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Bidirectional Pathological Axis Between Alzheimer's Disease and Circadian Rhythm Disturbance: Mechanisms and Therapeutic Strategies

Jiajia Qin[1] | Xianfeng Yu[1] | Yayu Wang[1] | Xiaohan Song[1] | Yuehua Wang[1] | Zhixin Wang[1] | Wei Miao[1] | Xudong Yang[2] | Jiajia Zhu[3] | Xiaoqun Zhu[1] | Maria-Trinidad Herrero[4]

[1]Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, China | [2]Department of Physical Education, University of Science and Technology of China, Hefei, China | [3]Department of Radiology, The First Affiliated Hospital of Anhui Medical University, Hefei, China | [4]Clinical & Experimental Neuroscience (NiCE group), Institute for Aging Research, Murcia Institute for Biomedical Research (IMIB), School of Medicine, University of Murcia, Murcia, Spain

Correspondence: Maria-Trinidad Herrero (mtherrer@um.es) | Xiaoqun Zhu (yfy126723@fy.ahmu.edu.cn) | Jiajia Zhu (zhujiajia@ahmu.edu.cn)

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ABSTRACT

Circadian rhythm disturbance is highly prevalent in patients with Alzheimer's disease (AD) and is consistently associated with more rapid cognitive decline and reduced quality of life. Accumulating evidence supports a bidirectional relationship between circadian rhythm disruption and AD pathology, in which each may reciprocally exacerbate the other. However, whether circadian rhythm disturbance acts as an independent causal driver of AD initiation or primarily as a factor that modifies and accelerates pathology once it is underway remains an open question. This article synthesizes current evidence on the proposed mechanisms linking circadian dysregulation to AD pathophysiology, with particular attention to the suprachiasmatic nucleus (SCN), glymphatic clearance, clock gene networks, and apolipoprotein E ε4 allele (APOE ε4) genotype. Emerging circadian-targeted interventions, including both pharmacological and nonpharmacological approaches, are also reviewed and their current limitations are discussed. A more complete understanding of this bidirectional axis may help inform future research directions and ultimately contribute to the development of early monitoring and combination treatment strategies for AD.

1 | Introduction

Alzheimer's disease (AD) is the most common type of dementia in the world, accounting for 60%–80% of all dementia cases. It has become a major public health challenge in our aging society, characterized by high prevalence, a rapid growth rate, and a severe social and economic burden [1]. The core pathological changes of AD are marked by amyloid-β (Aβ) deposition and tau protein phosphorylation. The course of the disease is long and insidious. Preclinical pathological abnormalities can appear more than 10 years before the diagnosis of dementia, seriously threatening the health and lives of older adults [2, 3].

Throughout the entire course of AD, sleep disturbance and circadian rhythm disturbance are among the comorbid phenotypes with the highest incidence, widest spread, and most insidious harm [4]. From the subjective cognitive decline (SCD) stage to the moderate-to-severe dementia stage, they are prevalent [5–7], manifesting as sleep-wake cycle fragmentation, day–night reversal, daytime lethargy, nocturnal restlessness, and sundown syndrome. These rhythm abnormalities not only

Jiajia Qin, Xianfeng Yu, and Yayu Wang contributed equally.

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significantly affect the lives of patients and increase the burden of care but are also closely related to rapid cognitive decline, abnormal mental behavior, and accelerated neurodegeneration [4]. In recent years, growing attention has focused on whether detectable circadian rhythm disorders have occurred in the SCD stage, but the existing evidence remains preliminary, and their value as a candidate marker for the preclinical stage of AD remains to be validated.

Traditionally, many viewpoints have regarded rhythm disorder as a secondary manifestation and accompanying symptom in the progression of AD and have mainly treated it symptomatically. However, the evidence accumulated in recent years suggests that circadian rhythm disorder may not only be a passive outcome of the disease but may also reciprocally influence the pathological process of AD through various pathways, and there may be a bidirectional relationship between the two. Based on this understanding, this paper focuses on two core issues: First, what evidence currently supports the bidirectional interaction between AD pathological changes and circadian rhythm disorders, and what are the underlying molecular and feedback loop mechanisms? Second, based on existing mechanism studies, what are the therapeutic potentials and existing limitations of rhythm-targeting intervention strategies (including pharmacological and nonpharmacological approaches)? This paper attempts to integrate multiple dimensions such as functional impairment of the suprachiasmatic nucleus (SCN), abnormal lymph-like system clearance, dysregulation of core clock gene expression, and genetic susceptibility to APOE ε4, in order to provide a relatively systematic understanding framework, but it should be noted that the causal relationships and hierarchical ordering among the pathways still need to be verified by further experimental and clinical studies.

2 | Clinical Manifestations: Circadian Rhythm Disturbances in Patients With Alzheimer's Disease

2.1 | Subtle Rhythm Variations and Subjective Cognitive Decline in the Preclinical Stage of AD

In the preclinical stage of Alzheimer's disease (AD), patients exhibit subjective cognitive complaints such as memory impairment without presenting objective cognitive dysfunction. This condition is clinically defined as subjective cognitive decline (SCD). As the earliest subjective manifestation in the AD clinical spectrum, SCD is frequently accompanied by core pathological alterations including cerebral amyloid-beta (Aβ) deposition. A 20-year longitudinal study confirmed that the preclinical pathological progression of AD can be traced back to 20 years before clinical diagnosis, following a clear temporal evolutionary sequence: Amyloid pathology abnormalities, including decreased cerebrospinal fluid (CSF) Aβ42 levels and a reduced Aβ42/40 ratio, manifest first, as early as 18 years prior to clinical diagnosis; these are followed by elevations in phosphorylated tau 181 (p-tau181), total tau, and neurofilament light chain (NfL), which reflect tau pathology and neuronal injury; brain structural damage such as hippocampal atrophy occurs relatively late [8]. Notably, the above pathological abnormalities are often concomitant with SCD, and individuals with SCD have a significantly elevated risk of progressing to mild cognitive impairment and even AD dementia [9], representing the core phenotypic feature of the preclinical stage of AD.

At present, there is no robust evidence to prove whether there is a detectable circadian rhythm disorder in the SCD stage. Manousakis et al. found in 25 elderly people with SCD that an earlier circadian phase was associated with more severe memory complaints ($r = -0.688$), but sleep fragmentation was instead associated with fewer subjective complaints, suggesting that the effects of different dimensions of rhythm and sleep on SCD may be heterogeneous [10]. Another study by Spira et al. involving 82 cognitively normal elderly people found that Aβ deposition-positive people had higher and more stable activity levels in the afternoon than Aβ deposition-negative people, but standard rhythm indicators (such as intraday variability and relative amplitude) were similar between the two groups. There was no significant difference between them, suggesting that rhythm abnormalities may appear before Aβ deposition, but their specificity as a marker still needs to be validated [11]. The current studies on whether circadian rhythm can be used as an early biomarker are all cross-sectional in design, and the sample sizes are limited (none of which exceeds 100 participants), and none of them have directly verified the chronological relationship between abnormal rhythm and pathological initiation of AD. Therefore, there is still insufficient evidence to establish the circadian rhythm index as an independent predictor of the SCD stage. A more appropriate interpretation is that circadian rhythm disorder should currently be regarded as a candidate marker for preclinical AD that needs to be further verified. Its specific manifestations in the SCD population, the temporal relationship with AD pathology, and its clinical application value still need to be clarified through large-sample, prospective cohort studies.

2.2 | Core Manifestations in the Typical Clinical Stage: Circadian Phase Misalignment and Sundown Syndrome

As the disease progresses from the preclinical stage to the stage of typical dementia, the clinical manifestations of circadian rhythm disruption show a gradual worsening over time and are quantitatively associated with the severity of AD. In the mild stage of AD, approximately 35%–45% of patients already exhibit a phase delay in their sleep-wake rhythm, manifested as a sleep onset time that is 1.5–2.0 hours later than that of healthy older adults; upon entering the moderate-to-severe stage, the proportion of patients with phase reversal rises to 65%–80%, and patients' sleep-wake cycles become completely desynchronized from external light-dark cues, exhibiting a reversed pattern of "nocturnal wakefulness and daytime sleepiness"—difficulty falling asleep at night and frequent awakenings. The proportion of total nighttime wakefulness relative to time in bed rises from approximately 25% in the mild stage to over 40% in the moderate-to-severe stage (compared to less than 15% in healthy older adults) [12, 13].

"Sundown Syndrome" is the most characteristic circadian-related behavioral phenotype in late-stage AD, with a prevalence as high as 45%–66% in severe cases, compared to only 10%–20% in the mild stage [12]. Its onset is typically concentrated in the late afternoon or early evening and is closely related to the timing of the decline in core body temperature and the degree of phase disruption in melatonin secretion peaks. In terms of measurement methods, the detection rate of

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sundown syndrome using caregiver-reported assessment tools is significantly lower than that from objective records obtained through continuous video monitoring, suggesting that subjective reports may underestimate its true incidence.

2.3 | Severe Impairment of Sleep Microstructure: Fragmentation of the Sleep-Wake Cycle

Sleep microstructural damage in patients with AD exhibits distinct quantitative and stage-specific characteristics. Studies based on polysomnography (PSG) show that patients' sleep latency increases from approximately 35–40 minutes in the mild stage to more than 50 minutes in the moderate-to-severe stage, compared to 22.6 $\pm$ 8.7 minutes in healthy older adults; the nocturnal arousal index (number of arousals per hour of sleep) increases from approximately 1.1 per hour in the mild stage to 2.3 per hour in the moderate-to-severe stage, compared to 0.4 $\pm$ 0.2 per hour in healthy controls [14].

In terms of sleep architecture, the proportion of deep sleep (non-rapid eye movement (NREM) Stage 3) relative to total sleep time decreases by approximately 25% in mild AD (from 18% to 22% in healthy older adults to 13%–16%) and by as much as 40%–50% in the moderate-to-severe stage (to 8%–11%); the proportion of REM sleep decreases by approximately 15% in the mild stage and by 30%–35% in the moderate-to-severe stage [14]. Consequently, sleep efficiency (actual sleep time/time in bed) shows a stepwise decline: an average of 72% $\pm$ 9% in mild AD (compared to $>$ 80% in healthy older adults), dropping to 58% $\pm$ 12% in moderate-to-severe AD. Total daytime sleep duration also increases with the disease stage: In mild AD, cumulative daytime napping amounts to approximately 1.5–2.5 hours, whereas in moderate-to-severe AD, it reaches 4–6 hours (compared to $<$ 1 hour in healthy older adults), creating a vicious cycle of "nighttime fragmentation–daytime overcompensation" [14].

Regarding measurement methods, PSG is the gold standard for quantifying sleep microstructure, but it is complex to administer and provides only short-term data; wrist-worn actigraphs allow for continuous monitoring in community settings, and their assessment of sleep-wake patterns correlates highly with total sleep time measured by PSG, but they have limited ability to distinguish between REM and NREM stages; therefore, staging data primarily rely on PSG studies [14].

2.4 | Disintegration of Multidimensional Biological Rhythms: Neuroendocrine and Thermoregulatory Abnormalities

Circadian rhythm disruptions in patients with AD involve multiple dimensions, including activity-rest patterns, core body temperature, melatonin, and cortisol, with each dimension exhibiting distinct changes across different disease stages [15].

Regarding activity-rest rhythms, quantitative studies using wrist-worn activity monitors show that healthy older adults exhibit good rhythm integrity; in patients with AD, diurnal variability (reflecting rhythm fragmentation) increases with the disease stage, while relative amplitude (reflecting rhythm intensity) decreases progressively [16]. Linear mixed-effects models indicate that AD significantly accelerates the age-related decline of circadian rhythms, with the rate of deterioration doubling as the disease progresses. Furthermore, Cox proportional hazards models further confirm that activity-rest rhythm disruption is an independent risk factor for AD onset [16].

Core body temperature rhythms are directly regulated by the SCN. In patients with AD, impaired SCN function leads to a significantly reduced amplitude of body temperature rhythms. Manifested by a smaller difference between daytime peaks and nighttime troughs, a flatter rhythm, and increased interindividual variability in the phase of the lowest body temperature, suggesting a decline in the stability of SCN output signals [17]. Regarding melatonin rhythms, patients with AD generally exhibit reduced nocturnal melatonin secretion, which is particularly pronounced in the moderate-to-severe stages of dementia; the peak of nocturnal melatonin secretion is approximately 30%–75% lower than that in healthy older adults. Furthermore, melatonin rhythms exhibit irregularities such as phase delays and inconsistent peak times; approximately 30%–40% of patients with moderate-to-severe dementia lose a recognizable 24-h rhythm, and the reliability of the rhythm as a "timing signal" is severely compromised [17].

Regarding cortisol rhythms, a 2023 systematic review synthesized 17 observational studies and found that cortisol levels in the cerebrospinal fluid of patients with AD were significantly elevated, with the degree of elevation positively correlated with APOE ε4 homozygosity [18]. Notably, this review indicated that cortisol levels at the mild cognitive impairment (MCI) stage did not differ significantly from those of healthy controls, and cortisol rhythm disturbances primarily occurred at the dementia stage [18]. In terms of measurement method stratification, cerebrospinal CSF-based testing revealed more significant differences in cortisol levels between patients with AD and controls, whereas saliva-based testing showed relatively smaller effect sizes. This suggests that different biological samples exhibit varying sensitivities in assessing cortisol rhythms, and methodological consistency must be ensured in clinical studies.

2.5 | Heterogeneity of Clinical Phenotypes: Sex-Specific Mechanisms of Circadian Rhythm Disturbances

In addition, circadian rhythm disturbances in patients with AD exhibit significant sex-specific differences in their clinical manifestations [19]. Multiple epidemiological studies and longitudinal clinical observations have indicated that female patients with AD often present more severe circadian rhythm disorders, higher degrees of sleep fragmentation, and a steeper trajectory of cognitive decline than male patients [20]. Such differences may be closely associated with the abrupt decline in estrogen levels after menopause in women. Estrogen not only exerts fundamental neuroprotective effects in the brain but also directly participates in regulating the electrophysiological activity of SCN neurons and the cyclic expression of clock genes [21]. Estrogen deficiency leads to a sharp decline in the sensitivity of the female central circadian clock to light signals and feedback regulation, resulting in impaired stability of the circadian network. This sex-based shift in the endocrine microenvironment exposes women to a higher risk of circadian collapse under the impact of AD pathology, suggesting that sex-stratified mechanisms should be given high

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priority in the early warning and intervention of circadian rhythm disturbances in the future.

2.6 | Current Evidence and Limitations of Circadian Rhythm Disruption as a Potential Clinical Biomarker for Early-Stage Alzheimer's Disease

As mentioned above, the evidence regarding whether detectable circadian rhythm disruptions are already present during the SCD stage remains preliminary, and the conclusions of various studies are not entirely consistent. However, when considering the broader preclinical stage of AD, an increasing body of evidence supports an association between circadian rhythm indicators and AD pathology.

In animal models, transgenic AD mice exhibit abnormalities in the sleep-wake cycle several months before the onset of cognitive symptoms, and Aβ deposition itself can directly disrupt the normal fluctuations of circadian signals [22]. In a population-based study, an analysis of UK Biobank data from approximately 90,000 individuals showed that for every interquartile range increase in the composite circadian phase deviation, hippocampal volume decreased by approximately 1.1%, and the risk of all-cause dementia increased by 37%; furthermore, phase deviation partially mediated the risk of dementia (mediation proportion of approximately 8.6%–13.5%) [23]. These findings provide novel insights into the mechanisms underlying neurological disorders caused by circadian rhythm disruption and may suggest potential preventive strategies. At the plasma biomarker level, a 27-h laboratory study of patients with AD found that common plasma biomarkers such as p-tau217, Aβ40, Aβ42, and NfL all exhibited significant diurnal time-dependent variability, suggesting that sampling time may influence the interpretation of biomarker levels [24]. Notably, a study published in 2025 showed that, beginning in the preclinical stage of AD (Aβ-positive but cognitively normal), blood-derived factors in patients' serum could already significantly prolong the circadian rhythm period of cells in vitro [25]. This result suggests that systemic rhythmic dysregulation associated with AD pathology may precede cognitive decline and can be detected through peripheral blood samples.

However, these findings raise an important yet often overlooked reverse question: Do the levels of AD biomarkers themselves exhibit circadian fluctuations? If biomarker levels fluctuate over time, measurements of "circadian dysrhythmia biomarkers" may be confounded by the time of sampling. Recent studies indicate that Aβ42 and Aβ40 levels in cerebrospinal fluid and plasma are approximately 4%–17% higher in the evening than in the morning; however, the Aβ42/Aβ40 ratio and markers such as p-tau217, p-tau181, p-tau231, NfL, and GFAP show no significant differences between morning and evening; 14 synaptic and lysosomal proteins in the cerebrospinal fluid also exhibit intraday increases of 4.5%–13.3% [26]. This suggests that selecting stable indicators, such as the Aβ42/Aβ40 ratio, will help guide the establishment of standardized sample collection times to avoid the influence of diurnal variations, thereby facilitating the application of Alzheimer's disease biomarkers in future clinical practice and drug trials.

Although the above evidence indicates a close association between circadian rhythm disturbances and AD pathology, characterizing them as AD-specific early biomarkers currently faces multiple challenges: First, there is a lack of disease specificity. Circadian rhythm disturbances are widely observed in various neurological and psychiatric disorders, such as Parkinson's disease, depression, and cerebrovascular disease, and are not unique to AD [13]. Second, the reproducibility of research findings is insufficient. Significant differences exist among studies in the circadian rhythm measurement metrics (amplitude, phase, diurnal variability, and stability) and measurement tools (wrist accelerometers, polysomnography, and home monitoring) used, making direct comparison of results difficult. Third, the temporal causal relationship has not yet been established. The vast majority of studies employ cross-sectional designs, making it impossible to clearly determine the temporal sequence in which "circadian rhythm disturbances precede the onset of AD pathology." Although animal studies suggest that Aβ deposition can directly lead to circadian rhythm abnormalities, the direction of causality between the two in humans remains controversial.

Based on the current evidence, a more reasonable characterization of circadian rhythm indicators is as a promising adjunct tool for AD risk stratification and a candidate biomarker, rather than a validated independent early diagnostic marker. Their core value lies in their noninvasive nature, the ability to track changes dynamically over the long term, and the potential for detection within a time window preceding cognitive decline; however, further evidence is needed to validate these findings, such as establishing multicenter, large-sample, long-term longitudinal cohort studies to clarify the temporal relationship between circadian rhythm disruption and the onset of AD pathology. Furthermore, further standardization of circadian rhythm measurement indicators and methodological standards is also a means to improve comparability across different studies; in terms of monitoring methods for circadian rhythm indicators, home-based rhythm monitoring technologies combining wearable devices and AI algorithms can be developed to enable low-cost, high-compliance, large-scale data collection.

3 | Potential Mechanisms: Bidirectional Interplay Between Circadian Rhythm Disturbances and AD Pathology

3.1 | From Circadian Rhythm Disturbances to Exacerbation of AD Pathology

Emerging evidence demonstrates that sleep fragmentation and circadian rhythm reversal are associated with amyloid-β (Aβ) accumulation, one of the pivotal pathological alterations in AD, and this association is more pronounced in APOE ε4 carriers. A study with a 7–8-year follow-up included dementia-free participants at baseline, with assessments of objective sleep-activity monitoring, subjective self-reported sleep evaluation, and Aβ positron emission tomography (PET) imaging. The results showed that greater 24-h sleep fragmentation was closely linked to more severe Aβ deposition, and this association remained significant after additional adjustment for sleep medications, education, potential sleep apnea, body mass index, hypertension,

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diabetes mellitus, smoking, physical activity, depressive symptoms, and employment status [27].

In a study by Eckhardt et al., 68 elderly participants (aged 55–80 years) with objective early cognitive impairment were enrolled. Circadian rhythms (acrophase of activity and intraday variability [IV]) were quantified using approximately 30 days of wrist accelerometer data, and PET imaging was applied to measure cerebral Aβ and tau levels. The results indicated that an earlier acrophase (lower acrophase value) was significantly associated with higher Aβ levels, and this correlation was stronger in APOE ε4 carriers. Meanwhile, an earlier acrophase was also related to higher tau levels, with the most significant association observed in early tau deposition regions of AD (Braak Stages I/II) and a weaker association in moderate-stage regions (Braak Stages III/IV). In contrast, higher intraday variability (higher IV value, representing more fragmented rhythms) was significantly associated only with higher tau levels in the entorhinal cortex (Braak Stages III/IV). This correlation was strengthened with aging and existed exclusively in males, whereas no significant association was found between Aβ and IV [28].

Studies in AD mouse models have revealed that circadian rhythm disturbances promote tau hyperphosphorylation, a core feature of AD pathology, mainly by regulating the activity of key kinases and phosphatases involved in tau phosphorylation. Circadian rhythm disruptions in AD mouse models, such as SCN lesions and abnormal expression of clock genes, activate tau phosphorylation-related kinases and elevate phosphorylation levels at critical tau sites (e.g., Ser396, Ser404, and Thr231). Furthermore, circadian rhythm disturbances reduce proteasomal activity in the hippocampus and decrease the expression of autophagy-related proteins by 35%–55%, which impairs the efficient clearance of hyperphosphorylated tau. Consequently, hyperphosphorylated tau aggregates to form neurofibrillary tangles (NFTs), thus accelerating tau aggregation [29].

The exacerbation of pathological protein deposition in Alzheimer's disease (AD) reflects profound dysregulation of underlying physiological mechanisms. Since the discovery of the glymphatic system in 2012, its role in cerebral waste clearance has garnered significant attention. Animal studies have linked glymphatic dysfunction to AD, yet human evidence remains limited. During sleep—particularly slow-wave non-rapid eye movement (NREM) sleep—the brain's extracellular space expands by ~60%, facilitating convective exchange between cerebrospinal fluid (CSF) and interstitial fluid (ISF) and enhancing the clearance of metabolic waste such as Aβ [30]. In AD, disrupted sleep rhythms reduce slow-wave sleep duration, impair glymphatic function, and diminish Aβ and other metabolic waste clearance, leading to their accumulation. Aquaporin 4 (AQP4), localized at astrocytic endfeet, is essential for normal glymphatic function; its loss or mislocalization markedly reduces Aβ clearance. Sleep deprivation in AD further disrupts AQP4 polarity, compromising glymphatic clearance and exacerbating the accumulation of Aβ and tau proteins [31] (Figure 1).

Emerging evidence positions oxidative stress and neuroinflammation as central drivers rather than bystanders in AD pathogenesis. Circadian rhythm disruption leads to clock gene (e.g., brain and muscle ARNT-like 1 (BMAL1), Period 2 (PER2), and REV-ERBα) dysregulation, mitochondrial dysfunction, and sustained reactive oxygen species (ROS) accumulation, creating an oxidative microenvironment [32]. Simultaneously, loss of circadian inhibition promotes microglial M1 polarization, triggering proinflammatory cytokine release, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), amplifying neuroinflammation. Critically, oxidative stress and neuroinflammation interact bidirectionally with core AD pathology, forming a positive feedback loop: ROS promotes amyloidogenic processing of amyloid precursor protein (APP) and activates kinases such as glycogen synthase kinase-3β (GSK-3β), inducing tau hyperphosphorylation; conversely, Aβ and tau aggregates

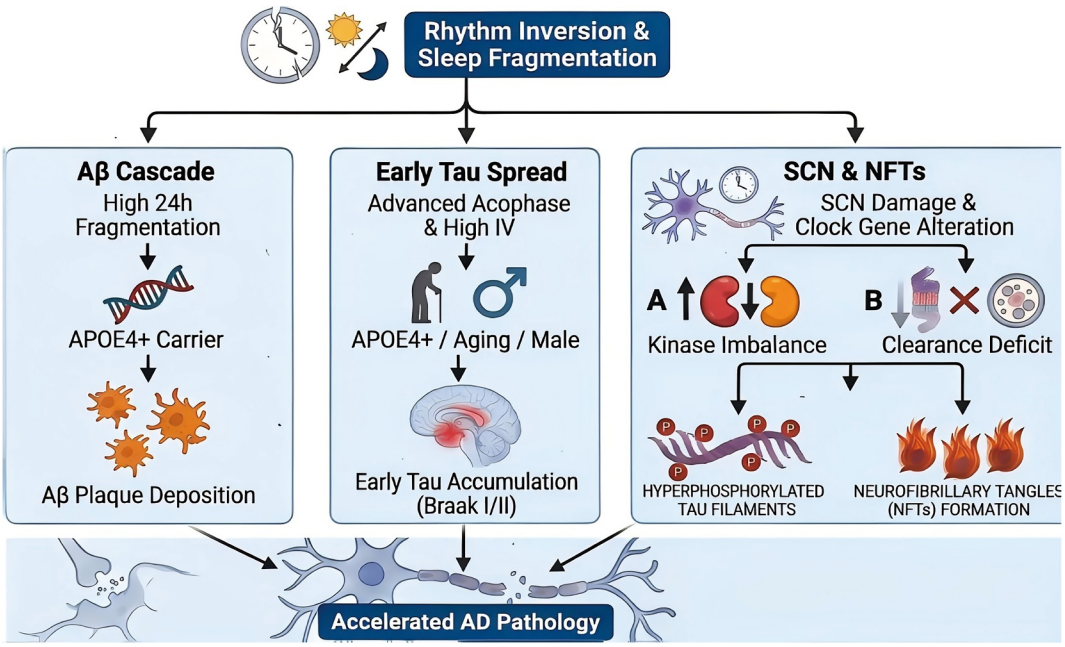


FIGURE 1 | Mechanistic link between sleep/circadian rhythm disruption and Aβ/tau pathology in Alzheimer's disease. Aβ, amyloid-β; APOE ε4, apolipoprotein E ε4 allele; NFTs, neurofibrillary tangles; SCN, suprachiasmatic nucleus.

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activate microglia, further increasing ROS and inflammatory cytokines [33]. Thus, oxidative stress and neuroinflammation function not only as accelerators but also as initiators of AD pathology. Circadian rhythm disruption, via clock gene dysregulation, acts as the "ignition," precipitating mitochondrial collapse, elevated oxidative stress, uncontrolled inflammatory signaling, and ultimately promoting the propagation of Aβ and tau pathology and neuronal loss.

During the prolonged preclinical phase of Alzheimer's disease (AD), dysregulation of neurotransmitter rhythms silently reshapes cerebral metabolism and cognitive dynamics. Circadian rhythms not only regulate the sleep-wake cycle but also precisely orchestrate the pulsatile secretion of key cognitive neurotransmitters, including acetylcholine (ACh), 5-hydroxytryptamine (5-HT), and norepinephrine (NE). When these rhythms are disrupted, the diurnal amplitude of neurotransmitter release collapses. Peak ACh release from basal forebrain cholinergic neurons disappears, attenuating cortical M1 receptor signaling, directly impairing attention and memory encoding, and relieving the suppression of microglia surrounding Aβ plaques, thereby promoting a proinflammatory phenotype [34]. Dysregulated circadian firing of dorsal raphe 5-HT neurons abolishes the nocturnal "clearance phase" of 5-HT along the cortico-hippocampal axis, reducing the disinhibition of gamma-aminobutyric acid (GABA)ergic interneurons and impairing the nocturnal clearance of Aβ oligomers, establishing a vicious "low 5-HT–high Aβ" cycle [35]. Loss of the morning NE peak from the locus coeruleus shortens synaptic plasticity windows, increases tau phosphorylation, and reduces cerebral perfusion and lymphatic clearance efficiency, accelerating Aβ and tau accumulation [36]. Importantly, neurotransmitter dysregulation is not merely a downstream consequence but forms a positive feedback loop with AD pathology: Aβ oligomers further inhibit choline transporter (CHT) and tryptophan hydroxylase (TPH) activity, reducing ACh and 5-HT synthesis; hyperphosphorylated tau disrupts vesicular monoamine transporter 2 (VMAT2), causing cytosolic NE to undergo auto-oxidation and generate ROS, exacerbating oxidative stress. Consequently, a self-perpetuating loop emerges: circadian rhythm disruption → loss of neurotransmitter rhythms → impaired clearance → Aβ/tau accumulation → further inhibition of neurotransmitter synthesis, driving the progression from the preclinical stage to symptomatic AD. In short, circadian dysregulation of neurotransmitter rhythms is not only one of the earliest sensitive indicators of AD but also a critical driver of Aβ/tau pathology propagation (Figure 2).

In summary, circadian rhythm disruption promotes the transition of Aβ and tau from metabolically clearable waste to pathological deposits through a triad of mechanisms: impaired lymphatic clearance, amplified oxidative-inflammatory stress, and neurotransmitter rhythm imbalance. These three axes are mutually reinforcing, forming a self-amplifying "rhythm–pathology" loop: The more severe the circadian rhythm disruption, the faster the pathological accumulation; conversely, greater pathology further fragments circadian rhythms. Accordingly, restoring circadian homeostasis has emerged as a potential disease-modifying strategy for early AD intervention.

3.2 | From AD Pathology to the Disruption of the Central Circadian Pacemaker

The SCN of the hypothalamus is widely regarded as the master circadian clock, and the integrity of its structure and function is fundamental to maintaining stable rhythmicity across the brain. Recent studies have demonstrated that the hypothalamic clock not only governs the sleep-wake cycle but also orchestrates global circadian outputs and preserves downstream neural homeostasis, further supporting the notion that SCN injury represents a core central mechanism underlying circadian rhythm disruption (CRD) in Alzheimer's disease (AD) [37].

Emerging evidence from postmortem analyses and transgenic animal models consistently indicates that the SCN is not spared in AD but rather constitutes an early and vulnerable pathological target subjected to the dual insults of amyloid-β (Aβ) and tau. At Braak Stages I–II, phosphorylated tau pretangles and diffuse Aβ plaques can already be detected within the SCN, even

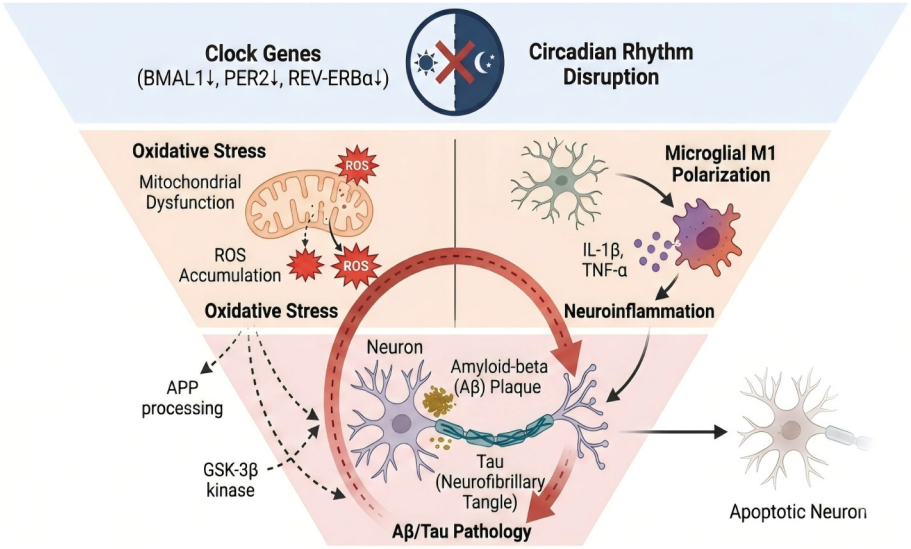


FIGURE 2 | Molecular mechanisms by which circadian rhythm disruption drives the progression of Alzheimer's disease pathology. Aβ, amyloid-β; APP, amyloid precursor protein; GSK-3β, glycogen synthase kinase-3β; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α.

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in the absence of classical neuritic inflammatory plaques. As the disease progresses, marked loss of key peptidergic neurons expressing vasoactive intestinal peptide (VIP) and arginine vasopressin (AVP), together with reactive astrocytosis, suggests a progressive weakening of SCN output signaling [38]. Experimental lesions of the SCN alone are sufficient to abolish free-running rhythms in mice, whereas in AD models, the degree of SCN neuronal loss correlates significantly with nighttime awakenings, daytime napping frequency, and the rate of cognitive decline. Collectively, these findings support the view that direct SCN degeneration constitutes a central etiological driver of circadian dysfunction in AD.

In the early stages of AD, circadian phase drift may already emerge before overt visual impairment becomes clinically apparent. One major explanation is that photic signals fail to reach the clock. Converging evidence from recent animal studies, molecular profiling, and clinical electrophysiological investigations indicates that degeneration of the retinal input pathway to the SCN is a key upstream contributor to CRD. Specifically, intrinsically photosensitive retinal ganglion cells (ipRGCs)—the specialized retinal neurons responsible for non-image-forming photoreception—and their axons undergo early degeneration, resulting in attenuated light signaling. In parallel, glutamatergic and pituitary adenylate cyclase-activating polypeptide (PACAP) neurotransmission to the SCN is reduced [39]. Consequently, the biological clock receives insufficient entrainment cues, leading to circadian desynchronization.

Neuroimaging studies further demonstrate that, compared with individuals with mild cognitive impairment (MCI) and cognitively normal older adults, patients with AD exhibit an average 18%–24% reduction in pineal gland volume, with the degree of atrophy positively associated with Mini-Mental State Examination (MMSE) scores [40]. Functionally, cerebrospinal fluid melatonin levels are reduced by approximately 50% even during the preclinical phase of AD (Braak Stages I–II), whereas the nocturnal melatonin peak disappears entirely during the symptomatic stage, with the circadian amplitude approaching zero. Both the reduction in melatonin output and the loss of rhythmic amplitude directly weaken feedback regulation of the SCN and synchronization of peripheral clocks, thereby promoting sleep-wake dysregulation manifested as prolonged sleep latency, increased nocturnal awakenings, and a higher incidence of sundown syndrome.

Taken together, AD pathology appears to target the circadian system through a precise "three-node" cascade: first, by directly damaging the master clock (SCN); second, by severing the photic input pathway (ipRGCs); and third, by silencing the nocturnal output signal (melatonin). Through this process, the circadian pacemaking system is transformed from a synchronizing hub into an amplifier of pathology.

Although the bidirectional vicious cycle between AD pathology and circadian rhythm disruption is now widely recognized, a more upstream hypothesis warrants consideration: During the subjective cognitive decline (SCD) stage of AD, subtle circadian phase drift and rhythm fragmentation may represent a physiological stress test of the aging brain as it attempts to compensate for the earliest accumulation of toxic proteins. When the microenvironment of key cortical and hippocampal regions undergoes incipient oxidative or inflammatory perturbation, the highly sensitive SCN and its output networks may be among the first systems to lose homeostatic stability. Circadian rhythm disruption, therefore, should not be viewed solely as a downstream consequence or accelerator of AD pathology but also as a sentinel signal reflecting early microscopic brain injury. This conceptual shift provides a compelling theoretical foundation for the use of noninvasive circadian monitoring as an ultra-early screening strategy for preclinical AD.

3.3 | Rhythmic Dysregulation of Other Molecular Pathways

In addition to structural damage to the SCN, impaired lymphoid-like clearance, and neurotransmitter rhythmic imbalances, circadian rhythm disruption also contributes to the pathological progression of AD through multiple molecular pathways. It should be noted that most of the evidence supporting the mechanisms described below comes from animal models and cellular experiments; their validation in patients with AD remains insufficient.

1. Genetic interaction between core clock genes and APOE ε4. At the genetic level, APOE ε4 is currently the only factor supported by evidence from both human longitudinal cohort studies and animal model studies. Population studies have confirmed a synergistic effect between APOE ε4 and sleep disturbances—Huang et al. tracked more than 320,000 nondemented adults for 12.3 years and found that individuals carrying APOE ε4 who had poor sleep quality had an approximately 37% higher risk of developing AD than noncarriers; inflammatory and metabolic pathways serve as the common biological basis linking the two [41]. Animal studies have further revealed that APOE ε4 can act synergistically with sleep deprivation to accelerate Aβ plaque aggregation and impair its clearance [42]. In contrast, the regulatory roles of core clock genes (BMAL1, CLOCK, PER2, etc.) have primarily been observed in transgenic mouse and cellular experiments; for example, BMAL1 deficiency relieves the inhibition of nuclear factor kappa-B (NF-κB) and exacerbates neuroinflammation [43], reduced activity of the CLOCK/BMAL1 complex causes genes such as APP and presenilin 2 (PSEN2) to lose their circadian oscillations, thereby increasing Aβ production [44], and disruption of PER2/Cry1/2 leads to the disappearance of nocturnal peaks in antioxidant enzymes [45]; however, these findings have yet to be directly validated in human SCN tissue.
2. Disruption of the autophagy rhythm. The autophagy system exhibits circadian oscillations, driven by the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway under the periodic regulation of BMAL1 and REV-ERBα; when this rhythm is disrupted, nocturnal autophagy flux decreases, leading to the accumulation of Aβ oligomers and phosphorylated tau protein due to impaired clearance [46]. The loss of rhythmicity in mitochondrial autophagy and chaperone-mediated autophagy further exacerbates ROS leakage and the accumulation of tau monomers [47, 48]. This mechanism is primarily based on observations in AD cell models and

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mouse brain tissue; evidence from humans is extremely limited.

3. Gut microbiota–circadian rhythm–brain axis. The abundance and metabolic activity of the gut microbiota exhibit 24-h oscillations in tandem with the sleep-wake cycle; circadian rhythm disruption leads to dysbiosis, reduces short-chain fatty acids, and alters tryptophan and bile acid metabolism, resulting in increased proinflammatory metabolites and weakened anti-inflammatory signaling [49–51]. A synchronized increase in the permeability of the intestinal mucosa and the blood–brain barrier allows harmful bacterial byproducts and pathogenic T cells to enter the brain parenchyma, activating an inflammatory response in microglia [52]. Most of the evidence in this area comes from animal models and human cross-sectional studies of fecal microbiota in AD; causal relationships and the efficacy of microbiota interventions remain to be verified.
4. Abnormal calcium signaling rhythms. Oscillations in intracellular Ca^{2+} homeostasis are fundamental to maintaining synaptic plasticity, and when this rhythm is disrupted, astrocytes fail to function as calcium wave clocks, leading to reduced glutamate transport efficiency across the synaptic cleft and glutamate spillover. This triggers sustained activation of N-methyl-D-aspartate (NMDA) receptors, causing calcium overload, which, in turn, activates proteases such as calpain, cleaving tau protein and disrupting the synaptic scaffold [53–56]. This mechanism is primarily based on electrophysiological recordings from isolated neurons and brain slices; there is virtually no validation of this mechanism in living patients with AD.

4 | Circadian-Based Interventions

Before systematically discussing specific pharmacological and nonpharmacological interventions, it is essential to introduce chronotherapy, a core strategy that underpins all circadian-targeted interventions. Chronotherapy does not refer to a single drug or device; rather, it represents a clinical paradigm in which therapeutic interventions are tightly coupled to an individual's circadian phase and the temporal dynamics of disease pathology [57]. Its guiding principle is “time-specific tailoring”: By precisely assessing the patient's endogenous rhythm, interventions—such as timed light exposure, scheduled feeding, or pharmacological targeting—are applied within optimal temporal windows, thereby maximizing therapeutic benefits while minimizing off-target effects and metabolic burden. In the context of AD management, adopting a chronotherapeutic approach signifies a paradigm shift from traditional “passive, symptom-focused hypnotic treatment” toward active restoration of circadian homeostasis, with the potential for disease-modifying effects.

4.1 | Evidence for Symptom-Improving Interventions

1. Nonpharmacological interventions

Time-restricted feeding (TRF) provides the peripheral circadian clock with a clear and strong daily rhythmic signal through a “fixed feeding window” and has been recognized as an emerging nonpharmacological strategy for regulating circadian rhythms in AD. TRF is a nonpharmacological intervention that restricts food intake to a 6–12-h window, with fasting during the remaining hours; its key advantage is that it does not require calorie restriction, leading to higher compliance. In a previous basic research study, AD model mice were subjected to a 3-month “6-h window” TRF regimen, after which a reduction in Aβ plaques in the mice's brains was observed, indicating improved Aβ clearance efficiency; the mice exhibited reduced nocturnal hyperactivity and more regular sleep-wake rhythms; the mice in the experimental group performed better on memory tests (Morris water maze) than those in the *ad libitum*-fed control group [58]. In a clinical trial, Zhao et al. reported that a 4-month course of TRF improved cognitive impairment in patients with AD [59].

Among the nonpharmacological “rhythm modulation” measures currently used for AD, bright light therapy (BLT) has the strongest evidence and is the simplest to administer. A study by Kim et al. identified a form of BLT—timed BLT—based on an individual's circadian rhythm phase, which focuses on regulating the circadian clock of patients with AD through light stimulation with specific parameters, thereby improving sleep and cognition [60]. The light therapy consisted of 1 hour per day for two consecutive weeks; efficacy was assessed immediately after treatment (T1) and 4 weeks later (T2). The study showed that, 4 weeks after the intervention, the treatment group had significantly better subjective sleep quality (Pittsburgh Sleep Quality Index (PSQI) score) than the control group, a significant improvement in overall cognitive function (MMSE-KC score) compared to baseline, and a significant reduction in caregiver burden (Zarit Burden Interview–Korean version (ZBI-K) score); objective sleep duration (total sleep time, TST) showed a trend toward improvement but did not reach statistical significance [61]. This indicates that this light therapy can improve the cognitive and sleep status of patients with AD to a certain extent and is suitable for long-term home use by patients, combining effectiveness with portability.

Among nonpharmacological circadian rhythm regulation measures for AD, scheduled physical activity is regarded as an intervention equally important to bright light therapy and feasible for daily implementation. Timed physical activity can resynchronize the central clock, thereby improving sleep efficiency and daytime alertness [62]. Its core value lies in strengthening the amplitude of the central clock and improving nighttime sleep structure and daytime alertness through the combined design of “when to move” and “how to move.” Experts in the guidelines for multifaceted rehabilitation interventions for Alzheimer's disease note that a combination of aerobic exercise, strength training, and mind-body exercises should be employed, with exercise duration and intensity tailored to the patient's cognitive level and physical condition to ensure personalized programs. For patients in the early to middle stages of AD, active participation should be the primary focus, whereas those in the late stages should primarily engage in passive limb movements or gentle exercises. The guidelines emphasize the importance of regularity and consistency, avoiding interruptions, as long-term intervention is necessary for results to become apparent. Multiple randomized controlled trials and meta-analyses have confirmed that aerobic exercise

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can significantly improve cognitive function in patients with AD and slow the rate of decline; strength training delays cognitive and memory decline by increasing the expression of neurotrophic factors in the hippocampus and reducing oxidative stress; and mind-body exercises such as Tai Chi can improve short-term cognitive function and mental health in patients with early-stage dementia, as well as increase cortical thickness in certain brain regions [63].

2. Pharmacological interventions (with symptom improvement as the primary endpoint)

Melatonin and its receptor agonists. Melatonin regulates the sleep-wake cycle by activating melatonin receptor Type 1/2 (MT1/MT2) receptors. A Dutch study conducted in nursing homes ($n \approx 200$, mean age 86 years, 87% with dementia) showed that oral administration of 2.5 mg of melatonin each night, combined with daytime exposure to bright light for 15 months, reduced nighttime agitation and prolonged total sleep time [64, 65]; however, some trials have not found significant improvements in sleep measures with melatonin alone, suggesting that an advanced disease stage or receptor gene polymorphism may diminish its efficacy. Several observations indicate that melatonin can reduce the incidence of evening agitation and delirium, but it does not significantly improve cognitive scores (MMSE, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)) [66]. Overall, the evidence for melatonin in AD supports its ability to improve sleep-behavioral symptoms but does not support a modulatory effect on cognitive function or AD pathology.

Orexin receptor antagonists (DORAs). DORAs (such as lemborexant and suvorexant) block the arousal-promoting effects of orexin by competitively binding to orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R), thereby prolonging REM and NREM sleep. A 1-month Phase III RCT demonstrated that lemborexant significantly shortened continuous sleep latency, reduced the time spent awake after falling asleep, and improved sleep efficiency [66]; suvorexant was also shown to improve total sleep time in patients with mild-to-moderate suspected AD [67]. A 2022 systematic review, which included 8 RCTs, confirmed that DORAs were significantly superior to placebo in improving insomnia efficacy measures [68]. However, enrollment in existing DORA trials was primarily based on a clinical diagnosis rather than biomarker-confirmed AD; study endpoints focused mainly on sleep parameters without CSF or PET-MR pathological indicators; and the intervention periods were relatively short (mostly $\leq$ 3 months). Therefore, the level of evidence is limited to "improving sleep structure in AD patients with insomnia," and there is currently no evidence to support that DORAs can slow the pathological progression of AD.

Sedative-hypnotics and psychotropic medications. Benzodiazepines and non-benzodiazepines (such as zolpidem) exert their hypnotic effects by enhancing GABAergic inhibition and have proven efficacy in the general population with insomnia. However, extreme caution is required in patients with AD: Their side effect of anterograde amnesia may exacerbate memory impairment, and long-term use may even increase the risk of dementia progression [69]; dependence and withdrawal symptoms are particularly problematic in patients with AD with psychomotor agitation. Antidepressants (e.g., trazodone) and antipsychotics (e.g., quetiapine) are primarily used to control the neuropsychiatric and behavioral symptoms associated with AD (such as sundown syndrome, hallucinations, and aggressive behavior); their sedative effects may indirectly improve sleep [70]. The clinical role of these drugs is "symptomatic treatment," and there is no evidence to support their impact on the core pathology of AD.

4.2 | Exploration of Disease-Modifying Hypotheses

REV-ERBα inhibitors—a pathological modification hypothesis in the laboratory stage. REV-ERBα inhibitors, which target circadian rhythm nuclear receptors, are molecular targets that have emerged in recent years; they regulate circadian rhythms by influencing BMAL1 expression. In animal studies, inhibiting REV-ERBα increases BMAL1 expression, stimulates the polarization of microglia toward the M2 phenotype, and accelerates the clearance of Aβ plaques [71], simultaneously raising NAD^+ levels to improve mitochondrial function [72]. It should be emphasized that all of the above findings come from transgenic mouse and cell experiments, and there are currently no human data available. Whether REV-ERBα inhibitors can achieve Aβ clearance or cognitive benefits in patients with AD remains purely hypothetical at this time, and there is still a substantial gap before clinical translation can be achieved.

In summary, pharmacological interventions for sleep disturbances in AD primarily focus on circadian modulation. Evidence suggests that melatonin and its analogs are particularly suited for patients with mild-to-moderate AD experiencing sleep onset difficulties or sundowning, serving as adjunctive circadian modulators. Orexin receptor antagonists demonstrate robust efficacy in enhancing sleep efficiency and mitigating behavioral agitation, with favorable short-term safety profiles. Both classes are most effective when combined with non-pharmacological strategies such as timed light exposure and scheduled physical activity, and their potential cognitive and disease-modifying effects require validation in larger, longer-duration randomized controlled trials. Conventional sedative-hypnotics carry substantial side-effect burdens, whereas psychotropic agents are primarily reserved for the symptom-driven treatment of behavioral disturbances. Emerging REV-ERBα inhibitors reveal the potential to improve mitochondrial function and cognition via circadian gene regulation, suggesting that sleep disturbances in AD may represent not merely symptomatic phenomena but key targets for biological clock modulation and neural repair.

The repeated bottlenecks in clinical trials targeting circadian rhythm interventions for patients with AD fundamentally stem from the fact that trial designs have not yet overcome the traditional "symptomatic treatment for insomnia" mindset, overlooking the phase dependency of rhythm-based interventions (Table 1). Future clinical translation should not merely focus on developing new drugs but rather aim to establish a "Precision Chronotherapy" system based on individual circadian phases.

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TABLE 1 | Pharmacological and nonpharmacological interventions for circadian rhythm regulation.

Intervention type	Specific intervention	Mechanism of action	Major effects	Evidence
Nonpharmacological	Time-restricted feeding (TRF)	Provides clear Zeitgeber signals to peripheral clocks	Improves sleep-wake rhythms, reduces nighttime hyperactivity, and enhances cognitive performance	AD model mice, 3 months, 6-h feeding window → reduced Aβ, decreased nighttime activity, improved Morris water maze performance [58]; 4-month TRF in patients with AD → improved cognitive function [59]
	Bright light therapy (BLT)	Synchronizes the SCN and modulates circadian clock genes	Improves sleep quality, cognitive function, and caregiver burden	Timed blue-white light, 1 h/day for 2 weeks → improved PSQI, MMSE-KC, and ZBI-K scores [60, 61]
	Timed physical activity	Synchronizes the central clock and enhances circadian amplitude	Improves nighttime sleep structure, daytime alertness, and cognition	Aerobic, resistance, and mind-body exercises → improved cognition, delayed decline, and increased cortical thickness [62, 63]
Pharmacological	Melatonin and receptor agonists (e.g., ramelteon)	Activate MT1/MT2 receptors to regulate the circadian rhythm	Shorten sleep latency, prolong total sleep time, and reduce nighttime agitation	Elderly dementia patients, 2.5 mg nightly + daytime light → extended total sleep, reduced agitation [64, 65]; limited effect on cognitive scores [66]
	Dual orexin receptor antagonists (DORAs, e.g., lemborexant and suvorexant)	Block OX1R/OX2R and suppress the wake drive	Extend REM/NREM sleep, improve sleep efficiency, and reduce nighttime awakenings	Multicenter RCTs → shorter sleep latency, longer sleep duration, and improved sleep efficiency [67–69]
	Sedative-hypnotics (benzodiazepines and non-benzodiazepines)	Enhance GABAergic inhibition	Improve sleep onset and duration	Rapid onset and effective in general insomnia, but high risk of side effects; cautious use in AD [70]
	Psychotropic drugs (antidepressants and antipsychotics)	Antagonize 5-HT, H1, and D2 receptors	Control psychiatric symptoms while aiding sleep	Sundown syndrome treatment hallucinations, and aggression; used for symptom-driven sleep disturbances in AD [66]
	Emerging targeted drugs (REV-ERBα inhibitors)	Modulate circadian clock genes (e.g., BMAL1) and promote microglial M2 polarization	Improve circadian rhythms, enhance Aβ clearance, and boost mitochondrial function and cognition	Animal studies → accelerated Aβ clearance, increased NAD+, and improved cognition [71, 72]

This entails that, before administering interventions such as melatonin or light therapy, patients' circadian phase profiles must be accurately mapped using continuous core body temperature monitoring or salivary rhythmic biomarkers. Only by precisely aligning exogenous interventions with patients' endogenous circadian vulnerable windows can the true disease-modifying potential of chronotherapy be realized, rather than merely providing sedative-hypnotic effects.

5 | Limitations

Current research on circadian rhythms in AD still has multiple limitations, which not only restrict the in-depth analysis of the pathological mechanisms of the disease but also constitute significant obstacles to clinical translation and application. First, this is prominently reflected in the insufficient compatibility between animal models and human clinical characteristics. Most

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existing studies rely on transgenic mouse models (such as APP/PS1, APP-KI, 3 × Tg-AD, etc.). Although such models can reproduce the core pathological features of AD through gene editing, there are fundamental differences in circadian rhythm-related phenotypes from those of humans [73]. In terms of species rhythmicity, mice are nocturnal animals, and their activity-rest cycle is completely opposite to that of humans (diurnal). However, AD-related rhythm disturbance phenotypes have obvious species specificity—in mouse models, rhythm disturbance is mostly manifested as excessive activity during the active period, and the degree of sleep fragmentation is positively correlated with activity, whereas the core rhythm abnormality in human patients with AD is the day-night reversal of "awake at night and sleepy during the day," often accompanied by "sundown syndrome" (mental and behavioral abnormalities such as confusion and emotional agitation) in the evening. The phenotypic differences between the two make it difficult to directly extrapolate the interaction mode of "rhythm disturbance-AD pathology" in animal experiments to humans. More importantly, animal models cannot replicate the complexity of the etiology of human AD: The occurrence of human AD is the result of the combined action of multiple factors such as genetic susceptibility (such as the APOE ε4 allele), environmental factors (such as long-term sleep deprivation and social isolation), and age-related physiological decline. However, existing transgenic models mostly focus on the overexpression of a single or a few pathological genes, making it difficult to simulate the heterogeneous etiology of clinical patients with AD, which poses significant challenges to the clinical translation of mechanistic research conclusions based on animal models.

Second, the causal relationship between rhythm disturbance and AD pathology has not yet been clarified, and most existing studies remain at the correlation level. A large number of studies have confirmed a close association between the two. For example, Aβ deposition can disrupt the circadian rhythm of microglia in the brain and inhibit their Aβ clearance function at night, whereas circadian rhythm disturbance can further aggravate the imbalance of Aβ metabolism and the progression of tau pathology in the brain, forming a vicious cycle of "pathological damage-rhythm disturbance" [74] (Figure 3). However, none of this evidence can directly prove that rhythm disturbance is an independent risk factor for the occurrence and development of AD. In addition, most existing studies are cross-sectional surveys or short-to-medium-term follow-up studies, lacking long-term, large-sample prospective cohort studies to clarify the temporal relationship that "rhythm disturbance occurs before the initiation of AD pathology," which also leads to the lack of core evidence for determining the direction of causality between the two.

To address the limitations in current research, breakthroughs can be promoted from multiple dimensions in the future. At the basic research level, animal models more closely resembling human clinical characteristics can be developed, such as constructing composite models through gene editing combined with environmental inducers (such as chronic sleep deprivation and circadian rhythm disruption) or using nonhuman primates (diurnal, with cognitive functions closer to those of humans) to explore the interaction mechanism between rhythm disturbance and AD pathology; at the same time, with the help of technologies such as single-cell sequencing and spatiotemporal transcriptomics, the molecular interaction mechanisms between the SCN regulatory network, clock genes, and core AD pathological pathways can be analyzed in depth. At the clinical research level, it is necessary to carry out long-term, large-sample prospective cohort studies, combined with multimodal assessment

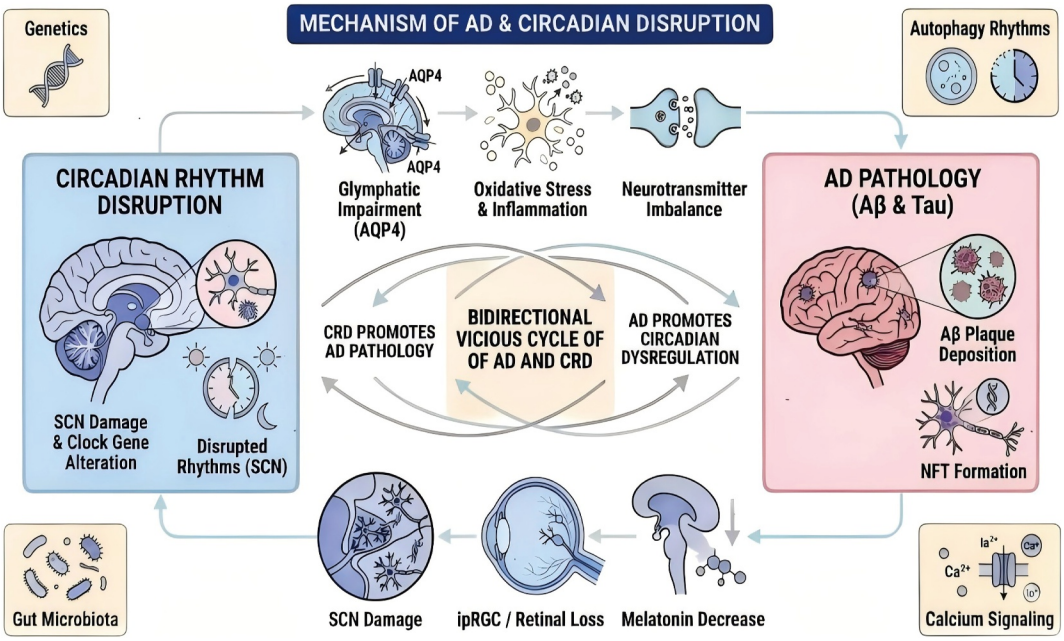


FIGURE 3 | Bidirectional vicious cycle between Alzheimer's disease pathology and circadian rhythm disruption. Aβ, amyloid-β; AD, Alzheimer's disease; AQP4, aquaporin 4; CRD, circadian rhythm disruption; ipRGC, intrinsically photosensitive retinal ganglion cells; NFT, neurofibrillary tangle; SCN, suprachiasmatic nucleus.

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methods (functional magnetic resonance imaging, biomarker detection, and cognitive assessment), to clarify the temporal relationship between rhythm disturbance and the initiation of AD pathology and elucidate the causal relationship between the two.

6 | Discussion and Perspectives

Circadian rhythm disturbances in Alzheimer's disease (AD) are not merely consequences of neurodegeneration; they represent central, mechanistic drivers of pathology and cognitive decline. Accordingly, interventions targeting circadian regulation—such as light therapy, time-restricted feeding, exercise, melatonin, and dual orexin receptor antagonists (DORAs)—hold promise for breaking this vicious cycle.

To translate these findings into effective therapies, future research must move beyond descriptive studies toward precision chronotherapy. Large-scale digital phenotyping of 24-h activity-rest cycles and physiological indicators, integrated with cerebrospinal fluid biomarkers and multimodal imaging, can identify high-risk individuals and predict disease progression. Personalized interventions, aligned with the individual circadian phase, are essential to maximize efficacy, whereas molecular circadian biomarkers and core pathological imaging can establish a rigorous link between rhythm improvement, pathological modulation, and cognitive benefit. Moreover, multimodal strategies combining behavioral and pharmacological interventions may achieve comprehensive circadian remodeling across central, peripheral, and sleep systems, enabling multi-target modulation of AD pathology.

In summary, a framework that integrates digital phenotyping, precise chronotherapy, biomarker-guided evaluation, and multimodal synergy could elevate circadian regulation from symptomatic management to a core disease-modifying strategy. This offers a new path for early prevention and comprehensive treatment of AD.

Author Contributions

Jiajia Qin: methodology, conceptualization, writing – original draft. **Xianfeng Yu:** methodology, conceptualization, writing – original draft. **Yayu Wang:** writing – original draft, data curation. **Xiaohan Song:** data curation, visualization. **Yuehua Wang:** investigation, formal analysis. **Zhixin Wang:** investigation, conceptualization. **Wei Miao:** data curation. **Xudong Yang:** data curation. **Jiajia Zhu:** writing – review and editing. **Xiaoqun Zhu:** writing – review and editing. **Maria-Trinidad Herrero:** writing – review and editing.

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Ethics Statement

The author have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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