment characterized by cumulative proteotoxic stress, which mirrors key histopathological signatures of neurodegenerative disorders.

2.4 Dysregulation of molecular clock genes

The circadian system operates through transcription-translation feedback loops involving core clock genes such as CLOCK, BMAL1, PER, and CRY. These oscillators regulate thousands of downstream targets controlling metabolism, DNA repair, oxidative stress responses, and synaptic signalling. Perturbations in these feedback loops, induced by environmental or pathological stressors, can thus have widespread neurobiological consequences (Konakchieva et al., 2025; Musiek et al., 2013).

Aberrant expression of clock genes has been reported in multiple brain regions (including the suprachiasmatic nucleus, hippocampus, and substantia nigra) in animal models and patients with Alzheimer's and Parkinson's diseases (Chen et al., 2024). Dysregulated clock gene expression disrupts circadian modulation of neuronal excitability, neurotransmitter synthesis, and synaptic plasticity, thereby impairing both cognitive and motor circuits. In murine models of Alzheimer's disease, BMAL1 and PER1 dysregulation correlates with accelerated amyloid deposition and neuronal loss (Carter et al., 2021).

Furthermore, BMAL1 deficiency has been shown to enhance neuroinflammation via activation of the NF-κB pathway, suggesting that circadian disruption and inflammation form a pathological feedback loop (Fagiani et al., 2022). This crosstalk between the molecular clock and immune signalling highlights how circadian dysfunction may not only reflect neuronal degeneration but actively drive it. The downstream transcriptional dysregulation also affects genes linked to mitochondrial maintenance and antioxidant defence, thereby connecting clock gene alterations to the broader network of oxidative and proteostatic stress.

2.5 Interactions and synergistic amplification

The aforementioned mechanisms are not independent phenomena but rather interlocking components of a self-reinforcing pathogenic network. Impaired clearance of neurotoxic proteins intensifies oxidative and inflammatory stress; oxidative stress in turn damages mitochondria and suppresses autophagic efficiency; circadian gene dysregulation further disrupts proteostasis and mitochondrial turnover (Baser et al., 2025; Lu & Guo, 2020).

This cyclical interaction creates a feed-forward loop wherein sleep and circadian disruption accelerate the very molecular processes driving neurodegeneration. For instance, glymphatic impairment not only allows toxic protein buildup but also exacerbates neuroinflammatory activation, which further compromises BBB integrity and glymphatic function. Similarly, mitochondrial dysfunction contributes to ROS accumulation that disrupts clock gene expression, linking metabolic collapse to circadian instability.

Consistent with this model, chronic sleep fragmentation in animal studies has been shown to amplify α-synuclein and tau pathology within cortical and hippocampal circuits critical for cognition and motor control (Rowe et al., 2024). Ultimately, these synergistic mechanisms establish a vicious cycle in which disrupted sleep and circadian rhythms both precipitate and perpetuate neurodegenerative cascades. Breaking this cycle through chronobiological or sleep-targeted interventions may therefore hold promise for delaying or mitigating the progression of neurodegenerative diseases.

3. Clinical Consequences

Disruptions in sleep and circadian rhythms exert profound effects on the clinical trajectory of neurodegenerative diseases: they worsen cognitive decline, exacerbate neuropsychiatric symptoms, accelerate biomarker progression, and degrade overall quality of life. Importantly, these alterations are not merely epiphenomena of underlying neurodegeneration, but appear to act as active modulators of disease course. Below are the major clinical consequences drawn from recent human studies, integrating behavioural, cognitive, and biomarker-based perspectives.

3.1 Cognitive decline and biomarker progression

Sleep abnormalities are increasingly recognized not only as comorbid symptoms but as predictors of cognitive decline and pathological biomarker evolution. In a large cohort spanning preclinical AD through AD dementia, longer total sleep time was paradoxically associated with greater buildup of tau pathology - particularly in the hippocampus, amygdala, insula, and precuneus, and with an increased risk of progression

to mild cognitive impairment or dementia (HR ≈ 1.55) compared to those with more moderate sleep durations (Yoon et al., 2023). These findings suggest that both insufficient and excessive sleep may reflect underlying neurobiological dysregulation, perhaps mediated by altered slow-wave sleep (SWS) architecture or compensatory neural changes secondary to synaptic loss.

Similarly, controlled experimental evidence in healthy adults shows that one night of total sleep deprivation significantly increases CSF concentrations of β-amyloid (Aβ42) and hyperphosphorylated tau. These shifts in proteopathic biomarkers support a causal link between acute sleep loss and early AD pathology (Lyckenvik et al., 2025). The temporal immediacy of these effects underscores how even transient perturbations of sleep may trigger molecular cascades resembling those in chronic neurodegeneration.

Longitudinal observations have found that reductions in SWS correlate with increased amyloid-β deposition in medial prefrontal cortex in cognitively healthy older adults. Disturbances in NREM architecture, especially delta power decline, predict both accelerated cognitive decline and exacerbation of biomarker burden (Aktan Süzgün et al., 2025; Lv et al., 2022; Morrone et al., 2023). Reduced SWS also leads to impaired memory consolidation and diminished synaptic homeostasis, mechanisms thought to underlie the cognitive deficits characteristic of early AD. Over time, cumulative loss of restorative sleep stages may therefore act as a silent driver of neuropathological progression, translating molecular disturbances into clinically evident decline.

3.2 Neuropsychiatric symptoms, sleep architecture, and behavioural impairments

Sleep and circadian disturbances are strongly associated with neuropsychiatric manifestations: mood disorders, heightened anxiety, increased irritability, hallucinations, agitation, and worse behavioural dysregulation. These symptoms often precede or accompany cognitive decline in AD, PD, or other neurodegenerative conditions (Shen et al., 2023). Sleep fragmentation and misaligned circadian phase appear particularly detrimental to emotional regulation, possibly through dysregulation of limbic circuits and monoaminergic neurotransmission.

Disrupted architecture of sleep is particularly relevant: reductions in REM sleep, increased REM latency, fragmentation of the sleep-wake cycle, and diminished sleep quality have all been linked to worse AD biomarkers. For example, prolonged REM latency has been correlated with elevated Aβ plaque burden and phosphorylated tau (p-tau181), alongside lower levels of brain-derived neurotrophic factor (BDNF), which in turn are associated with worse outcomes in memory and cognitive performance (J. Jin et al., 2025). These relationships suggest that REM sleep contributes to neuroplastic restoration, emotional processing, and synaptic recalibration, processes that are compromised when sleep continuity and timing are disturbed.

Moreover, sleep-wake cycle irregularities, including fragmented rest-activity rhythms and misalignment of circadian timing, have been shown in actigraphy studies to precede observable cognitive decline and structural brain changes. In older adults, reduced diurnal amplitude and instability in 24-hour activity patterns are associated with increased risk of AD (Aktan Süzgün et al., 2025). Behaviourally, these circadian rhythm alterations manifest as day-night confusion, sundowning, and erratic patterns of alertness, all of which contribute to functional impairment and caregiver strain. Taken together, such evidence highlights the dual cognitive and affective burden of sleep-circadian disturbances across neurodegenerative phenotypes.

3.3 Increased risk of neurodegenerative disease, early onset, and prodromal markers

Beyond worsening established disease, sleep disturbances act as significant risk factors for disease onset. In large epidemiologic studies using electronic health records (EHRs) and cohort designs, various sleep disorders, including insomnia, sleep apnoea, and fragmented sleep patterns, have been associated with elevated risk of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, vascular dementia, and dementia more broadly. Often, these associations are evident up to 10-15 years before clinical diagnosis suggesting that sleep abnormalities may represent one of the earliest detectable clinical indicators of neurodegenerative vulnerability (Aktan Süzgün et al., 2025; Lv et al., 2022; Simmonds et al., 2023).

Prodromal features are also documented. REM Sleep Behaviour Disorder, for example, frequently heralds synucleinopathies such as PD or Lewy Body Dementia many years in advance. Its presence is a robust predictor of phenoconversion to overt neurodegenerative disease, with risk estimates exceeding 80% over long-term follow-up. Additionally, in AD, early tauopathies in wake-sleep-regulating centres (e.g. locus coeruleus, basal forebrain) correspond temporally with initial sleep disturbances, even before amyloid plaque deposition becomes widespread (Lew et al., 2021; Lloret et al., 2020). These findings underscore a

bidirectional relationship: neurodegenerative changes disrupt sleep circuits, while chronic sleep disturbance accelerates molecular pathology, closing a pathogenic feedback loop.

Furthermore, emerging evidence indicates that specific sleep parameters, such as reduced REM proportion or decreased circadian amplitude, can serve as early markers of neurodegenerative risk, potentially complementing fluid and imaging biomarkers. Integrating sleep metrics into longitudinal monitoring frameworks could therefore enhance early detection and preventive strategies.

3.4 Quality of life, physical health, caregiver burden

Sleep and circadian dysfunction impose heavy burdens on both patients and caregivers. Poor sleep contributes to daytime sleepiness, reduced vigilance, impaired attention and executive function, increased falls risk, and greater morbidity. Neurodegenerative disease patients with disrupted sleep often report worse mood, heightened emotional instability, and diminished social functioning (Gao et al., 2019). Such functional deterioration compounds cognitive decline, eroding independence and amplifying care needs.

Physical health is also adversely affected. Sleep disorders are associated with greater cardiovascular risk, metabolic dysregulation, immune dysfunction, and higher rates of hospitalization. Sleep deprivation enhances systemic inflammation and dysregulates endocrine homeostasis, which may further exacerbate neurodegenerative progression. Disease trajectories tend to be faster and more severe where sleep quality is poor, underscoring the systemic interdependence between brain and body health.

For caregivers, nocturnal sleep disturbances in patients are tied to increased stress, poorer mental health, and greater overall care burden (Benca et al., 2022). Frequent awakenings, nocturnal wandering, and behavioural agitation disrupt caregivers' own sleep, leading to exhaustion and burnout. The cumulative psychosocial strain contributes to reduced quality of life for the entire caregiving dyad and is a major determinant of institutionalization in advanced disease stages. Consequently, addressing sleep pathology is not only a clinical priority for patients but also a critical component of holistic care for families and support networks.

3.5 Disease heterogeneity and moderating factors

Not all individuals are equally affected. Several moderating variables influence how sleep/circadian disruptions translate into clinical outcomes:

- Genetic factors (e.g. APOE ε4) appear to modulate vulnerability: carriers may show stronger associations between sleep dysfunction and amyloid or tau pathology (Blackman et al., 2022).
- Age: sleep architecture naturally degrades with aging; thus, older individuals with disruption may be more susceptible (Edwards et al., 2010).
- Severity, chronicity, and timing of sleep disruption: chronic fragmented sleep, long durations of poor sleep over many years, or repeated acute sleep loss appear worse. Sleep measured longitudinally (rather than cross-sectionally) gives a clearer picture of risk (Minakawa et al., 2019).
- Comorbidities: presence of sleep breathing disorders, mood disorders, metabolic disease, or cardiovascular disease increases risk and worsens consequences (Edwards et al., 2010; Ogbu et al., 2024).

3.6 Summary of clinical implications

Taken together, the evidence indicates that sleep and circadian disturbances are not passive consequences of neurodegenerative disease - they actively contribute to pathological progression, correlate with earlier onset, and mediate worsening of cognitive and behavioural symptoms. They also compromise quality of life, physical health, and emotional well-being, extending their impact beyond the patient to caregivers and families.

Recognizing and treating sleep disorders early offers a powerful opportunity to alter disease trajectories, delay onset, slow progression, and ameliorate symptom burden. Clinically, this calls for the integration of sleep assessments into standard diagnostic and monitoring frameworks for neurodegenerative disorders. Therapeutic approaches that restore circadian alignment and improve sleep continuity (through behavioural, pharmacological, or chronotherapeutic strategies) may hold substantial potential to mitigate both molecular and clinical consequences of neurodegeneration.

4. Preventive and Therapeutic Strategies

Growing evidence underscores that sleep and circadian restoration may represent actionable, disease-modifying avenues in the management of neurodegenerative disorders. Preventive and therapeutic strategies can be conceptualized across behavioural, chronobiological, and pharmacological domains, complemented by emerging neuroprotective and personalized approaches. Importantly, these interventions do not act in isolation but rather form part of an integrated framework targeting both symptom alleviation and pathophysiological modification. Optimizing sleep and circadian function holds potential to modulate neuroinflammation, protein clearance, synaptic integrity, and cognitive resilience, making it a cornerstone of holistic neurodegenerative care.

4.1 Behavioural and lifestyle interventions

Sleep hygiene and environmental optimization.

The foundational step in addressing sleep disturbances involves promoting optimal sleep hygiene: maintaining consistent sleep-wake schedules, minimizing nocturnal light exposure, reducing stimulants such as caffeine and alcohol, and ensuring an environment conducive to rest. These seemingly simple measures are supported by neurobiological evidence linking environmental light and temperature to circadian entrainment and melatonin secretion dynamics. In individuals with neurodegenerative disease, where circadian cues are often blunted due to retinal degeneration or reduced outdoor exposure, environmental optimization can restore rhythmicity and reduce nocturnal agitation. Studies demonstrate that even modest environmental interventions (such as improved lighting cycles, reduced bedroom noise, and temperature regulation) can significantly enhance sleep efficiency and next-day alertness (Liu et al., 2022).

Cognitive Behavioural Therapy for Insomnia (CBT-I).

CBT-I remains the gold standard non-pharmacologic intervention for chronic insomnia and has shown particular promise in older adults and those with early cognitive impairment. Beyond improving subjective sleep quality, CBT-I exerts effects on neural plasticity and emotional regulation, potentially mediated by normalization of HPA-axis activity and reduction of limbic hyperreactivity. In populations with MCI or early AD, sustained improvements in sleep continuity have been associated with stabilization of cognitive trajectories and reduced progression to dementia (J. W. Jin et al., 2021). The combination of cognitive restructuring and behavioural conditioning inherent to CBT-I also mitigates maladaptive beliefs about sleep, which are common in individuals experiencing memory loss and anxiety.

Physical activity and timing of exercise.

Physical exercise acts as a potent zeitgeber, influencing both circadian rhythmicity and sleep architecture. Regular aerobic or resistance training - particularly when performed in the morning or early afternoon - can deepen slow-wave sleep, enhance glymphatic clearance, and reduce inflammatory cytokine load (Milot et al., 2025). Exercise-induced upregulation of brain-derived neurotrophic factor and mitochondrial biogenesis also contributes to neuroprotection, supporting neuronal energy metabolism and resilience against oxidative stress. Importantly, consistent timing of exercise sessions amplifies their chronobiological impact, reinforcing circadian stability.

Dietary timing and caloric restriction.

Nutritional timing represents another modifiable factor with circadian implications. Aligning food intake with daylight hours enhances metabolic synchronization between central and peripheral clocks. Time-restricted feeding and caloric moderation have been associated with improved metabolic efficiency, enhanced autophagy, and reduced neuroinflammation (H.-B. Wang et al., 2018). These mechanisms collectively support neuronal longevity and may attenuate age-related proteostatic decline. Integrating dietary interventions with behavioural therapies thus provides a multidimensional framework for sleep optimization.

4.2 Chronotherapy and circadian realignment

Circadian realignment strategies aim to restore synchrony between endogenous rhythms and environmental zeitgebers. Light therapy has become a cornerstone of this approach, as exposure to bright light in the morning, particularly wavelengths in the blue spectrum, suppresses melatonin secretion during wakefulness and reinforces diurnal rhythmicity. In Alzheimer's and Parkinson's diseases, structured light interventions have been shown to reduce sleep fragmentation, stabilize rest-activity cycles, and alleviate mood disturbances (Endo et al., 2020). The therapeutic potential of light exposure extends beyond circadian correction, influencing clock gene expression within the SCN and peripheral tissues, thereby modulating global homeostasis.

Melatonin supplementation and melatonergic agonists such as ramelteon and agomelatine represent pharmacologic adjuncts that strengthen circadian alignment. Their benefits extend to improving sleep onset latency, reducing nocturnal awakenings, and possibly modulating oxidative stress and mitochondrial dynamics. In mild AD, regular melatonin administration has been linked to improvements in cognitive function and behavioural stability. Combination protocols, integrating timed bright light exposure with evening melatonin, yield additive effects by reinforcing both photic and hormonal signals, thereby restoring robust circadian amplitude (Riemersma-van Der Lek, 2008).

Moreover, structured daily routines function as social zeitgebers, offering behavioural scaffolding for patients with blunted circadian drive. Timed meals, regular social interaction, and consistent activity schedules strengthen entrainment cues, reducing sundowning, agitation, and nocturnal confusion (Aktan Süzgün et al., 2025). Collectively, these interventions highlight the potential of multimodal chronotherapy to reestablish internal rhythmic coherence and improve overall functional stability.

4.3 Pharmacological interventions

Pharmacologic management of sleep and circadian disturbances in neurodegenerative diseases must balance therapeutic benefits with the risk of cognitive or motor side effects. Hypnotic agents such as low-dose doxepin or trazodone can improve sleep continuity and maintenance but should be prescribed cautiously, as oversedation or altered sleep architecture may exacerbate confusion and falls. Benzodiazepines, while effective in the short term, are best avoided in older populations due to risks of dependence, cognitive blunting, and paradoxical agitation (McCleery & Sharpley, 2020).

Orexin receptor antagonists (e.g., suvorexant, lemborexant) represent a new generation of targeted therapeutics. By selectively inhibiting the wake-promoting orexin system, these agents promote physiological sleep without impairing next day alertness or cognition. Clinical trials have demonstrated their efficacy in both insomnia and AD, where they reduce nocturnal agitation, enhance REM stability, and improve caregiver reported outcomes (Carpi et al., 2024). Their favourable safety profile makes them particularly suited to frail or cognitively vulnerable populations.

Dopaminergic agents such as pramipexole and ropinirole remain essential in managing comorbid sleep-related movement disorders in Parkinsonian syndromes, including restless legs syndrome and periodic limb movement disorder (Jiménez-Jiménez et al., 2021). In parallel, clonazepam and melatonin remain first-line for REM sleep behaviour disorder, especially in synucleinopathies, where early intervention may delay neurodegenerative conversion (Yan et al., 2021).

Finally, experimental neuroprotective compounds, including antioxidants, anti-inflammatory drugs, and mitochondrial protectors (e.g., coenzyme Q10, nicotinamide riboside, N-acetylcysteine), offer additional strategies to mitigate oxidative cascades triggered by chronic sleep deprivation (Ahmadi et al., 2025; Mantle & Hargreaves, 2022). Although primarily studied in preclinical models, these agents illustrate a mechanistic bridge between metabolic restoration and disease modification.

4.4 Neuroprotective potential of sleep restoration

Accumulating translational evidence supports the concept that restoring physiological sleep does not merely relieve symptoms but actively counteracts neurodegenerative progression. Enhanced SWS, for instance, increases glymphatic clearance of amyloid-β, tau, and α-synuclein aggregates, directly reducing neurotoxic load and supporting neuronal homeostasis. Concurrently, improved sleep stabilizes BBB integrity, attenuates neuroinflammatory signalling, and facilitates synaptic remodelling necessary for learning and memory (Lee et al., 2020; Reddy & van der Werf, 2020; Wafford, 2021).

Studies demonstrate that better sleep efficiency predicts slower accumulation of amyloid pathology on PET imaging and delayed clinical decline. In animal models, chronic sleep deprivation accelerates misfolded protein deposition and mitochondrial dysfunction, whereas restoring consolidated sleep reverses microglial activation and oxidative stress markers (Rowe et al., 2024; X. Wang et al., 2022). These data collectively reinforce the notion that sleep improvement functions as a disease-modifying intervention, capable of reestablishing physiological resilience and halting pathological cascades leading to neuronal death.

4.5 Future directions and precision sleep medicine

The convergence of digital health, chronobiology, and neuroscience is paving the way for precision sleep medicine. Wearable devices and actigraphy-based monitoring now allow continuous assessment of rest-activity rhythms and sleep architecture in naturalistic settings (de Zambotti et al., 2019). Such data facilitate early detection of subclinical circadian disruption, often preceding clinical symptom onset.

Machine learning algorithms analysing sleep and circadian parameters can detect subtle rhythm irregularities predictive of conversion from MCI to AD, suggesting their potential as digital biomarkers (Xu et al., 2024). Integration of these digital biomarkers with neuroimaging and genomic data could enable individualized monitoring and stratification of patients based on their circadian phenotypes.

On the therapeutic frontier, pharmacologic modulation of clock genes (BMAL1, PER2, REV-ERBα) represents an exciting and rapidly developing field (Pu et al., 2025; S. Wang et al., 2020). By restoring rhythmic transcriptional feedback loops, these interventions could harmonize systemic and cellular timekeeping, optimizing metabolic efficiency and neuronal resilience. Future models of care will likely combine behavioural interventions, chronotherapeutic scheduling, and gene-targeted pharmacology into comprehensive, multidisciplinary precision sleep protocols (Ruan et al., 2021).

5. Conclusions

Sleep and circadian rhythms, once regarded as passive or secondary biological phenomena, have emerged as central regulators of brain homeostasis and pivotal determinants of neurodegenerative disease trajectories. The collective evidence from molecular biology, neuroimaging, and longitudinal clinical research converges on a consistent narrative: chronic sleep deprivation and circadian misalignment not only exacerbate neurodegenerative pathology but can initiate and amplify its underlying pathogenic cascades. This recognition has transformed sleep from a mere symptom of brain dysfunction into a potential upstream therapeutic target.

Mechanistically, persistent sleep loss disrupts the glymphatic system, diminishes clearance of neurotoxic waste, induces oxidative and inflammatory stress, destabilizes proteostasis, and dysregulates clock gene expression essential for neuronal resilience. These molecular perturbations operate synergistically to accelerate the deposition of amyloid-β, tau, α-synuclein, and other misfolded proteins. Moreover, they compromise mitochondrial function, synaptic stability, and neurovascular coupling, leading to a self-reinforcing cycle of neuronal injury and metabolic inefficiency. The cumulative consequence is a progressive erosion of neural networks crucial for cognition, behaviour, and motor control.

Clinically, the repercussions are profound and far-reaching. Disturbed sleep and circadian rhythms correlate with faster cognitive decline, more severe neuropsychiatric manifestations, earlier disease onset, and poorer overall quality of life across Alzheimer's disease, Parkinson's disease, and related disorders. Importantly, such disturbances often precede overt neurodegenerative changes, suggesting that they may serve as prodromal biomarkers and early indicators of neural vulnerability. This preclinical phase provides an invaluable window for preventive strategies aimed at mitigating disease risk before irreversible neuronal loss occurs.

Emerging data now support the concept that restoring healthy sleep architecture and circadian alignment may exert robust neuroprotective effects. Improvements in sleep continuity and circadian synchronization enhance glymphatic clearance, stabilize the blood-brain barrier, attenuate neuroinflammatory signalling, and preserve synaptic plasticity. Interventions spanning behavioural and cognitive-based therapies, light and chronotherapy, melatonin supplementation, orexin receptor antagonism, and structured daily routines demonstrate promising translational potential. These approaches, though diverse in mechanism, share a common goal: reestablishing temporal homeostasis to slow neurodegenerative progression and improve patient outcomes.

Looking ahead, integrating sleep health into the core framework of neurodegenerative disease management is both a scientific and ethical imperative. Advances in wearable and digital sleep monitoring, biomarker discovery, and precision chronotherapeutic approaches are opening new avenues for personalized medicine. A future in which clinicians can track circadian integrity in real time, tailor interventions to individual chronotypes, and modulate neural resilience through targeted sleep optimization is becoming increasingly attainable.

Ultimately, preserving the architecture of sleep may be as fundamental to preserving the architecture of the brain itself. Recognizing sleep as a modifiable determinant of neurodegeneration reframes it from a passive state into an active biological defence mechanism - one that sustains neuronal health, cognitive longevity, and overall quality of life throughout aging.

Conflicts of interest

All authors have read and approved the manuscript. The authors declare no conflicts of interest.

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