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NEUROPROTECTION

REVIEW

Circadian rhythms and chronotherapy in Alzheimer's disease: Mechanisms and therapeutic implications

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Abstract

Alzheimer's disease (AD), the most prevalent form of dementia, has been increasingly associated with disruptions in circadian rhythms and sleep–wake regulation. This narrative review synthesizes recent literature on how circadian dysfunction may contribute to AD pathogenesis, biomarker profiles, and treatment response. Mechanistic studies suggest important interactions between core clock genes and neurodegenerative cascades involving oxidative stress, neuroinflammation, glial reactivity, and proteostasis. Disruptions in circadian-regulated molecular pathways, including brain and muscle ARNT-like 1 (*BMAL1*)–sirtuin 1 (*SIRT1*), nuclear factor kappa B (*NF-κB*)–NOD-like receptor family pyrin domain containing 3 (*NLRP3*), and period circadian regulator 2 (*PER2*)–antioxidant signaling pathways, may compromise neuronal resilience and worsen AD-related pathology. Emerging evidence also suggests distinct circadian patterns in AD-relevant biomarkers, including melatonin, cortisol, orexin, core body temperature, blood–brain barrier permeability, and glial marker oscillations. These rhythmic patterns may have diagnostic and prognostic relevance and support the need for time-aware biomarker interpretation. Chronotherapeutic strategies targeting circadian biology, including melatonin receptor agonists, light therapy, time-restricted feeding, and circadian-aligned drug delivery systems, may help improve targeted clinical endpoints in AD. This review also discusses chronoepigenetics as an emerging area in which clock-regulated epigenetic modifications may influence neurodegenerative trajectories. Future directions include next-generation chronotherapeutic targets, such as glial clocks, clock-gated inflammatory mechanisms, and systemic comorbidities with circadian modulation, including diabetes and hypertension. Overall, the available evidence supports a close association between circadian disruption and both AD pathology and therapeutic response, while also highlighting important gaps in large-scale clinical trials. This time-oriented perspective may support the development of personalized, biomarker-guided, and rhythm-informed approaches to AD care. By bridging chronobiology and neurodegeneration, this review highlights how circadian precision medicine may refine future approaches to understanding and managing AD.

KEYWORDS

Alzheimer disease, biomarkers, chronobiology, chronotherapy, circadian rhythm

Highlights

- Circadian dysfunction may be an early, modifiable contributor to Alzheimer's disease rather than solely a secondary consequence. Core clock genes and

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circadian-regulatory factors, including *BMAL1*, *CLOCK*, *PER2*, and *SIRT1*, intersect with oxidative stress, neuroinflammation, and proteostasis pathways that may influence amyloid-β and tau pathology.
- This review integrates circadian biomarkers (melatonin, cortisol, body temperature, retinal changes, BBB dynamics) with emerging chronotherapeutic strategies and identifies chronoepigenetics, glial clock dysfunction, and gut–brain–circadian interactions as next-generation precision medicine targets in AD.

1 | INTRODUCTION

Alzheimer's disease (AD) was first described by Alois Alzheimer in 1906 in a 50-year-old woman with progressive memory loss, disorientation, and behavioral disturbances. Postmortem examination revealed hallmark neuropathological features, including amyloid plaques and neurofibrillary tangles, which remain central to AD research.[1] Despite decades of investigation, the precise mechanisms driving amyloid-β (Aβ) and tau accumulation remain unclear. Current perspectives increasingly view AD as a multifactorial condition shaped by genetic susceptibility, environmental exposures, and systemic health factors. Some researchers have questioned whether AD should be considered a distinct disease entity or a maladaptive outcome of aging and comorbidities.[2]

The global burden of AD continues to rise, and the condition remains highly disabling because disease-modifying treatment options remain limited. Between 1990 and 2016, the number of individuals living with dementia more than doubled, reaching 43.8 million. According to the Global Burden of Disease Study, dementia was the fifth leading cause of death globally and accounted for an estimated 2.4 million deaths in 2016. More than 6.4 million disability-adjusted life-years (DALYs) were attributed to modifiable risk factors, highlighting opportunities for prevention.[3] Rapid population aging creates additional challenges, particularly in low- and middle-income countries. A systematic review estimated the prevalence of AD in China at 3.48% and its incidence at 7.9 per 1000 person-years.[4] Globally, AD and other dementias are projected to affect 153 million individuals by 2050, compared with 57 million in 2019, with an economic burden exceeding international dollars (INT$) 14 trillion between 2020 and 2050. Informal caregiving accounts for the largest share of this cost, particularly in lower-middle-income regions.[5]

Circadian biology has emerged as an important framework for understanding modifiable contributors to AD pathogenesis. Disrupted circadian rhythms are increasingly recognized not only as consequences of neurodegeneration but also as early features that may contribute to AD pathogenesis. Dysfunction of the suprachiasmatic nucleus (SCN), altered sleep–wake cycles, and impaired circadian regulation of stress and immune responses may contribute to neuronal injury and disease progression.[6] Clinically, circadian-linked disturbances such as sundowning syndrome, which is characterized by evening agitation, confusion, and behavioral dysregulation, illustrate the relevance of circadian disruption to AD symptoms and patient care.[7]

Foundational work in chronobiology, from the discovery of clock genes to systems-level models of coupled oscillators, has positioned circadian biology as a field that bridges molecular, physiological, and behavioral science.[8] These advances have laid the foundation for "circadian medicine," in which timing is considered a therapeutic variable across oncology, neurology, metabolic disease, and cardiovascular medicine.[9] Within this framework, applying circadian principles to AD may provide mechanistic insights into disease progression and symptom expression. It may also inform practical strategies for prevention, symptom management, and treatment optimization. In this narrative review, we summarize core circadian mechanisms and their links to neurodegeneration, examine circadian-informed biomarkers and therapeutic strategies, and outline future directions for integrating chronotherapy into AD research and care.

2 | METHODOLOGY

In this narrative review, we synthesized current evidence on the interplay between circadian rhythms and AD. We conducted a structured literature search using PubMed as the primary database. Where additional depth was required, such as for emerging mechanistic pathways or biomarker-specific subsections, we conducted focused manual searches and screened reference lists to identify additional studies. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to AD, circadian rhythms, clock genes (*BMAL1*, *CLOCK*, *PER*, and *CRY*), sleep–wake regulation, biomarkers (melatonin, cortisol, body temperature, retinal changes, and the blood–brain barrier [BBB]), glial cells (astrocytes and microglia), the gut–brain axis, chronoepigenetics, and chronotherapy. Boolean operators (AND and OR) were used to refine searches; example search strings included "Alzheimer's disease AND circadian rhythm," "Alzheimer's disease AND melatonin AND biomarker."

We included articles published between January 2000 and May 2025, with particular emphasis on recent literature from 2020 to 2025 to capture emerging insights. Relevant studies were screened independently

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by two reviewers, and disagreements were resolved through discussion or, when required, adjudication by a third reviewer. Eligible articles included peer-reviewed original studies, systematic reviews, and clinical trials addressing circadian biology, biomarkers, or therapeutic interventions in AD. Non-English publications, conference abstracts, case reports, and editorials were excluded. Studies unrelated to circadian regulation or AD were also excluded. Overall, 109 studies met the inclusion criteria and were incorporated into the core narrative synthesis. Additional supporting references were included where necessary to provide background context and mechanistic clarification.

Because this was a narrative review, no formal systematic flow diagram, such as a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, was applied. Study quality and relevance were assessed qualitatively based on methodological clarity, thematic relevance to the review aims, and consistency with the broader evidence base. The synthesis was then organized into thematic sections covering mechanistic insights, circadian disruption in AD pathogenesis, biomarkers, therapeutic strategies, and future directions.

3 | CIRCADIAN RHYTHMS AND AD

3.1 | Basic principles of circadian rhythms

The circadian rhythm is an intrinsic 24-h cycle that regulates physiological processes. It is governed by coordinated interactions between central and peripheral clocks. The central clock is located in the SCN, a small cluster of neurons in the anterior hypothalamus, whereas peripheral clocks are distributed across most tissues and remain synchronized by SCN signals. *Zeitgebers* are external cues that entrain the central clock, with light being the strongest cue. Other cues, including food intake, temperature, physical activity, and social interactions, also contribute to circadian timing. At the molecular level, circadian clock genes regulate a wide range of physiological processes, including sleep–wake cycles, metabolism, and hormonal secretion.[10]

Circadian misalignment, defined as a mismatch between the endogenous circadian clock and the external environment, has become increasingly prevalent because of modern lifestyle factors, including evening exposure to artificial light, increased screen use, reduced physical activity, and irregular work schedules. This misalignment is increasingly recognized as an early and potentially modifiable feature of AD. It may contribute to sleep fragmentation and sundowning and may also be associated with the accumulation of pathological hallmarks such as amyloid-β and tau. These disruptions may worsen disease progression and increase caregiver burden. Because light is the most potent zeitgeber, meta-analyses suggest that light therapy may improve sleep quality and reduce nocturnal awakenings in older adults with dementia. Together, these findings highlight the relevance of circadian rhythms across the AD continuum, from risk and symptom expression to disease progression and treatment optimization, and support further evaluation of circadian-targeted strategies in AD care and prevention.[11–13]

3.2 | Circadian disruption as a potentially modifiable risk factor in AD

Growing evidence suggests that circadian disruption is not merely a consequence of AD but may also be a modifiable risk factor. Changes in circadian rhythms are often observed before cognitive symptoms appear, suggesting early dysfunction of the SCN and altered hormonal, metabolic, and sleep–wake regulation.[14,15] This disruption may create a bidirectional feedback loop in which neurodegeneration worsens circadian misalignment, while circadian misalignment may further contribute to neurodegenerative processes.[16]

Core clock genes, such as brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)-like 1 (*BMAL1*) and circadian locomotor output cycles kaput (*CLOCK*), regulate circadian rhythms and are involved in oxidative stress, inflammation, and memory, making them potential therapeutic targets. Dysregulation of microRNAs, including downregulation of microRNA-16 (miR-16) and its interaction with CLOCK proteins, further supports the potential relevance of circadian misalignment as a therapeutic entry point.[17] The hypocretin/orexin system may also be involved, as elevated orexin levels can impair glymphatic clearance and may link prolonged arousal states to Alzheimer's pathology.[18]

Environmental circadian disruption may add another layer of risk. For example, night shift work has been associated with oxidative stress and DNA damage, processes linked to neurodegeneration.[19–21] Taken together, these findings suggest that circadian dysfunction may be detectable early and may provide opportunities for prevention and targeted intervention.

3.3 | Circadian gating and sleep disturbances in AD

Circadian gating regulates physiological processes across the 24-h cycle by determining when biological events such as hormone secretion, immune responses, metabolism, and gene expression are most active. Disruption of this mechanism can impair immune homeostasis, metabolic clearance, and sleep quality, all of which are implicated in AD pathogenesis.[22]

Modern lifestyles increasingly contribute to circadian misalignment, as greater exposure to artificial light at night (ALAN), shift work, and irregular eating or sleep schedules can disrupt circadian rhythms and contribute to sleep disturbances, endothelial dysfunction, altered hemostasis, metabolic alterations, and heightened inflammation.[23] These changes may contribute to cerebrovascular pathology and cognitive decline. Dysregulation of circadian clock genes, particularly within the renin–angiotensin–aldosterone system, has been observed in both cardiovascular

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and neurodegenerative conditions, suggesting shared mechanistic pathways and the potential value of rhythm-targeted strategies.[24]

Among behavioral interventions, time-restricted eating (TRE) has emerged as a practical approach that may support circadian alignment.[25] Gasmi et al.[26] reported that TRE was associated with lower Aβ42 deposition, reduced systemic inflammation, and stronger central and peripheral circadian rhythm integrity, with potential benefits for sleep regulation and cognitive performance. These findings suggest that circadian gating may represent a biologically actionable target in AD management, although further clinical validation is needed.

3.4 | Impact of circadian rhythms on molecular degradation pathways

Proteostasis refers to the balance among protein synthesis, folding, and degradation and is tightly regulated by circadian rhythms.[27] In AD, disruption of circadian timing may impair these proteostasis mechanisms. Fessel suggested that correcting circadian dysfunction could help restore key neurobiological processes, including the degradation and clearance of misfolded proteins.[28] Similarly, Festus et al. highlighted that circadian-aligned interventions, such as structured rest, feeding schedules, and small molecules targeting core clock pathways, can modulate cellular stress responses and may enhance molecular repair.[29]

Protein degradation systems, including autophagy and the ubiquitin–proteasome system, are also under circadian control and are impaired in AD. Gasmi et al.[26] further reported that TRE reduced brain amyloid-β42 (Aβ42) levels, potentially by improving circadian regulation of glymphatic clearance and inflammatory tone. These findings suggest that restoring circadian alignment through personalized chronobiological strategies may help rebalance disrupted proteostasis networks in AD.

4 | MECHANISMS LINKING CIRCADIAN RHYTHMS AND NEURODEGENERATION

4.1 | Molecular mechanisms linking circadian disruption and neurodegeneration

Although circadian disruption is consistently observed in patients with AD, much of the detailed molecular evidence linking clock gene dysfunction to oxidative stress, proteostasis failure, and neuroinflammation is derived from animal models and cellular systems. Human studies support associations among circadian disturbance, sleep fragmentation, amyloid burden, and cognitive decline. However, direct causal confirmation of specific molecular clock mechanisms in human Alzheimer's pathology remains limited; therefore, current understanding relies on converging lines of preclinical and translational evidence.

BMAL1 and *CLOCK* are core circadian genes involved in oxidative stress, inflammation, and neuronal homeostasis, as shown mainly in preclinical and translational studies. Neurodegeneration and circadian gene dysfunction appear to have a bidirectional relationship. Neurodegenerative processes can impair circadian gene activity; in turn, this dysfunction may heighten neuroinflammatory and stress-related pathways and exacerbate disease progression.[30] At the cellular level, these genes also regulate genome-maintenance pathways, including DNA replication, checkpoint signaling, and DNA repair, as supported by evidence from multiple model systems. Disruption of these rhythms may reduce repair fidelity and promote genomic instability, processes increasingly implicated in AD.[31]

Farshadi et al.[32] further described mechanistic coupling between the circadian clock and the cell cycle. These observations are supported largely by single-cell and other experimental studies, including studies in mouse fibroblasts. In these systems, clock-controlled genes synchronize mitotic timing and DNA repair. Loss of this coordination may impair neurogenesis and contribute to age-related neuronal decline, providing a rationale for time-based therapeutic strategies.

Circadian clock genes also help gate cognitive processes such as memory and synaptic plasticity, based largely on experimental and translational neuroscience evidence.[33] In AD, desynchronization between the central SCN and regional brain clocks has been proposed to disrupt plasticity rhythms and contribute to cognitive deterioration, primarily on the basis of mechanistic and circuit-level studies. This proposed feed-forward loop, in which circadian disruption may worsen neurodegenerative pathology, supports further evaluation of chronotherapy aimed at resynchronizing brain clocks.[33]

These findings are not limited to AD. Comparative work by Asadpoordezaki et al.[34] in Parkinson's disease described similar early circadian alterations, drawing on clinical observations as well as systems-level, cellular, and molecular evidence. These observations support the potential translational value of personalized rhythm-based interventions across neurodegenerative conditions.

4.2 | Glial cells and their role in circadian regulation of neurodegeneration

Astrocytes, once regarded as passive supporting cells, are now recognized as important regulators of circadian rhythms, as demonstrated primarily in experimental models of the circadian system. They modulate neuronal signaling, neurotransmitter cycling, and sleep–wake regulation. In AD, disruptions in astroglial clocks have been implicated in circadian and neurodegenerative changes. These alterations may contribute to sleep fragmentation, neuroinflammation, and cognitive decline.[35] Circadian dysfunction within astrocytes may therefore act as an upstream modulator

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of neurodegenerative processes and represents a potential target for chronotherapeutic intervention.

Astrocytes also exhibit intrinsic Ca^{2+} rhythmicity that facilitates coordination of SCN neuronal firing and stabilizes downstream sleep–wake rhythms, particularly in studies of SCN pacemaker circuitry. Interference with these Ca^{2+} oscillations can diminish clock-gene rhythmicity and attenuate SCN output strength. This provides a mechanistic explanation for how astrocytic signaling abnormalities may contribute to circadian decline in AD.[35]

Tau pathology, a hallmark of AD, may also impair neuronal and glial components of the SCN, the brain's central circadian pacemaker. Tau accumulation within the SCN can alter core clock-gene expression and compromise astrocytic support. These changes may contribute to circadian misalignment and have been associated with worse cognitive outcomes in animal models and human studies, including human SCN investigations.[36] These findings underscore the bidirectional vulnerability of glial–neuronal circuits within the SCN and support further investigation of astrocyte-based circadian interventions in AD.

4.3 | Bi-directional feedback loop models (circadian–SCN–AD)

A bidirectional feedback loop may exist between circadian rhythm disruption and AD. Figure 1 provides an overview of the proposed circadian–SCN–AD feedback loop, illustrating how early SCN dysfunction, sleep–wake fragmentation, reduced glymphatic clearance, and amyloid-β/tau accumulation may interact with neuroinflammatory and metabolic pathways. Disruption of circadian regulation may promote inflammation, oxidative stress, and accumulation of misfolded proteins, while AD pathology may further impair circadian output and perpetuate a self-sustaining pathological cycle.[37]

Several clinical and mechanistic observations suggest that sleep disturbances are both early symptoms of AD and potential contributors to its progression. Impaired slow-wave sleep can reduce glymphatic clearance of amyloid-β (Aβ), while progressive neurodegeneration may fragment circadian-regulated sleep architecture and contribute to Aβ and tau deposition.[38,39] Astrocyte-mediated neuroinflammation and dysregulation of pathways such as mechanistic target of rapamycin (mTOR) may further link circadian dysfunction to the molecular framework of AD.[39]

Circadian misalignment extends beyond the brain and may also involve the gut microbiota. Cheng et al.[40] described how circadian misalignment may disrupt microbiota rhythmicity, impair neuroimmune communication through the microbiota–gut–brain axis, and promote systemic inflammation and cognitive decline. Emerging evidence suggests that communication between SCN and hippocampal circadian networks is important for maintaining diurnal patterns in synaptic

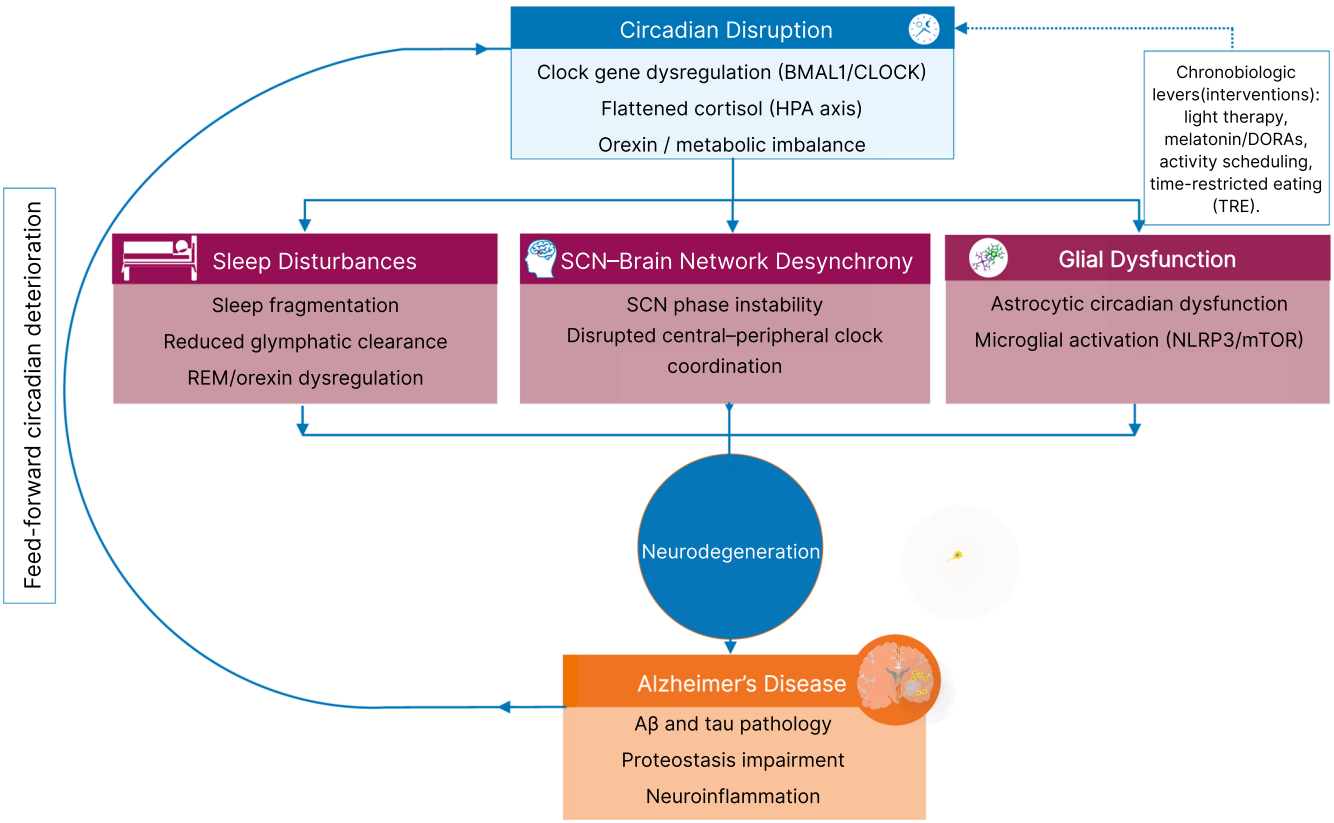

FIGURE 1 Multimodal circadian disruption–neurodegeneration feedback loop in Alzheimer's disease. Aβ, amyloid-β; BMAL1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; DORAs, dual orexin receptor antagonists; HPA, hypothalamic–pituitary–adrenal; mTOR, mechanistic target of rapamycin; NLRP3, NOD-like receptor family pyrin domain containing 3; NREM, non-rapid eye movement; REM, rapid eye movement; SCN, suprachiasmatic nucleus; TRE, time-restricted eating.

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plasticity and memory function. When this coordination diminishes, as may occur in the early stages of AD, cognitive performance may fluctuate more across the day, contributing to the temporal fragmentation of behavior observed in clinical settings. Similarly, hypothalamic dysregulation, particularly in metabolic and endocrine pathways, may contribute to neurodegenerative cascades. Toljan and Homolak[41] advocated aligning lifestyle and pharmacological interventions with circadian timing to mitigate these effects.

Obstructive sleep apnea (OSA) and non-dipper hypertension are important circadian-linked comorbidities that can compromise neurovascular health. Nagai et al.[42] emphasized that these conditions can disrupt central autonomic regulation, leading to BBB impairment, intermittent hypoxia, and enhanced neuroinflammation. These findings suggest an interconnected circadian–neurodegenerative axis in which sleep, metabolism, autonomic rhythms, and gut microbiota converge, offering potential chronobiological targets for early intervention and disease modification.

4.4 | Circadian and sleep disturbances in molecular pathways of AD

Circadian disruptions can interfere with physiological processes such as metabolism, synaptic plasticity, and memory consolidation. These disruptions may contribute to neurodegeneration rather than acting solely as secondary consequences.[43]

As noted earlier, proteostasis is under circadian control, and age-related declines in proteasome function may impair both clock-gene regulation and clearance of misfolded proteins, thereby compounding Alzheimer's pathology.[44] In AD, the SCN remains structurally intact in most cases, but downstream circadian signaling may be impaired, leading to widespread rhythmic disturbances.[45] These disruptions may extend to peripheral oscillators and sensory circuits, contributing to systemic rhythm breakdown.[46]

Both SCN and non-SCN brain clocks appear vulnerable in AD. Circadian dysregulation may promote amyloid accumulation and impair neurophysiological homeostasis.[47] Beyond cognitive symptoms, circadian timing may also influence motor function, with studies showing improved gait and balance in the afternoon; these findings suggest that time-of-day considerations may help enhance rehabilitation outcomes in patients with AD.[48]

Sleep deprivation may further exacerbate AD through mechanisms that include glymphatic dysfunction, tau pathology, glial activation, and orexin dysregulation. These mechanisms are closely linked to circadian control.[49] Similarly, metabolic disorders such as type 2 diabetes mellitus may intersect with AD through shared circadian mechanisms involving insulin resistance, oxidative stress, and clock-gene disruption. These findings support further evaluation of rhythm-aligned strategies such as melatonin, light therapy, and time-restricted feeding.[50] Table 1 summarizes how circadian misalignment, sleep–orexin signaling, hormonal rhythms, proteostasis, and inflammatory cascades may contribute to AD pathogenesis.

5 | CIRCADIAN DISRUPTION AND ITS IMPACT ON AD

5.1 | Circadian desynchrony and AD pathogenesis

Circadian desynchrony reflects the breakdown of coordinated biological timing across central and peripheral systems. In AD, this desynchrony affects multiple domains relevant to disease expression and progression, including mood regulation, sleep, hormonal axes, and proteostasis.

Amidfar et al.[51] described shared molecular vulnerabilities among aging, major depressive disorder, and AD, in which disruptions in clock-gene expression and nitro-oxidative stress pathways may converge to promote neurodegeneration through impaired redox balance and synaptic instability. Fishbein et al.[52] further emphasized bidirectionality: circadian misalignment may increase vulnerability to neurologic disease, whereas ongoing pathology may progressively disrupt circadian control, reinforcing a feed-forward cycle relevant to AD progression.

Francis and Porcu[53] explained how clock genes regulate neuronal excitability, synaptic plasticity, and neurotransmitter release through cell-type-specific mechanisms in mood-related brain circuits, including the SCN and limbic system. These mechanisms offer a plausible basis for neuropsychiatric symptoms in AD, including anxiety and sundowning, which may be mediated partly by stress-related circadian disruption and altered limbic–SCN coupling.

Sleep is both a behavioral output of the circadian system and a potential prodromal marker of cognitive decline. In a systematic review, Gonzales et al.[54] reported that nearly 45% of individuals with cognitive impairment had sleep disorders, including insomnia, OSA, and abnormal sleep duration. These disturbances were observed before clinical manifestation and were associated with increased amyloid-β burden and rapid eye movement (REM) sleep abnormalities.

The orexin system also influences the sleep–cognition axis. Carpi et al.[55] evaluated dual orexin receptor antagonists (DORAs), which improved sleep quality and may modulate amyloid and tau pathology. These findings support DORAs as candidates with symptomatic benefit and possible biomarker effects, although larger and longer-term studies are needed to determine whether they have disease-modifying effects. Knezevic et al.[56] explored the role of cortisol rhythmicity in neuroinflammation, hippocampal atrophy, and tau hyperphosphorylation. Because cortisol rhythmicity is governed by the circadian clock and the hypothalamic–pituitary–adrenal (HPA) axis, flattened or reversed cortisol patterns, often observed in chronic stress states, may further contribute to AD-related brain changes.

At the mechanistic level, proteostasis failure can disrupt sleep regulation and reduce the clearance of

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TABLE 1 Key mechanistic themes linking circadian disruption and Alzheimer's disease.

Mechanism	Authors (year)	Key findings
Circadian misalignment & neurodegeneration	Amidfar et al.[51]	Clock gene disruption and oxidative stress may promote neurodegeneration.
	Fishbein et al.[52]	Circadian disruption and AD pathology reinforce each other in a feedback loop.
	Francis and Porcu[53]	Clock gene dysfunction contributes to anxiety and sundowning in AD.
Sleep & orexin pathways	Gonzales et al.[54]	Sleep disorders precede AD and are linked to amyloid-β and REM disruption.
	Carpi et al.[55]	Orexin antagonists improve sleep and may modulate amyloid/tau pathology.
Hormonal dysregulation	Knezevic et al.[56]	Abnormal cortisol rhythms may contribute to neuroinflammation and tau pathology.
	Chen et al.[57]	Circadian misalignment may accelerate vascular aging and hormone imbalance.
	Figueroa et al.[58]	Thyroid dysfunction is associated with cognitive decline in AD.
	Mercadante and Bellastella[59]	Light and melatonin therapy may restore endocrine stability.
Proteostasis & glymphatic dysfunction	Morrone et al.[60]	Impaired proteostasis may reduce protein clearance and worsen cellular dysfunction.
	Nyamugenda et al.[6]	Circadian clocks regulate oxidative stress and proteostasis in early AD.
Inflammatory Pathways	Pourcet and Duez[61]	Clock disruption amplifies NLRP3-driven neuroinflammation.

Abbreviations: AD, Alzheimer's disease; NLRP3, NOD-like receptor family pyrin domain containing 3; REM, rapid eye movement.

neurotoxic proteins through autophagy and glymphatic pathways, thereby worsening neuronal circuit dysfunction. This feed-forward loop was described by Morrone et al.[60] Consistent with this, Nyamugenda et al.[6] argued that circadian clocks regulate oxidative stress responses, mitochondrial homeostasis, and protein degradation pathways. Failure of these core processes may mark early stages of AD pathology. Pourcet and Duez[61] also revealed that circadian control of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome governs daily inflammatory oscillations, with clock disruption potentially amplifying sterile neuroinflammation through dysregulated interleukin-1β (IL-1β) and interleukin-18 (IL-18) signaling.

Collectively, these studies suggest that circadian desynchrony may be a multifaceted contributor to AD rather than only a correlate. It intersects with mood circuits, hormonal rhythms, neuroinflammation, and protein homeostasis, potentially forming self-perpetuating pathological loops. Targeting these disruptions through chronotherapy, circadian-aligned pharmacology, and behavioral timing may help modify disease trajectories, although much of the mechanistic evidence remains observational or preclinical.

5.2 | Hormonal dysregulation in neurodegeneration

Hormonal dysregulation is closely tied to circadian rhythm disruption and may play an important role in AD pathogenesis. The rhythmic secretion of key hormones, including cortisol, melatonin, insulin, and thyroid hormones, may become altered when central circadian control is disrupted. These alterations may have systemic and neuroinflammatory consequences.

Chen et al.[57] highlighted how circadian misalignment may accelerate vascular aging through oxidative stress and inflammation, thereby indirectly impairing neuroendocrine feedback loops involving cortisol and melatonin.Similarly, thyroid hormone disturbances have been associated with cognitive decline, altered cerebral metabolism, and circadian abnormalities in patients with AD, suggesting a complex neuroendocrine–circadian interplay.[58]

Mercadante and Bellastella[59] reinforced these findings by emphasizing that hormonal rhythms are centrally governed by the SCN and by advocating circadian-aligned interventions. Approaches such as light therapy and melatonin supplementation may help restore endocrine stability and protect against cognitive deterioration.

Overall, these studies support further evaluation of hormonal rhythmicity in chronotherapeutic strategies for Alzheimer's prevention and care, while highlighting the need for robust clinical trials that formally test hormone-timed interventions in AD populations.

5.3 | Biomarkers and chronotherapy in AD circadian-related molecular biomarkers

Circadian biology plays an important role in shaping biomarker profiles for early detection, risk stratification, and therapeutic monitoring in AD. Emerging studies

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suggest that numerous AD-related biomarkers exhibit diurnal variation, which may influence their diagnostic accuracy and biological interpretation. The BBB, once considered a static interface, is now recognized as exhibiting circadian variation in permeability and transport functions. Avila and Zhang[62] reported that this rhythmic regulation influences drug delivery, sleep behavior, and neurodegenerative vulnerability, positioning the BBB as a dynamic, clock-controlled biomarker candidate in AD. However, because most evidence is preclinical or early translational, the clinical applicability of BBB rhythmicity as a routine biomarker remains preliminary rather than definitive. Similarly, systemic circadian markers such as the circadian rhythm of body temperature (CRBT) may serve as real-time indicators of circadian phase and immune homeostasis. Coiffard et al.[63] suggested that CRBT disruption may signal immune dysregulation and circadian misalignment in AD and may provide a noninvasive guide for chronotherapeutic research. At present, CRBT is best viewed as a research tool for phenotyping circadian status rather than as a standalone diagnostic marker for AD.

At the cellular level, microglia, the brain's resident immune cells, are also regulated by circadian clock genes that influence their phagocytic activity and inflammatory output. Geng et al.[64] reported that circadian misalignment may impair amyloid clearance and enhance neuroinflammation, identifying microglial rhythmicity as a potential target for immunochronotherapy in AD. Microglia exhibit circadian metabolic cycles characterized by fluctuations in glycolytic activity, mitochondrial function, and nicotinamide adenine dinucleotide (NAD^+)–dependent redox balance, which influence their inflammatory profile throughout the 24-h cycle. Circadian misalignment may disrupt these metabolic cycles, increase microglial reactivity, and diminish amyloid-clearance capacity, thereby intensifying early neuroinflammatory signaling in AD.[64]

These findings emphasize a mechanistic connection between circadian timing and microglial activity, although microglia-focused chronotherapeutic approaches have not advanced beyond preclinical stages. Among circadian-linked biomarkers, melatonin is one of the most widely studied.[64] This pineal-derived hormone regulates autophagy, oxidative stress, mitochondrial function, and clock-gene expression. It may have value as both a biomarker and a therapeutic agent. Hossain et al. and Luo et al. highlighted melatonin's role in autophagic clearance of toxic proteins, while Mihardja et al. demonstrated its potential support for hippocampal neurogenesis and circadian realignment.[65–67] Mechanistically, these studies suggest a plausible disease-modifying role; however, most evidence derives from animal and cellular models, and direct translation to human AD remains limited.

Melatonin rhythm loss, particularly low cerebrospinal fluid and salivary melatonin levels, has been associated with early tau accumulation in the hippocampus, suggesting that circadian disruption may precede cognitive decline in AD.[68] These findings suggest that altered melatonin secretion may serve as an early biomarker of vulnerability to AD, although cutoff values, assay standardization, and sampling schedules must be clarified before routine clinical implementation.

Current studies more cautiously indicate that melatonin decline may assist in risk stratification within well-phenotyped cohorts, whereas melatonin and light therapy are best regarded as supplementary chronotherapeutic interventions rather than universally established first-line treatments across all stages of AD. Minich et al.[69] introduced the concept of "darkness deficiency," in which artificial light exposure suppresses melatonin synthesis in a manner compared with vitamin D deficiency caused by inadequate sunlight exposure, potentially further driving circadian imbalance in AD.

Despite mixed clinical trial results, reviews by Prodhan et al.[70] and Steinbach and Denburg[71] suggest that melatonin may provide modest cognitive and behavioral benefits in early-stage AD, particularly when administered in a circadian-aligned manner. Overall effect sizes are modest to moderate, and variability in study design, formulation, and timing limits definitive conclusions; nonetheless, signals of benefit for sleep and behavioral outcomes warrant additional focused trials in well-defined AD subgroups. Shen et al.[72] further extended melatonin's relevance to type 2 diabetes mellitus (T2DM), suggesting a role in countering shared AD–T2DM mechanisms such as insulin resistance, oxidative stress, and inflammation. Although further studies are needed, these findings position melatonin as a candidate for addressing both central and peripheral risk factors in AD. Clinically, this supports a broader view of melatonin as part of a multimodal approach that also considers metabolic, vascular, and lifestyle factors.

Large-scale longitudinal studies provide further evidence that circadian rhythm degradation may predict AD risk. In a study of more than 1400 older adults using actigraphy, Li et al.[73] showed that reduced amplitude and increased fragmentation of daily activity rhythms predicted higher AD incidence and faster disease progression. These findings support the argument that objectively assessed circadian rest–activity patterns may function as early risk indicators and endpoints in prevention studies, although they have not been incorporated into standard diagnostic protocols. More specifically, current data support their prognostic significance at the cohort level; further research is required to establish individual-level thresholds and cost-effective implementation strategies. Not all rhythmic biomarkers are impaired in AD. Saelzler et al.[74] observed that although basal cortisol levels are elevated, the circadian rhythm of cortisol secretion remains intact, suggesting that cortisol hypersecretion may serve as a time-sensitive biomarker independent of core circadian disruption. This finding indicates that certain endocrine markers may provide AD-related information through alterations in amplitude or set point rather than through complete disruption of rhythmicity, an important nuance for biomarker interpretation.

Together, these findings highlight a complex biomarker landscape shaped by circadian biology. From molecular clocks within microglia and the BBB to

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systemic signals such as body temperature, melatonin, and cortisol, these biomarkers may help guide personalized and time-targeted interventions in AD. At the same time, most circadian-sensitive biomarkers remain in the research or early translational stage; future efforts should focus on establishing standardized sampling protocols, conducting longitudinal validation, and integrating these biomarkers with established AD indicators, including Aβ, tau, and neurodegeneration, to clarify their added value.

5.4 | Biomarker-informed chronotherapeutic targets in AD

Circadian rhythms regulate physiological homeostasis, and growing evidence supports their role as potential targets for therapeutic innovation in AD. Melatonin, a circadian-regulated hormone, is among the most widely studied chronotherapeutic agents. It can modulate sleep–wake cycles, oxidative stress, neuroinflammation, and toxic protein aggregation. In AD, melatonin levels are often decreased, and supplementation has shown symptomatic and possible disease-modifying potential, although clinical results remain heterogeneous across studies.[75] Sleep disorders, which commonly manifest during the prodromal stage of AD, may further contribute to amyloid-β and tau pathology through circadian misalignment and neurotransmitter imbalance. Interventions targeting sleep architecture and orexinergic systems may therefore offer early-stage neuroprotection, although the evidence remains limited by short trial durations and modest sample sizes.[76]

The endocannabinoid system is another potential chronobiological modulator. Cannabinoid receptors interact with core clock genes to regulate neurotransmission and immune responses, and dysfunction in this system may worsen neurodegeneration through tau misprocessing and microglial activation.[77] Lee et al.[78] emphasized that circadian misalignment may heighten vulnerability to neurodegeneration and affect drug efficacy, suggesting that incorporating circadian phase into therapeutic protocols could enhance treatment outcomes and reduce adverse effects. However, most data linking endocannabinoid signaling to circadian intervention in AD derive from preclinical rather than clinical studies.

Insights from cancer chronotherapy suggest that targeting transcription–translation feedback loop (TTFL) regulators, such as BMAL1, CLOCK, and cryptochrome (CRY) genes, may also be relevant to AD because these elements are closely linked to protein clearance and metabolic homeostasis.[79] These mechanistic parallels are compelling but remain largely extrapolated because AD-specific clock-gene-targeted trials are not yet available. Proteomic analyses further support these targets by showing that circadian rhythm disorders dysregulate proteins involved in autophagy, inflammation, and synaptic signaling; these findings support the development of precision chronotherapy in AD while highlighting gaps in standardized, time-resolved sampling strategies.[80]

Clinical evidence includes a Phase 2 trial of lemborexant, a DORA, which improved circadian alignment and sleep efficiency in patients with AD and irregular sleep–wake rhythm disorder without worsening cognition.[81] This evidence remains preliminary because of the trial's short duration and small sample size. Similarly, the Tg-SwDI mouse model, which replicates both parenchymal and vascular amyloid pathology alongside circadian disruption, provides a translational platform for evaluating time-sensitive interventions in AD and cerebral amyloid angiopathy, although its generalizability to human AD phenotypes is limited.[82]

Ruan et al.[83] broadened this therapeutic scope by advocating circadian phenotyping and clock-targeted agents to address systemic circadian disruption in AD. Aryl hydrocarbon receptor (AhR) activation, for example, disrupts BMAL1 and CLOCK expression and impairs glymphatic clearance, creating a mechanistic link between gut–brain axis dysfunction and AD pathology and positioning AhR as a potential circadian target.[84] However, no interventional studies have yet tested AhR modulation in AD, representing an important evidence gap. Molecular crosstalk between circadian regulators and protein homeostasis pathways highlights additional targets, such as PARP1 and E3 ligases. Circadian misalignment may enhance their activity, promote tau and α-synuclein aggregation, and accelerate neurodegeneration. Current evidence remains predominantly preclinical, and modulating these pathways could help interrupt the feedback loop between circadian dysfunction and neurodegenerative progression.[85]

Overall, these studies suggest that circadian biology is not simply a consequence of AD but may contribute to disease progression. Chronotherapeutic targets such as melatonin, orexin, endocannabinoids, clock genes, and peripheral regulators such as AhR may offer symptomatic benefits and possible disease-modifying opportunities, although supportive evidence varies substantially across mechanistic, preclinical, and clinical tiers. Phase-stratified evaluation of these interventions is needed to clarify which targets may meaningfully influence AD progression.

5.5 | Metabolic and systemic circadian biomarkers and chronotherapeutic implications

Therapeutic strategies aligned with the body's circadian rhythm may improve selected outcomes in neurodegenerative diseases such as AD. Chronopharmacology shows that circadian timing influences drug pharmacokinetics and pharmacodynamics, including absorption, efficacy, and toxicity. Fujimura and Ushijima[86] argued that circadian-aligned drug delivery, or chronotherapy, could improve treatment precision in AD, particularly given the disorder's intrinsic circadian dysregulation. However, the clinical application of chronotherapy remains limited by insufficient regulatory guidance, inadequate provider education, and the absence of structured chronotherapy networks. Melatonin is a circadian-regulated hormone with multiple potential neuroprotective actions, including

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antioxidant, anti-inflammatory, and autophagy-modulating effects. Luo et al.[66] emphasized melatonin's ability to regulate mitophagy and limit the toxic accumulation of misfolded proteins such as amyloid-β and tau, supporting its potential role as a chronotherapeutic agent that may restore circadian alignment while protecting against neurodegeneration. Its effects remain supported primarily by mechanistic and early-stage clinical studies, underscoring the need for larger, time-stratified AD trials. Adropin, a peptide with circadian rhythmicity, has been identified as a potential mediator linking metabolism, endothelial function, and autonomic tone. Kolben et al.[87] proposed a "metabolic–autonomic nervous system–circadian" axis in which dysregulated adropin may contribute to vascular dysfunction and cognitive impairment in AD. These findings suggest that personalized chronotherapy guided by melatonin, adropin, and other circadian biomarkers may provide a tailored treatment approach that integrates metabolic health with biological timing.[87] However, evidence directly connecting adropin dynamics to AD progression remains predominantly conceptual and preclinical.

Circadian regulation plays a major role in maintaining brain and systemic metabolic homeostasis and is increasingly implicated in AD pathophysiology and treatment. The molecular circadian clock orchestrates key metabolic functions such as lipid utilization, glucose metabolism, mitochondrial activity, and insulin sensitivity, operating both centrally and in peripheral organs such as the liver and adipose tissue.[88] Disruption of these rhythms, often because of aging, irregular lifestyle patterns, or environmental misalignment, may compromise metabolic efficiency and may contribute to neurodegenerative progression. Emerging biomarker technologies, such as plasma metabolome-based predictors of circadian phase, may provide opportunities for personalizing interventions by aligning treatment timing with an individual's endogenous rhythms, although these models still require validation in diverse physiological and pathological conditions.[89] Within the brain, clock genes such as CLOCK, BMAL1, PER, and CRY regulate lipid metabolism, and their desynchronization may trigger oxidative stress, neuroinflammation, and synaptic instability, which are linked to amyloid and tau pathology in AD.[90] These mechanistic links, while compelling, are derived largely from preclinical models and require further human validation. Moreover, sleep disturbances, which are closely linked to circadian misalignment, may amplify these metabolic imbalances and worsen cognitive symptoms. Javed et al.[91] emphasized the therapeutic potential of combining nonpharmacological approaches, such as light therapy and activity scheduling, with chronotherapeutic agents such as melatonin and DORAs to support circadian control, although outcomes likely vary by safety profile and disease stage. These findings support a multifaceted strategy in which metabolic chronotherapy, incorporating behavioral, pharmacological, and biomarker-guided interventions, may help preserve neurophysiological stability; however, the translational evidence base remains uneven across mechanistic, observational, and clinical tiers.

Disruption of circadian rhythms and gut microbiota integrity represents a converging pathophysiological mechanism in AD. These processes form a dynamic gut–clock–brain axis that may modulate neurodegenerative progression. Gut dysbiosis can increase intestinal permeability. This may permit systemic translocation of proinflammatory and neurotoxic metabolites, including trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), and calprotectin. These metabolites have been implicated in Aβ and tau pathology.[92] Metabolite signatures, particularly TMAO, calprotectin, and kynurenine, have been recognized as candidate biomarkers of gut–brain–circadian dysregulation in AD. At the molecular level, the circadian clock gene BMAL1 plays a central role in maintaining gut immune rhythmicity and microbial balance. Its dysfunction may disrupt mucosal immunity and oxidative homeostasis, thereby aggravating neuroinflammation.[93] Recent mechanistic reviews further suggest that BMAL1 dysregulation alters immunoglobulin A (IgA) secretion rhythms and microbial composition, reinforcing downstream neuroinflammatory cascades. Bidirectional signaling may reinforce this interaction. Gut-derived metabolites may alter peripheral and central clock-gene expression, creating a feed-forward loop of circadian and microbial dysregulation.[94] Sleep–circadian rhythm disturbances (SCRD), which are commonly observed in early AD, may further dampen microbial rhythmicity, reduce SCFA-producing taxa, and promote systemic inflammation, thereby worsening circadian misalignment and neuropathological burden.[95] Shared alterations across AD, SCRD, and gut dysbiosis include reduced SCFA-producing bacteria and increased proinflammatory taxa. These overlapping features suggest a multidirectional sleep–circadian rhythm disturbance–gut microbiota–AD (SCRD–GM–AD) loop. In addition, circadian dysregulation of gut–brain lipid metabolism may impair membrane dynamics and calcium homeostasis, triggering endoplasmic reticulum stress and amplifying neurodegenerative cascades.[96] Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA)–mediated calcium dysregulation and endoplasmic reticulum (ER) stress have been highlighted as downstream consequences of lipid rhythm disruption within the gut–brain axis.

These findings highlight the gut–circadian interface as a potential area for biomarker discovery and chronobiotic or nutritional intervention, supporting its translational relevance for early diagnosis and targeted treatment in AD. Much of the mechanistic evidence underlying this gut–clock–brain axis derives from experimental and observational studies, and causal validation in large, longitudinal human cohorts remains limited.

5.6 | Retinal biomarkers for AD

The retina forms the inner layers of the eye and is an extension of the nervous system. It may provide a noninvasive window into AD pathology. Mirzaei et al.[97] introduced the concept of "Alzheimer's retinopathy," showing that hallmark features of AD, such as amyloid-β plaques, hyperphosphorylated tau, neuronal loss, and

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gliosis, are detectable in the retina and may precede overt cognitive decline. Retinal vascular abnormalities, including pericyte loss and reduced platelet-derived growth factor receptor-β (PDGFR-β) expression, correlate with cerebral amyloid angiopathy, strengthening the retina–brain pathological link. Because the retina contributes to photic entrainment of the circadian system through melanopsin-containing retinal ganglion cells, retinal degeneration may also contribute to circadian rhythm disruptions observed in AD. Advanced imaging modalities, such as optical coherence tomography (OCT), hyperspectral imaging, and amyloid-targeted retinal scans, may provide chronobiological and diagnostic insights, positioning the retina as both a mechanistic contributor and a biomarker platform for circadian-linked neurodegeneration.[97]

5.7 | Chronoepigenetics: A new frontier in AD

Chronoepigenetics may play an important role in AD pathophysiology, with emerging evidence suggesting that epigenetic regulation of circadian rhythms is an important mechanism. Guu et al.[98] demonstrated that inadequate light exposure in care environments may exacerbate sundowning and behavioral symptoms through disruption of neuroendocrine and circadian networks, implicating light as a modulator of epigenetically influenced rhythms. At the molecular level, Lim[99] reported that diurnal and seasonal gene-expression patterns in the neocortex are blunted in AD, accompanied by dampened DNA methylation and histone modifications, which are hallmarks of circadian desynchrony in the aging brain. This finding was supported by Liu et al.,[112] who described sirtuin 1 (SIRT1) as a central epigenetic integrator of circadian and neuroprotective pathways. The interplay among SIRT1, DNA methylation pathways, and histone deacetylation provides a mechanistic basis for how epigenetic dysregulation may undermine circadian stability in AD. SIRT1, through deacetylation of BMAL1 and period circadian regulator 2 (PER2), sustains rhythmic transcriptional cycles while modulating neuroinflammatory, oxidative, and amyloidogenic pathways, suggesting a direct role for epigenetic clock regulation in Alzheimer's pathogenesis. The observed loss of diurnal methylation rhythms and impaired chromatin cycling in Alzheimer's cortical tissue further supports this framework, positioning the SIRT1–DNA methyltransferase (DNMT)–histone deacetylase (HDAC) axis as a potential regulatory node that may be amenable to therapeutic intervention. These findings suggest that restoring epigenetically governed circadian rhythms could represent a potential strategy for AD prevention and chronotherapy. Figure 2 provides a comprehensive overview of circadian disruptions, mechanistic cascades, and emerging chronotherapeutic targets in AD.

6 | THERAPEUTIC APPROACHES AND CHRONOTHERAPY

6.1 | Chronotherapy as a potential therapeutic approach in AD

Chronotherapy is emerging as a strategy that may optimize selected therapeutic outcomes in AD,

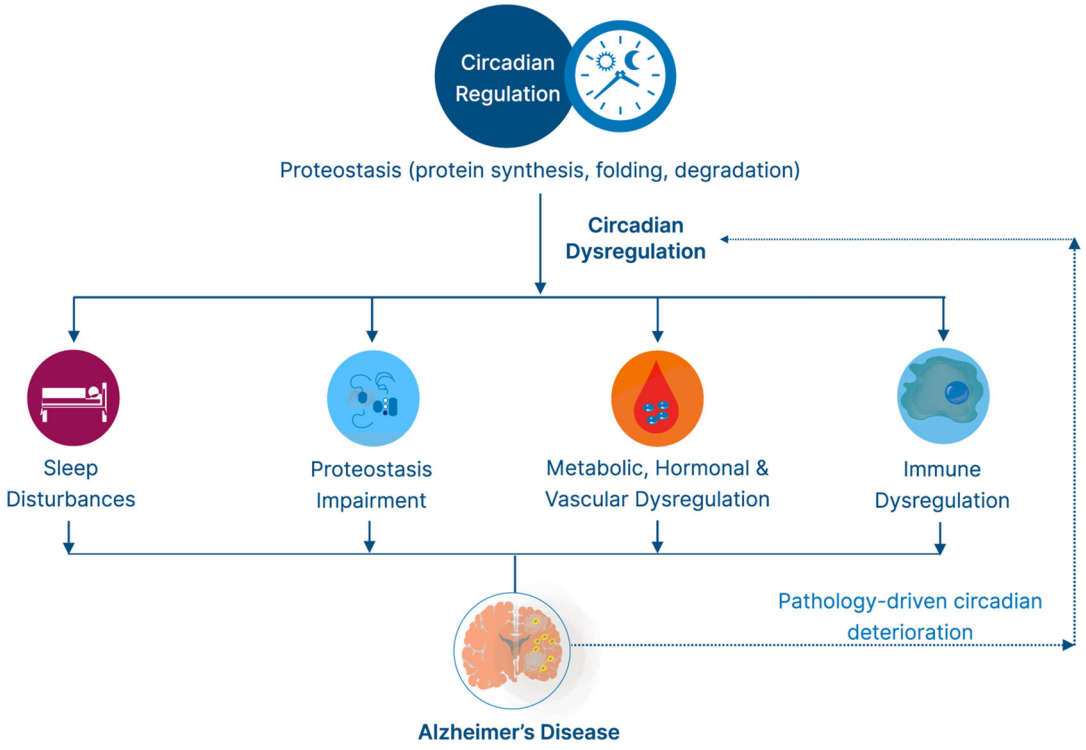

FIGURE 2 Circadian dysregulation as a multimodal contributor to Alzheimer's disease pathophysiology.

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particularly sleep regulation, behavioral symptoms, treatment tolerability, and biomarker-informed intervention timing. Cardinali et al.[100] described chronotherapy as a dual approach involving rhythm restoration, such as melatonin or light therapy, and time-based drug administration tailored to individual chronotypes. Butler et al.[101] extended this concept through chrono-tailored drug delivery systems, which are designed to enhance efficacy and minimize adverse effects by synchronizing drug release with biological rhythms. This time-dependent pharmacological optimization is further supported by Dong et al.,[102] who showed that circadian regulation of absorption, metabolism, and excretion, mediated by clock-controlled genes, can affect drug safety and potency.

The existing clinical evidence for chronotherapy in AD remains heterogeneous. Interventions such as light therapy and melatonin have been evaluated in human trials. These studies show modest and often inconsistent benefits for sleep and behavioral symptoms. Their potential to modify underlying disease processes remains uncertain. Chronotype-informed drug timing and biomarker-guided treatment strategies are also emerging. However, these strategies require larger, phase-specific validation studies before routine clinical adoption. Several mechanistic targets, including clock-gene modulation, rhythm-synchronized neuromodulation, and molecular clock–metabolic interfaces, remain largely confined to preclinical or early-phase investigations. A clear distinction between established symptomatic benefit and hypothesis-generating translational approaches is therefore essential for responsible clinical integration.

Colita et al.[103] reinforced this perspective in psychiatric care, showing that biomarker-guided chronotherapy may improve outcomes when personalized according to melatonin, cortisol, and clock-gene expression. Cummings et al.[104] identified circadian pathways as emerging disease-modifying targets in the evolving AD drug pipeline and called for biomarker-linked trials that integrate time-of-day effects. Fleming et al.[105] introduced rhythm-synchronized neuromodulation as a future extension of chronotherapy, proposing real-time brain stimulation aligned with patient-specific circadian patterns. To improve translational relevance, circadian-aligned techniques in AD trials require standardized circadian phase measurement. They should also be evaluated alongside current disease-modifying therapies, such as lecanemab. In addition, well-defined time-of-day dosing regimens are essential. These findings emphasize time-aware, rhythm-aligned therapeutic strategies as an emerging frontier in personalized AD management.

6.2 | Chronotherapeutic sleep management framework for AD

Sleep disturbances are increasingly recognized as modifiable contributors to AD pathogenesis and progression. Chauhan et al.[106] highlighted that insomnia, OSA, and circadian rhythm disorders (CRDs) are prevalent in both prodromal and advanced AD stages and may contribute to neurodegeneration by impairing glymphatic clearance of amyloid-β and tau proteins. The authors cautioned against overreliance on sedative pharmacotherapy because of the risks of falls and cognitive worsening, particularly in older adults. Instead, they advocated early and sustained management of sleep disorders through nonpharmacologic and chronotherapeutic interventions. These sleep-based therapies may serve as preventive measures in early dysregulation and as therapeutic strategies in symptomatic stages, a distinction that is important for clinical application. These findings emphasize the central role of sleep–wake regulation in neuroprotection and support further integration of sleep-based interventions into comprehensive AD management frameworks.[106]

6.3 | Circadian hygiene and environmental risk factors in AD

Circadian hygiene may play an important role in mitigating AD risk and progression. It includes structured behavioral patterns, environmental alignment, and metabolic regulation. TRE, a lifestyle-based intervention that aligns food intake with biological rhythms, has shown potential benefits for neuroplasticity, sleep, and cognitive function.[107] In contrast, environmental disruptors such as artificial light exposure and light pollution can chronically impair circadian signaling and may trigger neuroinflammation, oxidative stress, and amyloid/tau dysregulation, thereby contributing to neurodegeneration.[108]

These environmental and lifestyle influences act partly through core circadian genes. In turn, these genes modulate autophagy, mitochondrial function, and neurotrophic signaling pathways, involving sirtuin 1 (SIRT1), mTOR, and forkhead box O (FoxO).[109] Clinically, sleep disturbances are common in AD and are increasingly recognized as active modulators of disease trajectory, underscoring the importance of early screening and nonsedative, circadian-aligned interventions.[110]

At the molecular level, SIRT1 acts as a bridge among circadian rhythms, metabolism, and neuroinflammation and is responsive to environmental inputs such as exercise, diet, and stress. However, several molecular insights into SIRT1-mediated neuroprotection are based predominantly on animal models or preliminary studies and should be interpreted cautiously. This supports further evaluation of precision, lifestyle-based chronotherapeutic approaches to AD care.[111]

These findings provide a basis for integrating circadian hygiene into preventive strategies and daily management frameworks for individuals at risk of, or living with, AD.

As shown in Table 2, emerging research highlights how circadian-regulated hormones, metabolic rhythms, gut–brain–clock signaling, retinal changes, and epigenetic mechanisms may contribute to AD progression and chronotherapy potential.

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TABLE 2 Summary of circadian-driven mechanistic pathways and chronotherapeutic targets in Alzheimer's disease.

Section/Mechanism	Authors (year)	Focus	Key findings
Chrono-metabolic hormones & chronopharmacology	Fujimura and Ushijima[86]	Chronotherapy	Circadian-timed drug delivery may optimize AD therapy but clinical evidence remains limited.
	Luo et al.[66]	Melatonin	Promotes mitophagy, limits amyloid/tau, and restores circadian alignment.
	Kolben et al.[87]	Adropin	Links circadian rhythm, metabolism, and autonomic tone; dysregulation worsens cognition.
Circadian regulation of brain metabolism	Dollet et al.[88]	Metabolic rhythms	Circadian clocks regulate lipid/glucose metabolism; disruption promotes neurodegeneration.
	Cogswell et al.[89]	Biomarkers	Plasma metabolomics predict circadian phase and support personalized therapy.
	Hussain et al.[90]	Clock genes	Desynchronized CLOCK/BMAL1/PER/CRY increase oxidative stress and amyloid/tau pathology.
	Javed et al.[91]	Therapeutics	Light, activity, and chronotherapy may help restore circadian stability in AD.
Gut–circadian–AD biomarker pathways	Kaur et al.[92]	Dysbiosis	Gut dysbiosis increases intestinal permeability and neurotoxic metabolites (TMAO, SCFAs, calprotectin).
	Khezri et al.[93]	BMAL1 & immunity	BMAL1 loss disrupts microbial balance and immune rhythmicity, driving inflammation.
	Khezri and Ghasemnejad-Berenji[94]	Feedback loop	Gut metabolites alter clock gene expression, reinforcing circadian–microbial dysregulation.
	Li et al.[95]	SCRD	Sleep–circadian disturbances reduce SCFA taxa and increase systemic inflammation.
	Su et al.[96]	Lipid metabolism	Misregulated gut–brain lipid metabolism triggers ER stress and accelerates AD.
Retinal biomarkers	Mirzaei et al.[97]	Retinal pathology	Retinal amyloid/tau and vascular changes reflect brain pathology; OCT/hyperspectral imaging may provide biomarkers.
Chronoepigenetics	Guu et al.[98]	Light exposure	Inadequate light worsens sundowning via epigenetic disruption of circadian networks.
	Lim et al.[99]	Gene expression	AD brains show blunted diurnal/seasonal expression and reduced epigenetic marks.
	Liu et al.[112]	SIRT1	SIRT1 stabilizes circadian rhythms and may suppress amyloidogenic and inflammatory cascades.

Abbreviations: AD, Alzheimer's disease; BMAL1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; DNMT, DNA methyltransferase; ER, endoplasmic reticulum; HDAC, histone deacetylase; OCT, optical coherence tomography; PER, period circadian regulator; SCFAs, short-chain fatty acids; SCRD, sleep–circadian rhythm disturbances; SIRT1, sirtuin 1; TMAO, trimethylamine N-oxide.

7 | FUTURE DIRECTIONS IN CHRONOTHERAPY FOR AD

7.1 | Next-generation chronotherapeutic targets

Interest in circadian science is increasing, and the therapeutic landscape for AD is shifting toward rhythm-informed precision interventions. Circadian rhythms influence a wide range of physiological processes and disease pathways. Their influence on drug metabolism and efficacy is increasingly recognized and is mediated partly by the oscillating activity of liver enzymes, such as cytochrome P450 enzymes (CYP450s), and clock-regulated nuclear receptors.[113,114] These insights support the mechanistic foundation of chronopharmacology and may enable safer, more effective, and individually time-tailored drug regimens, although robust AD-specific chronotherapeutic trials remain scarce.[102]

Melatonin is one of the most widely studied circadian hormones, and its melatonin receptors 1 and 2 (MT1 and MT2) represent potential molecular targets. Dysfunction of these receptors may contribute to circadian and cognitive disruption in AD. Therapeutics targeting these receptors, including prolonged-release melatonin, ramelteon, tasimelteon, and agomelatine, may help restore circadian integrity and improve sleep and memory outcomes.[115,116] Agomelatine, with its additional antagonism of 5-hydroxytryptamine receptor subtype 2C (5-HT_2C), enhances dopaminergic and noradrenergic tone and may provide cognitive or mood-related benefits in AD; however, evidence for disease-modifying effects remains preliminary and is largely

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extrapolated from sleep and mood outcomes rather than dedicated AD trials.[116]

Molecular chaperones and stress regulators are also gaining attention as next-generation therapeutic targets. FK506-binding protein 51 (FKBP51), which lies at the intersection of circadian timing, glucocorticoid sensitivity, and tau pathology, may be modulated by agents such as LA1011 to attenuate tau aggregation and realign stress–circadian responses.[117] Similarly, sirtuin 1 (SIRT1), a circadian-regulated deacetylase, links neuroinflammation, metabolic homeostasis, and clock-gene function. Activation of SIRT1 through nicotinamide adenine dinucleotide (NAD^+) precursors or lifestyle interventions may offer a chrono-metabolic strategy for delaying neurodegeneration. Some studies describe a "SIRT1 circadian paradox," in which SIRT1 can both enhance and dampen circadian amplitude, underscoring the complexity of targeting this pathway in neurodegenerative diseases.[111] However, current evidence for FKBP51 and SIRT1 modulation in AD is derived predominantly from experimental and early translational models, and robust clinical validation remains limited.

Advances in drug delivery systems may also expand therapeutic opportunities. Pulsatile drug delivery systems (PDDS), designed to release compounds after biologically matched lag phases, are being developed using artificial intelligence and smart polymers to target circadian peaks of disease activity.[118] Ohdo[119] further suggested that circadian molecular profiling could guide not only drug timing but also drug discovery itself, allowing precision compounds to be designed according to rhythmic vulnerabilities. However, most PDDS and chrono-tailored platforms have been evaluated primarily in non-AD indications, and their direct applicability to dementia care remains to be established.

Circadian principles are also being explored in immune and vascular therapeutics, although much of this evidence remains indirect for AD. Programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) checkpoint inhibitors demonstrate time-dependent immunomodulation,[120] whereas cardiovascular chronotherapy, evaluated in large-scale studies such as the Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC) trial, has suggested benefits of bedtime antihypertensive dosing for reducing neurovascular burden and stroke risk.[121] These approaches conceptually intersect with AD because vascular dysfunction, inflammation, and oxidative stress are central to AD pathology; however, most current evidence comes from oncology and cardiovascular cohorts rather than AD populations, so extrapolation should be cautious.

Overall, these findings support further investigation of a shift from static treatment schedules to dynamic, circadian-informed therapies. Such approaches integrate drug metabolism, receptor pharmacodynamics, molecular clock targets, and behavioral synchrony.[122,123] As research progresses, AD management may increasingly incorporate clock-based biomarkers, sex-specific circadian variation, and digital health monitoring to support therapy delivery at the optimal biological time. Future work should clearly distinguish mechanisms supported by robust human evidence from those grounded mainly in preclinical or early-phase studies.

7.2 | Chronotherapy in systemic comorbidities

Circadian disruption has diverse effects and intersects with systemic comorbidities that may influence AD progression. Hypertension, diabetes, and other metabolic or vascular disorders may amplify neurodegenerative risk, making circadian-timed interventions relevant to AD research and care.

Hermida et al.[124] reported that bedtime dosing of antihypertensive medications improved nocturnal blood pressure control and reduced cardiovascular risk, suggesting a potential chronotherapeutic benefit. However, subsequent large trials, including the TIME study and the recent BedMed trial, found no significant reduction in major cardiovascular events or mortality with evening dosing compared with morning dosing, although both confirmed the safety of bedtime administration.[125,126] More recently, the OMAN (Optimal Monitoring of Antihypertensive Dosing at Night) randomized clinical trial showed that bedtime dosing significantly lowered nocturnal systolic and diastolic blood pressure and improved circadian rhythm alignment without increasing adverse events.[127] Chawla et al.[128] emphasized the need for healthcare systems to adopt personalized, cross-scale chronotherapeutic strategies that integrate circadian principles into systemic disease management. These findings indicate that although bedtime dosing may improve nocturnal blood pressure regulation and circadian patterns, its long-term benefits for major cardiovascular outcomes remain uncertain, warranting further large-scale investigations. For AD, in which vascular and metabolic comorbidities are common, these mixed cardiovascular results highlight both the promise and uncertainty of comorbidity-focused chronotherapy and reinforce the need for dedicated AD-oriented trials rather than simple extrapolation from non-dementia cohorts.

8 | DISCUSSION

This narrative review demonstrates that circadian disturbance in AD is not merely a secondary outcome of neurodegeneration but also a contributing factor operating across molecular, cellular, systemic, and behavioral levels. Unlike earlier reviews that primarily catalogued sleep and circadian abnormalities or presented isolated findings on clock genes, this synthesis highlights a multi-level circadian framework that integrates clock gene biology, glial and immune mechanisms, metabolic and vascular rhythms, gut–brain interactions, retinal alterations, and epigenetic regulation. Collectively, these findings suggest that AD may represent, in part, a disorder of disrupted temporal organization with physiological effects that extend beyond the central nervous system.

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Several domains now have substantial and converging evidence, forming an established foundation for circadian-informed AD care. These include the vulnerability of the SCN and strong associations between disrupted rest–activity rhythms and future dementia risk. Also documented is a reciprocal relationship between sleep deprivation, impaired glymphatic clearance, and the accumulation of amyloid and tau proteins. Endocrine axes, including cortisol, show altered set points despite preserved rhythmicity, underscoring the systemic nature of circadian involvement in AD. Collectively, these mechanisms contribute to cognitive deterioration, behavioral symptoms such as sundowning, and increased caregiver burden, and may offer measurable circadian-linked markers for identifying risk and monitoring progression.

Other circadian-related processes remain at early or mechanistic stages of investigation. Microglial and astrocytic rhythms, gut–brain circadian interactions, lipid rhythm disturbances, and epigenetic mechanisms involving SIRT1 and related regulators provide plausible explanations for how environmental timing, diet, and light exposure influence neurodegeneration, although the supporting evidence is largely derived from animal studies or small human cohorts. Similarly, emerging targets such as the aryl hydrocarbon receptor, endocannabinoid pathways, and clock-modulating molecular chaperones show promise but require extensive validation. This review therefore distinguishes mechanisms supported by robust human evidence from those that represent credible but preliminary avenues for future exploration.

The translational implications of this framework fall into three principal areas. First, circadian-sensitive biomarkers including melatonin profiles, actigraphy-derived rest–activity metrics, body temperature rhythms, retinal imaging markers, and gut-derived metabolites may help characterize individual circadian phenotypes, identify high-risk groups, and select patients most likely to benefit from rhythm-based interventions. Second, rhythm-aligned therapies such as melatonin, orexin antagonists, light-based treatment, TRE, and structured sleep–wake schedules may be integrated with current and investigational disease-modifying therapies, treating timing as a modifiable dimension of care. Third, future AD trials could incorporate circadian design strategies including standardized sampling times, baseline circadian profiling, time-specific dosing, and long-term digital monitoring to determine whether synchronizing treatment with internal phase improves efficacy or reduces adverse effects.

This review draws a clear distinction between chronotherapeutic strategies supported by human clinical evidence and those that are largely hypothesis-generating or preclinical. Interventions such as light therapy, melatonin for sleep–wake stabilization, DORAs, and structured behavioral circadian alignment have demonstrated symptomatic benefit. However, effect sizes remain modest and heterogeneous, and disease-modifying impact has not been conclusively established. In contrast, approaches including direct clock-gene modulation, SIRT1 activation, aryl hydrocarbon receptor targeting, endocannabinoid pathway modulation, epigenetic clock regulation, and rhythm-synchronized neuromodulation are currently supported primarily by mechanistic, animal, or early-phase translational data. Although biologically compelling, these strategies require rigorous, adequately powered clinical validation. Time-stratified designs are therefore essential before routine integration into AD management.

Overall, this synthesis highlights the need to advance circadian precision medicine in Alzheimer's research and clinical practice. Although mechanistic work has progressed rapidly, its translation into large clinical trials remains limited, and mixed results from melatonin and light therapy highlight the importance of rigorous, time-resolved study designs. Progress will depend on adequately powered trials that distinguish preventive from therapeutic aims and clarify symptomatic versus disease-modifying mechanisms. Such trials should also integrate circadian measures with established AD biomarkers. As a narrative review, this article may be subject to selection bias because a formal systematic search strategy was not used. In distinguishing established evidence from emerging concepts and translational gaps, this review provides a structured framework to guide future circadian-informed approaches to AD.

9 | CONCLUSION

The global burden of AD is increasing, with profound consequences for patients, caregivers, and health systems. The urgent need for effective treatment is clear. With limited disease-modifying agents available, exploring the relationship between circadian disruption and AD suggests that circadian dysfunction is not simply a consequence but also an active contributor to its onset and progression. Mechanistic studies suggest that disturbances in circadian clock genes, the SCN, glial function (e.g., disrupted astrocytic rhythms and aberrant microglial inflammatory activity), and sleep–wake regulation may accelerate amyloid-β and tau pathology. These disturbances also impair proteostasis, exacerbate neuroinflammation, and extend to metabolic, endocrine, and immune networks, reinforcing AD as a systemic disorder with strong circadian underpinnings.

Circadian-linked measures, including melatonin rhythms, cortisol profiles, actigraphy, circadian rhythm of body temperature (CRBT), retinal changes, and gut microbiome signatures, may serve as valuable tools for early diagnosis, risk stratification, and therapeutic monitoring. Advances in chronotherapy include melatonin supplementation, orexin antagonists, light therapy, TRE, and circadian-informed drug delivery. These approaches highlight the potential of rhythm-aligned interventions. At the same time, heterogeneous outcomes in melatonin and light-therapy trials, and the limited number of large-scale chronotherapy studies, indicate that many of these approaches remain investigational and require further validation before routine clinical adoption. Environmental and lifestyle factors, including artificial light exposure and disrupted sleep

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hygiene, represent modifiable risks amenable to precision lifestyle-based chronotherapeutic strategies.

Future directions point toward personalized chronomedicine, where circadian biomarkers and digital monitoring may guide individualized treatment schedules and drug regimens. Novel targets such as melatonin receptors, SIRT1, FKBP51, and the gut–brain–clock axis may offer opportunities for innovative therapies, while chrono-optimized drug delivery systems may improve both efficacy and safety. Integrating circadian biology into AD research and care reframes AD not only as a neurodegenerative disorder but also as a disorder of disrupted temporal biology. Progress in this field will depend on rigorous, adequately powered clinical trials that incorporate circadian endpoints, standardized biomarker panels, and careful appraisal of preclinical–clinical translation. The broad narrative scope was intentionally chosen to integrate evidence from molecular, translational, and clinical perspectives on circadian rhythms and AD.

In conclusion, aligning Alzheimer's prevention, diagnosis, and treatment with circadian principles has the potential to shift care from static and symptom-based to dynamic, time-sensitive, and personalized strategies. Restoring biological rhythms through chronotherapy may help slow disease progression, improve quality of life, and open a new frontier in the management of AD.

AUTHOR CONTRIBUTIONS

Bivek Singh: Conceptualization (lead), investigation (lead), methodology (lead), visualization (lead), writing—original draft (lead). **Filippo Pigazzani**: Formal analysis (supporting), supervision (equal), validation (equal), writing—review and editing (equal). **Roberto Manfredini**: Conceptualization (supporting), supervision (lead), validation (lead), writing—review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in this study.

ETHICS STATEMENT

This article is a narrative review and does not involve studies with human participants or animals. Ethical approval and informed consent were not required.

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REFERENCES

1. Hippius H, Neundörfer G. The discovery of Alzheimer's disease. *Dialogues Clin Neurosci*. 2003;5(1):101-108. doi:10.31887/DCNS.2003.5.1/hhippius
2. Korczyn AD, Grinberg LT. Is Alzheimer's disease a disease? *Nat Rev Neurol*. 2024;20(4):245-251. doi:10.1038/s41582-024-00940-4
3. Nichols E, Szoeke CEI, Vollset SE, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(1):88-106. doi:10.1016/S1474-4422(18)30403-4
4. Ji Q, Chen J, Li Y, Tao E, Zhan Y. Incidence and prevalence of Alzheimer's disease in China: a systematic review and meta-analysis. *Eur J Epidemiol*. 2024;39(7):701-714. doi:10.1007/s10654-024-01144-2
5. Chen S, Cao Z, Nandi A, et al. The global macroeconomic burden of Alzheimer's disease and other dementias: estimates and projections for 152 countries or territories. *Lancet Glob Health*. 2024;12(9):e1534-e1543. doi:10.1016/S2214-109X(24)00264-X
6. Nyamugenda E, Rosensweig C, Allada R. Circadian clocks, daily stress, and neurodegenerative disease. *Annu Rev Pathol: Mech Dis*. 2025;20(1):355-374. doi:10.1146/annurev-pathmechdis-031521-033828
7. Reimus M, Siemiński M. Sundowning syndrome in dementia: mechanisms, diagnosis, and treatment. *J Clin Med*. 2025;14(4):1158. doi:10.3390/jcm14041158
8. Chawla S, Oster H, Duffield GE, et al. Reflections on several landmark advances in circadian biology. *J Circadian Rhythms*. 2024;22(1):236. doi:10.5334/jcr.236
9. Kelters IR, Koop Y, Young ME, Daiber A, van Laake LW. Circadian rhythms in cardiovascular disease. *Eur Heart J*. 2025;46(36):3532-3545. doi:10.1093/eurheartj/ehaf367
10. Allada R, Bass J. Circadian mechanisms in medicine. *N Engl J Med*. 2021;384(6):550-561. doi:10.1056/NEJMra1802337
11. Steele TA, St Louis EK, Videnovic A, Auger RR. Circadian rhythm sleep-wake disorders: a contemporary review of neurobiology, treatment, and dysregulation in neurodegenerative disease. *Neurotherapeutics*. 2021;18(1):53-74. doi:10.1007/s13311-021-01031-8
12. Tan JSI, Cheng LJ, Chan EY, Lau Y, Lau ST. Light therapy for sleep disturbances in older adults with dementia: a systematic review, meta-analysis and meta-regression. *Sleep Med*. 2022;90:153-166. doi:10.1016/j.sleep.2022.01.013
13. Xiong X, Hu T, Yin Z, Zhang Y, Chen F, Lei P. Research advances in the study of sleep disorders, circadian rhythm disturbances and Alzheimer's disease. *Front Aging Neurosci*. 2022;14:944283. doi:10.3389/fnagi.2022.944283
14. Colwell CS. Defining circadian disruption in neurodegenerative disorders. *J Clin Invest*. 2021;131(19):148288. doi:10.1172/JCI148288
15. Rigat L, Ouk K, Kramer A, Priller J. Dysfunction of circadian and sleep rhythms in the early stages of Alzheimer's disease. *Acta Physiologica*. 2023;238(2):e13970. doi:10.1111/apha.13970
16. Uddin MS, Sumsuzzman DM, Jeandet P, et al. Deciphering the interacting mechanisms of circadian disruption and Alzheimer's disease. *Neurochem Res*. 2021;46(7):1603-1617. doi:10.1007/s11064-021-03325-x
17. Tasker R, Rowlands J, Ahmed Z, Di Pietro V. Co-expression network analysis of micro-RNAs and proteins in the Alzheimer's brain: a systematic review of studies in the last 10 years. *Cells*. 2021;10(12):3479. doi:10.3390/cells10123479
18. Dauvilliers Y. Hypocretin/Orexin, sleep and Alzheimer's disease. *Front Neurol Neurosci*. 2021;45:139-149. doi:10.1159/000514967
19. Gibson M. A systematic review of the relationship between night shift work and oxidative stress. *Chronobiol Int*. 2022;39(2):285-298. doi:10.1080/07420528.2021.1989446
20. Ling Y, Yuan S, Huang X, et al. The association of night shift work with the risk of all-cause dementia and Alzheimer's disease: a longitudinal study of 245,570 UK Biobank participants. *J Neurol*. 2023;270(7):3499-3510. doi:10.1007/s00415-023-11672-8
21. Rahman MA, Khatun MT, Mim AK, et al. Oxidative stress in DNA damage and neurodegenerative diseases: unveiling the mechanisms and therapeutic opportunities. *Cell Biochem*

2770730x, 2026, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nep3.70046 by CochraneItalia, Wiley Online Library on [02/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Biophys. 2025;83(4):4233-4252. doi:10.1007/s12013-025-01845-9
22. Paajanen P, Kimmey JM, Dodd AN. Circadian gating: concepts, processes, and opportunities. *Philos Trans R Soc, B*. 2025;380(1918):20230346. doi:10.1098/rstb.2023.0346
23. Xu Y, Shen Y, Li J, et al. Real-ambient bedroom light at night increases systemic inflammation and disrupts circadian rhythm of inflammatory markers. *Ecotoxicol Environ Safety*. 2024;281:116590. doi:10.1016/j.ecoenv.2024.116590
24. Geng YJ, Smolensky MH, Sum-Ping O, Hermida R, Castriotta RJ. Circadian rhythms of risk factors and management in atherosclerotic and hypertensive vascular disease: modern chronobiological perspectives of an ancient disease. *Chronobiol Int*. 2023;40(1):33-62. doi:10.1080/07420528.2022.2080557
25. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab*. 2018;27(6):1212-1221.e3. doi:10.1016/j.cmet.2018.04.010.
26. Gasmi M, Silvia Hardiany N, van der Merwe M, Martins IJ, Sharma A, Williams-Hooker R. The influence of time-restricted eating/feeding on Alzheimer's biomarkers and gut microbiota. *Nutr Neurosci*. 2025;28(2):156-170. doi:10.1080/1028415X.2024.2359868
27. Stangherlin A, Seinkmane E, O'neill JS. Understanding circadian regulation of mammalian cell function, protein homeostasis, and metabolism. *Curr Opin Syst Biology*. 2021;28:100391. doi:10.1016/j.coisb.2021.100391
28. Fessel J. Formulating treatment to cure Alzheimer's dementia: approach #2. *Int J Mol Sci*. 2024;25(6):25063524. doi:10.3390/ijms25063524
29. Festus ID, Spilberg J, Young ME, et al. Pioneering new frontiers in circadian medicine chronotherapies for cardiovascular health. *Trends Endocrinol Metab*. 2024;35(7):607-623. doi:10.1016/j.tem.2024.02.011
30. Carter B, Justin HS, Gulick D, Gamsby JJ. The molecular clock and neurodegenerative disease: a stressful time. *Front Mol Biosci*. 2021;8:644747. doi:10.3389/fmolb.2021.644747
31. Kolinjivadi AM, Chong ST, Ngeow J. Molecular connections between circadian rhythm and genome maintenance pathways. *Endocr Relat Cancer*. 2021;28(2):R55-R66. doi:10.1530/ERC-20-0372
32. Farshadi E, van der Horst GTJ, Chaves I. Molecular links between the circadian clock and the cell cycle. *J Mol Biol*. 2020;432(12):3515-3524. doi:10.1016/j.jmb.2020.04.003
33. Hoyt KR, Obrietan K. Circadian clocks, cognition, and Alzheimer's disease: synaptic mechanisms, signaling effectors, and chronotherapeutics. *Mol Neurodegener*. 2022;17(1):35. doi:10.1186/s13024-022-00537-9
34. Asadpoordezaki Z, Coogan AN, Henley BM. Chronobiology of Parkinson's disease: past, present and future. *Eur J Neurosci*. 2023;57(1):178-200. doi:10.1111/ejn.15859
35. Hastings MH, Brancaccio M, Gonzalez-Aponte MF, Herzog ED. Circadian rhythms and astrocytes: the good, the bad, and the ugly. *Annu Rev Neurosci*. 2023;46(1):123-143. doi:10.1146/annurev-neuro-100322-112249
36. Son G, Neylan TC, Grinberg LT. Neuronal and glial vulnerability of the suprachiasmatic nucleus in tauopathies: evidence from human studies and animal models. *Mol Neurodegener*. 2024;19(1):4. doi:10.1186/s13024-023-00695-4
37. Nassan M, Videnovic A. Circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol*. 2022;18(1):7-24. doi:10.1038/s41582-021-00577-7
38. Lucey BP. It's complicated: the relationship between sleep and Alzheimer's disease in humans. *Neurobiol Dis*. 2020;144:105031. doi:10.1016/j.nbd.2020.105031
39. Mueed Z, Rai PK, Kamal MA, Poddar NK. Decoding the Inter-Relationship between sleep disorders and Alzheimer's disease pathogenesis. *CNS & Neurol Disord - Drug Targets*. 2021;20(8):723-735. doi:10.2174/1871527319666200903161249
40. Cheng WY, Ho YS, Chang RCC. Linking circadian rhythms to microbiome-gut-brain axis in aging-associated neurodegenerative diseases. *Ageing Res Rev*. 2022;78:101620. doi:10.1016/j.arr.2022.101620
41. Toljan K, Homolak J. Circadian changes in Alzheimer's disease: neurobiology, clinical problems, and therapeutic opportunities. *Handb Clin Neurol*. 2021;179:285-300. doi:10.1016/B978-0-12-819975-6.00018-2
42. Nagai M, Dote K, Park S, et al. Obstructive sleep apnea and non-dipper: epiphenomena or risks of Alzheimer's disease?: a review from the HOPE Asia Network. *Hypertension Res*. 2024;47(2):271-280. doi:10.1038/s41440-023-01440-6
43. Canever JB, Queiroz LY, Soares ES, de Avelar NCP, Cimarosti HI. Circadian rhythm alterations affecting the pathology of neurodegenerative diseases. *J Neurochem*. 2024;168(8):1475-1489. doi:10.1111/jnc.15883
44. Davidson K, Pickering AM. The proteasome: a key modulator of nervous system function, brain aging, and neurodegenerative disease. *Front Cell Dev Biol*. 2023;11:1124907. doi:10.3389/fcell.2023.1124907
45. Fernandez FX, Kaladchibachi S, Negelspach DC. Resilience in the suprachiasmatic nucleus: implications for aging and Alzheimer's disease. *Exp Geront*. 2021;147:111258. doi:10.1016/j.exger.2021.111258
46. Fifel K, Videnovic A. Circadian alterations in patients with neurodegenerative diseases: neuropathological basis of underlying network mechanisms. *Neurobiol Dis*. 2020;144:105029. doi:10.1016/j.nbd.2020.105029
47. Chang YC, Kim JY. Therapeutic implications of circadian clocks in neurodegenerative diseases. *J Neurosci Res*. 2020;98(6):1095-1113. doi:10.1002/jnr.24572
48. Halpern AI, Jansen JAF, Giladi N, Mirelman A, Hausdorff JM. Does time of day influence postural control and gait? A review of the literature. *Gait Posture*. 2022;92:153-166. doi:10.1016/j.gaitpost.2021.10.023
49. Han Z, Yang X, Huang S. Sleep deprivation: a risk factor for the pathogenesis and progression of Alzheimer's disease. *Heliyon*. 2024;10(7):e28819. doi:10.1016/j.heliyon.2024.e28819
50. Peng X, Fan R, Xie L, et al. A growing link between circadian rhythms, type 2 diabetes mellitus and Alzheimer's disease. *Int J Mol Sci*. 2022;23(1):504. doi:10.3390/ijms23010504
51. Amidfar M, Garcez ML, Kim YK. The shared molecular mechanisms underlying aging of the brain, major depressive disorder, and Alzheimer's disease: the role of circadian rhythm disturbances. *Prog Neuropsychopharmacol Biol Psychiatry*. 2023;123:110721. doi:10.1016/j.pnpbp.2023.110721
52. Fishbein AB, Knutson KL, Zee PC. Circadian disruption and human health. *J Clin Invest*. 2021;131(19):48286. doi:10.1172/JCI148286
53. Francis TC, Porcu A. Emotionally clocked out: cell-type specific regulation of mood and anxiety by the circadian clock system in the brain. *Front Mol Neurosci*. 2023;16:1188184. doi:10.3389/fnmol.2023.1188184
54. Gonzales PNG, Villaraza SG, Rosa JACD. The association between sleep and Alzheimer's disease: a systematic review. *Dement Neuropsychol*. 2024;18:e20230049. doi:10.1590/1980-5764-dn-2023-0049
55. Carpi M, Mercuri NB, Liguori C. Orexin receptor antagonists for the prevention and treatment of Alzheimer's disease and associated sleep disorders. *Drugs*. 2024;84(11):1365-1378. doi:10.1007/s40265-024-02096-3
56. Knezevic E, Nenic K, Milanovic V, Knezevic NN. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. *Cells*. 2023;12(23):2726. doi:10.3390/cells12232726
57. Chen Z, Xiong Z, Liu X. Research progress on the interaction between circadian clock and early vascular aging. *Exp Geront*. 2021;146:111241. doi:10.1016/j.exger.2021.111241
58. Figueroa PBS, Ferreira AFF, Britto LR, Doussoulin AP, Torrão AS. Association between thyroid function and Alzheimer's disease: a systematic review. *Metab Brain Dis*. 2021;36(7):1523-1543. doi:10.1007/s11011-021-00760-1
59. Mercadante S, Bellastella A. Chrono-Endocrinology in clinical practice: a journey from pathophysiological to therapeutic aspects. *Life*. 2024;14(5):14050546. doi:10.3390/life14050546
60. Morrone CD, Raghuraman R, Hussaini SA, Yu WH. Proteostasis failure exacerbates neuronal circuit dysfunction and

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sleep impairments in Alzheimer's disease. *Mol Neurodegener*. 2023;18(1):27. doi:10.1186/s13024-023-00617-4
61. Pourcet B, Duez H. Circadian control of inflammasome pathways: implications for circadian medicine. *Front Immunol*. 2020;11:1630. doi:10.3389/fimmu.2020.01630
62. Avila A, Zhang SL. A circadian clock regulates the blood-brain barrier across phylogeny. *Vitam Horm*. 2024;126:241-287. doi:10.1016/bs.vh.2024.04.004
63. Coiffard B, Diallo AB, Mezouar S, Leone M, Mege JL. A tangled threesome: circadian rhythm, body temperature variations, and the immune system. *Biology*. 2021;10(1):10010065. doi:10.3390/biology10010065
64. Geng F, Zhao N, Ren Q. Circadian rhythm, microglia-mediated neuroinflammation, and Alzheimer's disease. *Neurosci Biobehav Rev*. 2025;170:106044. doi:10.1016/j.neubiorev.2025.106044
65. Hossain MF, Wang N, Chen R, et al. Exploring the multifunctional role of melatonin in regulating autophagy and sleep to mitigate Alzheimer's disease neuropathology. *Ageing Res Rev*. 2021;67:101304. doi:10.1016/j.arr.2021.101304
66. Luo F, Sandhu AF, Rungratanawanich W, et al. Melatonin and autophagy in Aging-Related neurodegenerative diseases. *Int J Mol Sci*. 2020;21(19):7174. doi:10.3390/ijms21197174
67. Mihardja M, Roy J, Wong KY, et al. Therapeutic potential of neurogenesis and melatonin regulation in Alzheimer's disease. *Ann NY Acad Sci*. 2020;1478(1):43-62. doi:10.1111/nyas.14436
68. Liu YJ, Swaab DF, Zhou JN. Sleep-wake modulation and pathogenesis of Alzheimer disease: suggestions for postponement and treatment. *Handb Clin Neurol*. 2025;206:211-229. doi:10.1016/B978-0-323-90918-1.00001-0
69. Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is melatonin the "next vitamin D"?: A review of emerging science, clinical uses, safety, and dietary supplements. *Nutrients*. 2022;14(19):3934. doi:10.3390/nu14193934
70. Prodhan AHMSU, Cavestro C, Kamal MA, Islam MA. Melatonin and sleep disturbances in Alzheimer's disease. *CNS & Neurol Disord - Drug Targets*. 2021;20(8):736-754. doi:10.2174/1871527320666210804155617
71. Steinbach MJ, Denburg NL. Melatonin in Alzheimer's disease: literature review and therapeutic trials. *J Alzheimer's Dis*. 2024;101(s1):S193-S204. doi:10.3233/JAD-230760
72. Shen S, Liao Q, Wong YK, et al. The role of melatonin in the treatment of type 2 diabetes mellitus and Alzheimer's disease. *Int J Biol Sci*. 2022;18(3):983-994. doi:10.7150/ijbs.66871
73. Li P, Gao L, Gaba A, et al. Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults. *Lancet Healthy Longev*. 2020;1(3):e96-e105. doi:10.1016/S2666-7568(20)30015-5
74. Saelzler UG, Verhaeghen P, Panizzon MS, Moffat SD. Intact circadian rhythm despite cortisol hypersecretion in Alzheimer's disease: a meta-analysis. *Psychoneuroendocrinology*. 2021;132:105367. doi:10.1016/j.psyneuen.2021.105367
75. Chen D, Zhang T, Lee TH. Cellular mechanisms of melatonin: insight from neurodegenerative diseases. *Biomolecules*. 2020;10(8):1158. doi:10.3390/biom10081158
76. Kuang H, Zhu YG, Zhou ZF, Yang MW, Hong FF, Yang SL. Sleep disorders in Alzheimer's disease: the predictive roles and potential mechanisms. *Neural Regen Res*. 2021;16(10):1965-1972. doi:10.4103/1673-5374.308071
77. Kumar D, Sharma A, Taliyan R, et al. Orchestration of the circadian clock and its association with Alzheimer's disease: role of endocannabinoid signaling. *Ageing Res Rev*. 2022;73:101533. doi:10.1016/j.arr.2021.101533
78. Lee Y, Field JM, Sehgal A. Circadian rhythms, disease and chronotherapy. *J Biol Rhythms*. 2021;36(6):503-531. doi:10.1177/07487304211044301
79. Liu H, Liu Y, Hai R, Liao W, Luo X. The role of circadian clocks in cancer: mechanisms and clinical implications. *Genes Diseases*. 2023;10(4):1279-1290. doi:10.1016/j.gendis.2022.05.014
80. Liu W, Ma R, Sun C, et al. Implications from proteomic studies investigating circadian rhythm disorder-regulated neurodegenerative disease pathology. *Sleep Med Rev*. 2023;70:101789. doi:10.1016/j.smrv.2023.101789
81. Moline M, Thein S, Bsharat M, et al. Safety and efficacy of lemborexant in patients with irregular sleep-wake rhythm disorder and Alzheimer's disease dementia: results from a phase 2 randomized clinical trial. *J Prev Alzheimer's Dis*. 2021;8(1):7-18. doi:10.14283/jpad.2020.69
82. Rodriguez-Lopez A, Esteban D, Domínguez-Romero AN, Gevorkian G. Tg-SwDI transgenic mice: a suitable model for Alzheimer's disease and cerebral amyloid angiopathy basic research and preclinical studies. *Exp Neurol*. 2025;387:115189. doi:10.1016/j.expneurol.2025.115189
83. Ruan W, Yuan X, Eltzschig HK. Circadian rhythm as a therapeutic target. *Nat Rev Drug Discov*. 2021;20(4):287-307. doi:10.1038/s41573-020-00109-w
84. Salminen A. Aryl hydrocarbon receptor impairs circadian regulation in Alzheimer's disease: potential impact on glymphatic system dysfunction. *Eur J Neurosci*. 2024;60(2):3901-3920. doi:10.1111/ejn.16450
85. Sharma A, Lee S, Kim H, Yoon H, Ha S, Kang SU. Molecular crosstalk between circadian rhythmicity and the development of neurodegenerative disorders. *Front Neurosci*. 2020;14:844. doi:10.3389/fnins.2020.00844
86. Fujimura A, Ushijima K. Understanding the role of chronopharmacology for drug optimization: what do we know? *Expert Rev Clin Pharmacol*. 2023;16(7):655-668. doi:10.1080/17512433.2023.2233438
87. Kolben Y, Weksler-Zangen S, Ilan Y. Adropin as a potential mediator of the metabolic system-autonomic nervous system-chronobiology axis: implementing a personalized signature-based platform for chronotherapy. *Obesity Reviews*. 2021;22(2):e13108. doi:10.1111/obr.13108
88. Dollet L, Pendergrast LA, Zierath JR. The role of the molecular circadian clock in human energy homeostasis. *Curr Opin Lipidol*. 2021;32(1):16-23. doi:10.1097/MOL.0000000000000722
89. Cogswell D, Bisesi P, Markwald RR, et al. Identification of a preliminary plasma metabolome-based biomarker for circadian phase in humans. *J Biol Rhythms*. 2021;36(4):369-383. doi:10.1177/07487304211025402
90. Hussain Y, Dar MI, Pan X. Circadian influences on brain lipid metabolism and neurodegenerative diseases. *Metabolites*. 2024;14(12):723. doi:10.3390/metabo14120723
91. Javed B, Javed A, Kow CS, Hasan SS. Pharmacological and non-pharmacological treatment options for sleep disturbances in Alzheimer's disease. *Expert Rev Neurother*. 2023;23(6):501-514. doi:10.1080/14737175.2023.2214316
92. Kaur S, Kumari D, Dandekar MP. Importance of gut microbiota dysbiosis and circadian Disruption-Associated biomarkers in emergence of Alzheimer's disease. *Mol Neurobiol*. 2025;62(5):6308-6316. doi:10.1007/s12035-024-04685-5
93. Khezri MR, Esmaeili A, Ghasemnejad-Berenji M. Role of Bmal1 and gut microbiota in Alzheimer's disease and Parkinson's disease pathophysiology: the probable effect of melatonin on their association. *ACS Chem Neurosci*. 2023;14(21):3883-3893. doi:10.1021/acschemneuro.3c00418
94. Khezri MR, Ghasemnejad-Berenji M. Gut microbiota and circadian rhythm in Alzheimer's disease pathophysiology: a review and hypothesis on their association. *NPJ Aging*. 2023;9(1):9. doi:10.1038/s41514-023-00104-6
95. Li Y, Shao L, Mou Y, Zhang Y, Ping Y. Sleep, circadian rhythm and gut microbiota: alterations in Alzheimer's disease and their potential links in the pathogenesis. *Gut Microbes*. 2021;13(1):1957407. doi:10.1080/19490976.2021.1957407
96. Su J, Zhao L, Fu R, Tang Z. Linking circadian rhythms to gut-brain axis lipid metabolism associated with endoplasmic reticulum stress in Alzheimer's disease. *CNS Neurosci Ther*. 2025;31(3):e70329. doi:10.1111/cns.70329
97. Mirzaei N, Shi H, Oviatt M, et al. Alzheimer's retinopathy: seeing disease in the eyes. *Front Neurosci*. 2020;14:921. doi:10.3389/fnins.2020.00921
98. Guu TW, Aarsland D, Ffytche D. Light, sleep-wake rhythm, and behavioral and psychological symptoms of dementia in care home patients: revisiting the sundowning syndrome. *Int J Geriatr Psychiatry*. 2022;37(5):5712. doi:10.1002/gps.5712
99. Lim ASP. Diurnal and seasonal molecular rhythms in the human brain and their relation to Alzheimer disease. *Handb*

2770730x, 2026, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nep3.70046 by CochraneItalia, Wiley Online Library on [02/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Clin Neurol. 2021;179:271-284. doi:10.1016/B978-0-12-819975-6.00017-0
100. Cardinali DP, Brown GM, Pandi-Perumal SR. Chronotherapy. *Handb Clin Neurol*. 2021;179:357-370. doi:10.1016/B978-0-12-819975-6.00023-6
101. Butler CT, Rodgers AM, Curtis AM, Donnelly RF. Chrono-tailored drug delivery systems: recent advances and future directions. *Drug Delivery Transl Res*. 2024;14(7):1756-1775. doi:10.1007/s13346-024-01539-4
102. Dong D, Yang D, Lin L, Wang S, Wu B. Circadian rhythm in pharmacokinetics and its relevance to chronotherapy. *Biochem Pharmacol*. 2020;178:114045. doi:10.1016/j.bcp.2020.114045
103. Colita CI, Hermann DM, Filfan M, et al. Optimizing chronotherapy in psychiatric care: the impact of circadian rhythms on medication timing and efficacy. *Clocks Sleep*. 2024;6(4):635-655. doi:10.3390/clockssleep6040043
104. Cummings JL, Osse AML, Kinney JW. Alzheimer's disease: novel targets and investigational drugs for disease modification. *Drugs*. 2023;83(15):1387-1408. doi:10.1007/s40265-023-01938-w
105. Fleming JE, Kremen V, Gilron R, et al. Embedding digital chronotherapy into bioelectronic medicines. *iScience*. 2022;25(4):104028. doi:10.1016/j.isci.2022.104028
106. Chauhan PS, Mishra M, Koul B, Sharma M, Yadav D. Modifiable risk factors associated with Alzheimer's disease with special reference to sleep disturbance. *CNS Neurol Disord - Drug Targets*. 2021;20(7):594-601. doi:10.2174/1871527320666210319111852
107. Currenti W, Godos J, Castellano S, et al. Time restricted feeding and mental health: a review of possible mechanisms on affective and cognitive disorders. *Int J Food Sci Nutr*. 2021;72(6):723-733. doi:10.1080/09637486.2020.1866504
108. Karska J, Kowalski S, Gładka A, et al. Artificial light and neurodegeneration: does light pollution impact the development of Alzheimer's disease? *GeroScience*. 2024;46(1):87-97. doi:10.1007/s11357-023-00932-0
109. Maiese K. Cognitive impairment and dementia: gaining insight through circadian clock gene pathways. *Biomolecules*. 2021;11(7):1002. doi:10.3390/biom11071002
110. Malhotra RK. Neurodegenerative disorders and sleep. *Sleep Med Clin*. 2022;17(2):307-314. doi:10.1016/j.jsmc.2022.02.009
111. Mehramiz M, Porter T, O'Brien EK, Rainey-Smith SR, Laws SM. A potential role for Sirtuin-1 in Alzheimer's disease: reviewing the biological and environmental evidence. *J Alzheimer's Dis Rep*. 2023;7(1):823-843. doi:10.3233/ADR-220088
112. Liu H, Xu S, Wang C, et al. The beneficial role of sirtuin 1 in preventive or therapeutic options of neurodegenerative diseases. *Neuroscience*. 2022;504:79-92. doi:10.1016/j.neuroscience.2022.09.021
113. Lu D, Zhao M, Chen M, Wu B. Circadian Clock-Controlled drug metabolism: implications for chronotherapeutics. *Drug Metab Dispos*. 2020;48(5):395-406. doi:10.1124/dmd.120.090472
114. Okyar A, Ozturk Civelek D, Akyel YK, Surme S, Pala Kara Z, Kavakli IH. The role of the circadian timing system on drug metabolism and detoxification: an update. *Expert Opin Drug Metab Toxicol*. 2024;20(6):503-517. doi:10.1080/17425255.2024.2356167
115. Oishi A, Gbahou F, Jockers R. Melatonin receptors, brain functions, and therapies. *Handb Clin Neurol*. 2021;179:345-356. doi:10.1016/B978-0-12-819975-6.00022-4
116. Su Q, Li T, Liu GW, et al. Agomelatine: a potential novel approach for the treatment of memory disorder in neurodegenerative disease. *Neural Regen Res*. 2023;18(4):727-733. doi:10.4103/1673-5374.353479
117. Johnson JL. FKBP51 functions in the regulation of circadian rhythm and Alzheimer's disease. *Cell Stress Chaperones*. 2025;30(2):81-83. doi:10.1016/j.cstres.2025.02.002
118. Rajput A, Pingale P, Telange D, Musale S, Chalikwar S. A current era in pulsatile drug delivery system: drug journey based on chronobiology. *Heliyon*. 2024;10(10):e29064. doi:10.1016/j.heliyon.2024.e29064
119. Ohdo S. Chrono-Drug discovery and development based on circadian rhythm of molecular, cellular and organ level. *Biol Pharm Bull*. 2021;44(6):747-761. doi:10.1248/bpb.b21-00277
120. Ohdo S, Koyanagi S, Matsunaga N. Chronopharmacology of immune-related diseases. *Allergol Int*. 2022;71(4):437-447. doi:10.1016/j.alit.2022.06.006
121. Smolensky MH, Hermida RC, Geng YJ. Chronotherapy of cardiac and vascular disease: timing medications to circadian rhythms to optimize treatment effects and outcomes. *Curr Opin Pharmacol*. 2021;57:41-48. doi:10.1016/j.coph.2020.10.014
122. Neves AR, Albuquerque T, Quintela T, Costa D. Circadian rhythm and disease: relationship, new insights, and future perspectives. *J Cell Physiol*. 2022;237(8):3239-3256. doi:10.1002/jcp.30815
123. Chai R, Ye Z, Wu Q, et al. Circadian rhythm in cardiovascular diseases: a bibliometric analysis of the past, present, and future. *Eur J Med Res*. 2023;28(1):194. doi:10.1186/s40001-023-01158-8
124. Hermida RC, Hermida-Ayala RG, Smolensky MH, et al. Does timing of antihypertensive medication dosing matter? *Curr Cardiol Rep*. 2020;22(10):118. doi:10.1007/s11886-020-01353-7
125. Mackenzie IS, Rogers A, Poulter NR, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. *Lancet*. 2022;400(10361):1417-1425. doi:10.1016/S0140-6736(22)01786-X
126. Garrison SR, Bakal JA, Kolber MR, et al. Antihypertensive medication timing and cardiovascular events and death: the BedMed randomized clinical trial. *JAMA*. 2025;333(23):2061-2072. doi:10.1001/jama.2025.4390
127. Ye R, Yang X, Zhang X, et al. Morning vs bedtime dosing and nocturnal blood pressure reduction in patients with hypertension: the OMAN randomized clinical trial. *JAMA Network Open*. 2025;8(7):e2519354. doi:10.1001/jamanetworkopen.2025.19354
128. Chawla S, O'Neill J, Knight MI, et al. Timely questions emerging in chronobiology: the circadian clock keeps on ticking. *J Circadian Rhythms*. 2024;22(1):2. doi:10.5334/jcr.237

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