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REVIEW ARTICLE

Circadian Rhythm Disruption and Sleep Disorders in Alzheimer's Disease: Mechanistic Insights and Therapeutic Potentials

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Abstract

Alzheimer's Disease (AD) is the leading cause of dementia worldwide, with significant cognitive and behavioural impairments that devastate individuals and their families. Cohort-level findings, demonstrate the broader population-level implications of Sleep and Circadian Rhythm Disruption (SCRD) in AD and underscore the need for early interventions, emphasizing the importance of timely action. However, the mechanism remains unclear. SCRD impairs the glymphatic system, which is responsible for the clearance of neurotoxic proteins such as amyloid-β and tau during slow-wave sleep, accelerating neurodegeneration. Moreover, SCRD exacerbates neuroinflammation by disrupting the circadian regulation of immune responses, mainly through the dysregulation of microglial activity and pro-inflammatory cytokine release, which further promotes neuronal damage. This review summarizes the current understanding of SCRD in AD, outlining the mechanistic links, evidence from animal models, and emerging treatments targeting SCRD in AD, as well as promising new drug targets emerging from preclinical studies. Circadian modulation may represent a novel therapeutic avenue for AD.

Abbreviations & units:

AD	- Alzheimer's Disease	PET	- positron emission tomography
SCRD	- Sleep and Circadian Rhythm Disruption	NFTs	- neurofibrillary tangles
SCN	- Suprachiasmatic Nucleus	GSK3β	- glycogen synthase kinase 3β
SWS	- During slow-wave sleep	AMPK	- Amp-activated protein kinase
PSG	- polysomnography	TTFL	- Transcription-Translation Feedback Loop
REM	- Rapid Eye Movement	APOE	- apolipoprotein E
NREM	- Non-rapid eye movement	PS1	- gene presenilin-1
AQP4	- astroglial aquaporin 4	APP	- amyloid precursor protein
TLR	- Toll-like receptor	CBTi	- Cognitive behavioural therapy

INTRODUCTION

Alzheimer's disease (AD), the leading cause of dementia worldwide, is characterized by progressive neurodegeneration that affects memory, thinking and behaviour (Lane *et al.* 2018). In AD, the early phase (cellular phase) co-occurs with the accumulation of amyloid-β, inducing the spread of tau pathology (Liao *et al.* 2022; Atri 2019), leading to synaptic loss, neuroinflammation, and neuronal death, especially in brain regions responsible for memory and learning, such as the hippocampus and cortex (Eimer *et al.* 2018). Despite the well-known cognitive symptoms, there is increasing evidence that Sleep and Circadian Rhythm Disruption (SCRD) is a pathological component of AD, possibly even before cognitive decline (Li *et al.* 2021). However, the Amyloid-Tau-Neurodegeneration (ATN) framework, which classifies AD biomarkers into amyloid, tau, and neurodegeneration categories, cannot fully explain the pathogenesis and progress of AD, especially the effects of vascular disease (Scheltens *et al.* 2021).

Sleep disorders in AD include insomnia and frequent nocturnal awakenings, as well as excessive daytime sleepiness and sleep apnea (Benca *et al.* 2022). Approximately 25 to 40% of patients with early AD report sleep problems, and this figure rises to 60 to 70% in patients with advanced AD (Ju *et al.* 2014). Interestingly, longitudinal studies have shown that SCRD can appear years before overt cognitive symptoms, suggesting that sleep disturbances may have a predictive role in AD (Li *et al.* 2021). Moreover, circadian rhythm abnormalities are common in AD patients, with delayed or advanced phases of the sleep-wake cycle (Vasey *et al.* 2021). These circadian disturbances are thought to be caused by degeneration of the suprachiasmatic nucleus (SCN), the brain's central circadian clock, and may contribute to the overall sleep disturbances observed in AD patients (Shen *et al.* 2023). In addition, sleep's importance in neurodegeneration becomes more apparent when the role of sleep in brain homeostasis is considered (Sahu *et al.* 2022). During slow-wave sleep (SWS), the brain's glymphatic system is more active and helps clear neurotoxic proteins such as amyloid-β (Leger *et al.* 2018). In AD, this natural clearance process is impaired by disrupted sleep cycles, leading to accelerated amyloid-β accumulation (Ju *et al.* 2014). For example, studies using polysomnography (PSG) and actigraphy in AD patients and animal models have consistently shown decreased slow-wave sleep, shortened Rapid Eye Movement (REM) sleep, and increased nocturnal awakenings, all of which lead to worsening amyloid and tau lesions (Zhang *et al.* 2022b).

However, it remains unclear whether SCRD is a cause or a consequence of AD (Li *et al.* 2021). Studies on SCRD are mostly correlational, and many fail to take into account confounding variables such as comorbidities and medications that may also affect sleep quality (Phan & Malkani 2019). This lack of longitudinal depth undermines the ability to definitively link SCRD to early AD, underestimating the need for studies that typically take 10 to 15 years to develop AD pathology (Boxer & Sperling 2023). This review summarizes the role of SCRD in AD, focusing on the molecular mechanisms and clinical applications by targeting circadian modulation to slow AD progression.

SLEEP AND CIRCADIAN RHYTHMS

Sleep and circadian rhythms are essential components of health, affecting various physiological processes, including mood, cognition, and immune function (Baranwal *et al.* 2023). Circadian rhythms are approximately 24-hour cycles that regulate various physiological processes, including sleep-wake cycles, hormone release, metabolism, and body temperature (Zhou *et al.* 2022). Sleep can be divided into two main phases according to polysomnography: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM can be further classified into three stages: N1, N2, and N3 (Ruan *et al.* 2021; Phan & Malkani 2019). Both phases of sleep and the rapid transition of sleep phases are essential for maintaining brain health and homeostasis (Phan & Malkani 2019). These rhythms are controlled primarily by the suprachiasmatic nucleus (SCN) in the hypothalamus, which synchronizes the body's internal clock with external environmental signals such as light (Ferrell & Chiang 2015). Light can affect melatonin production in the pineal gland, and lower light levels at night stimulate melatonin release, thereby promoting sleep (Melendez-Fernandez *et al.* 2023).

ASSOCIATIONS OF SCRD AND AD-COHORT-LEVEL FINDINGS

Recent large-scale cohort studies, such as those conducted using data from the UK Biobank, highlight that individuals experiencing sleep disruptions are at a notably higher risk of developing AD in later life (Ling *et al.* 2023; Winer *et al.* 2024). Actigraphy data from the UK Biobank further suggested that disturbances in daily activity patterns, such as increased variability and decreased stability, are associated with an increased risk of cognitive impairment and neurodegenerative diseases such as AD (Winer *et al.* 2023; Winer *et al.* 2024). The longitudinal nature of the UK Biobank study may monitor SCRD and cognitive changes over extended periods, thus providing deeper insights into how SCRD contributes to AD progression. Ultimately, individuals with more significant variability in their daily activity patterns and diminished circadian stability are more susceptible to cognitive impairment, potentially accelerating their progression toward AD (Winer *et al.* 2024).

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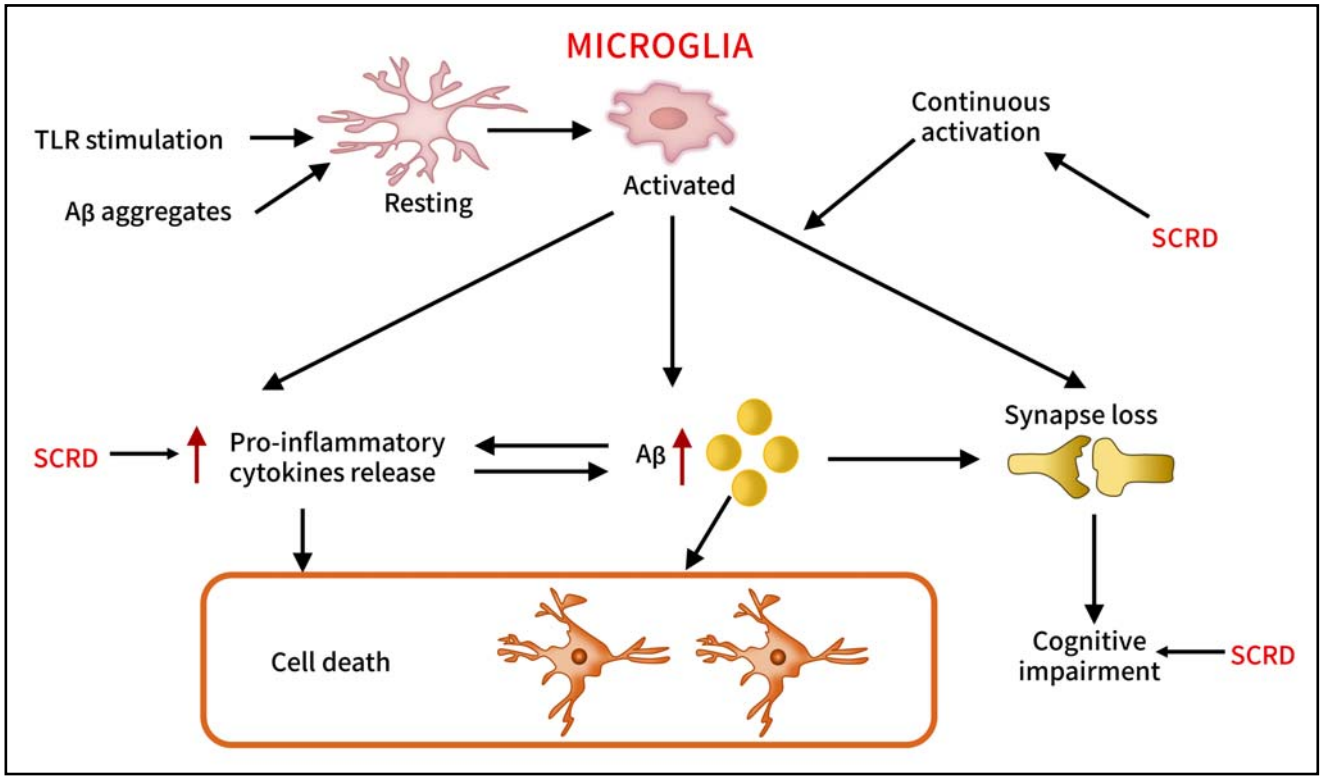

Fig. 1. Impact of SCRD on microglial activation and its role in AD progression. A schematic illustration of how SCRD influences microglial activation, contributing to neuroinflammation and cognitive decline. TLRS are activated by Aβ aggregates or other inflammatory signals, leading to A transition of microglia from a resting to an activated state. SCRD exacerbates pro-inflammatory cytokine release from activated microglia, further amplifying Aβ aggregation and perpetuating a feed-forward loop of neurotoxicity. Chronic activation of microglia disrupts synaptic integrity, leading to synapse loss and eventual neuronal death, critical features of AD pathology. Elevated cytokine levels, driven by SCRD, also enhance Aβ-mediated neurotoxicity and promote cognitive impairment through continuous activation of neuroinflammatory pathways. Key cellular responses include increased oxidative stress, sustained inflammation, and neuronal cell death, ultimately driving AD progression. Abbreviations: SCRD, sleep and circadian rhythm disruption; Aβ, amyloid β; AD, Alzheimer's disease.

MOLECULAR MECHANISTIC LINKS BETWEEN SCRD AND AD

In AD, SCRD manifests as fragmented sleep, reduced efficiency, altered sleep stages, and daytime activity changes (Leng *et al.* 2019). Studies have linked SCRD in AD to decreased melatonin production, delayed cortisol peaks, and abnormal circadian gene expression (Phan & Malkani 2019). Age-related degeneration of the SCN exacerbates these disruptions in AD patients, leading to more pronounced sleep disturbances (Wang *et al.* 2015). Moreover, circadian dysfunction impairs the glymphatic system, reducing the clearance of toxic proteins such as β-amyloid and tau, which contribute to their accumulation (Rasmussen *et al.* 2018). The evidence indicates that SCRD may be not only a symptom of AD but also a driver of its progression.

Clearance of Aβ

Research has shown that the decline in sleep quality and duration can significantly hinder the clearance of Aβ and increase its accumulation in the brain (Xie *et al.* 2013). The glymphatic system is enhanced during sleep (Baranwal *et al.* 2023), and the cortical interstitial space expands by about 60%, boosting the flow of cerebrospinal fluid to facilitate Aβ clearance (Xie *et al.* 2013). The primary clearance pathway for Aβ relies on the movement of interstitial fluid (ISF), which is facilitated by astroglial aquaporin 4 (AQP4) (Feng *et al.* 2020). AQP4, a water channel in the perivascular end feet of astrocytes and ependymal cells, is crucial for the rapid transport of water into and out of brain tissue (Nielsen *et al.* 1997). Lack of AQP4 expression or mislocation of AQP4 away from perivascular endfeet has been found to impair glymphatic clearance, increase Aβ accumulation and plaque deposition (Pedersen *et al.* 2023). Thus, proper perivascular AQP4 polarization is crucial for efficient Aβ removal. In aging and AD, reactive astrogliosis and neuroinflammatory changes coincide with a loss of AQP4 polarity, disrupting its water-channel function (Simon *et al.* 2022; Mader & Brimberg 2019). AQP4 depolarization, often accompanied by blood–brain barrier impairment and microvascular damage, hinders glymphatic Aβ drainage and may further promote neuroinflammation (Chen *et al.* 2025; Mader & Brimberg 2019). Ultimately, these findings implicate AQP4 dysfunction in exacerbating Aβ deposition and AD progression, highlighting AQP4 as

a potential therapeutic target for enhancing amyloid clearance.

Microglia, the brain's resident immune cells, play a pivotal role in neuroinflammation and neurodegeneration in AD (Borst *et al.* 2021). Figure 1 illustrates how SCRD exacerbate microglial activation and contributes to AD pathology. Resting microglia are activated in response to Aβ aggregation and Toll-like receptor (TLR) stimulation, leading to a pro-inflammatory state (Kwon & Koh 2020). Specifically, SCRD shows continuous activation of microglia. SCRD amplifies the release of pro-inflammatory cytokines, which in turn leads to a vicious cycle of microglial cell hyperactivation and continued Aβ accumulation, thus contributing to the development of AD (Chen *et al.* 2021). SCRD amplifies the inflammatory response and impacts synaptic integrity and neuronal viability to promote AD development further. Since SCRD disrupts microglial status, circadian dysfunction is linked to neurodegenerative processes typical of AD, pointing out putative targets of therapy to reduce inflammation and neurotoxicity (Prinz *et al.* 2019).

Clinical studies with positron emission tomography (PET) imaging have found that sleep deprivation is associated with an increase in Aβ plaques (Ooms *et al.* 2014). Accumulation of Aβ may further disrupt sleep architecture, but it is equally possible that early neurodegenerative changes contribute to sleep disturbances, complicating the determination of causality (He *et al.* 2020). However, fluorescent molecular tracing in the mouse brain indicated that metabolite diffusion in the brain during sleep or anaesthesia is primarily caused by diffusion rather than the volumetric flow of fluid and that clearance is significantly reduced in these states (Miao *et al.* 2024). These findings question the idea that the central function of sleep is to clear toxins, not just sleep duration. Future longitudinal studies to define further the specific mechanisms by which Aβ clearance is affected by sleep disturbances.

Abnormal Phosphorylation of Tau Protein

The abnormal phosphorylation of tau protein is a hallmark pathological feature of AD (Scheltens *et al.* 2021). Tau plays a role in stabilizing microtubules in neurons, guaranteeing axonal transport (Hu *et al.* 2023). However, in AD, tau is hyperphosphorylated and forms neurofibrillary tangles (NFTs), which are toxic to neurons and ultimately lead to cell death (Congdon & Sigurdsson 2018), and SCRD may accelerate the development of tau pathology (Holth *et al.* 2019).

In vivo studies and clinical trials found that sleep deprivation can promote tau hyperphosphorylation through multiple molecular pathways (Holth *et al.* 2019), especially the activation of glycogen synthase kinase 3β (GSK3β) (Congdon & Sigurdsson 2018). In AD, GSK-3β hyperphosphorylated tau, which causes its detachment from microtubules, tau aggregation, and NFTS formation (Sayas & Avila 2021). Thus, the role of GSK-3β in tau pathology is consistent with the idea that disruption of processes such as circadian rhythms may indirectly affect GSK-3β activity and tau aggregation (Niu *et al.* 2022; Sayas & Avila 2021). Furthermore, tau transgenic models have shown that circadian disruption leads to hyperphosphorylated tau accumulation in brain regions responsible for memory and cognitive functions, such as the hippocampus and entorhinal cortex (Niu *et al.* 2022; Holth *et al.* 2019).

Mechanistically, long-term sleep deprivation or circadian disruption has enhanced tau phosphorylation and exacerbated tau pathology (Holth *et al.* 2019). Amp-activated protein kinase (AMPK), a protein associated with energy homeostasis and circadian rhythms, is also involved in tau hyperphosphorylation (Um *et al.* 2011). Disruption of circadian rhythm dysregulates AMPK, which may promote tau phosphorylation and accelerate the spread of neurofibrillary tangles in cortical and subcortical regions (Domise *et al.* 2016; Kaur *et al.* 2023). However, there is a lack of direct evidence of SCRD-induced AMPK dysregulation in AD.

The activation of GSK3β and AMPK plays a crucial roles in sleep deprivation or circadian rhythm disruption, as well as in various cellular processes, such as stress response, metabolic regulation, and synaptic activity (Cortés-Vieyra *et al.* 2012; Liu *et al.* 2021; Park *et al.* 2023). Thus, assessing the specific effects of sleep and circadian rhythms on tau pathology separately remains challenging, especially when other factors known to drive tau pathology, such as oxidative stress (Eckert *et al.* 2011), inflammation, and metabolic dysfunction, are considered (Jadiya *et al.* 2021; Song *et al.* 2024). Thus, research on AD and SCRD requires interdisciplinary collaboration, including fields such as neuroscience, geriatrics, and molecular biology, to better understand these intertwined pathological mechanisms.

Circadian Clock Dysregulation in AD

Heredity plays a crucial role in regulating circadian rhythms and can influence individual susceptibility to circadian misalignment and sleep disorders (Ferrell & Chiang 2015). Circadian clock proteins, including clock, BMAL1, PER1, PER2, CRY1 and CRY2, are involved in maintaining the regularity of the circadian rhythm (Takahashi 2017). Figure 2 summarizes molecular mechanisms regulating and operating circadian rhythms.

Transcription-Translation Feedback Loop (TTFL) cycle is initiated by a heterodimer formed between the cytoplasm of BMAL1 and the CLOCK protein, with which BMAL1 forms a complex to drive the expression of target genes (Laothamatas *et al.* 2023). The complex regulates downstream circadian feedback loops by interacting with multiple regulatory elements (e.g., RORE and E-box), thereby controlling circadian gene expression in the other direction (Takahashi

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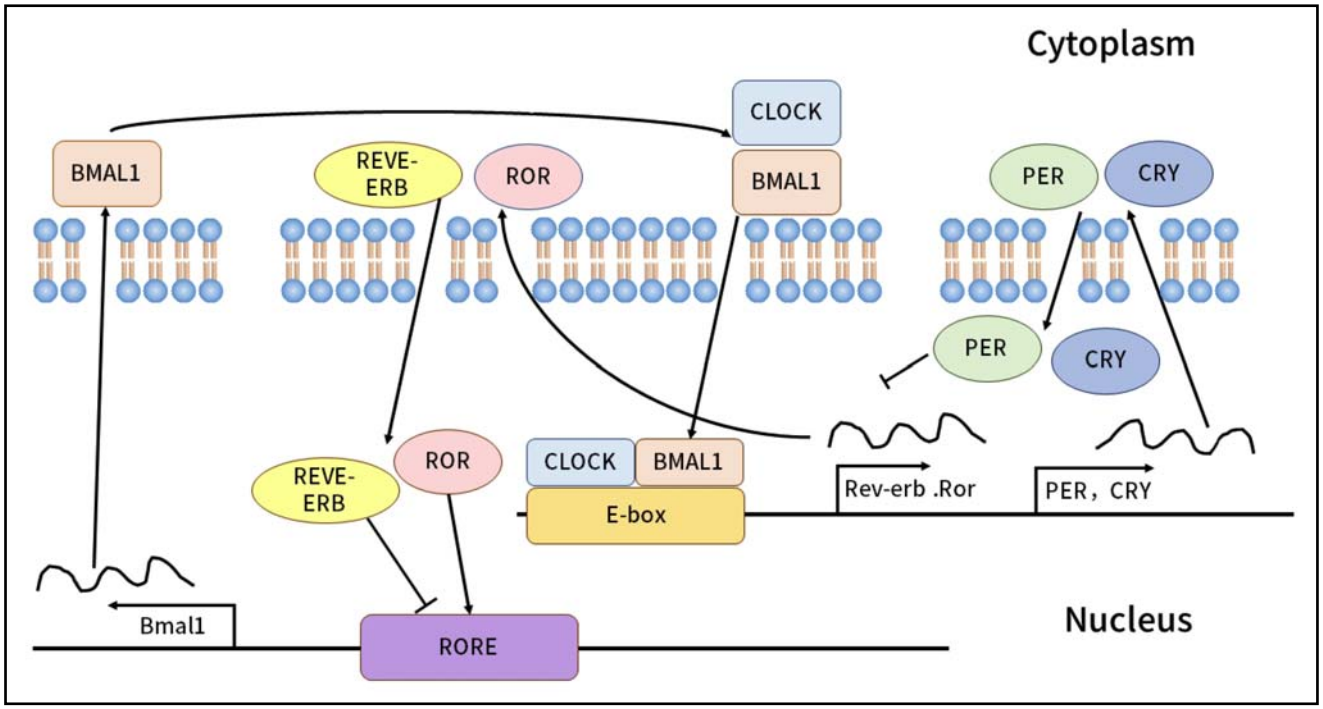

Fig. 2. Molecular mechanisms of the core circadian clock regulation. A schematic representation of the TTFL governing circadian rhythms. The CLOCK-BMAL1 complex binds to E-box elements in the nucleus, activating the transcription of PER and CRY genes. PER and CRY proteins accumulate in the cytoplasm and translocate into the nucleus to inhibit CLOCK-BMAL1 activity, creating a negative feedback loop. Stable oscillatory expression of clock genes and maintenance of circadian homeostasis are associated with the binding of ROR and REV-ERB to RORE to regulate BMAL1 transcription, respectively. ROR activates BMAL1 expression, whereas REV-ERB inhibits it. Abbreviations: CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle ARNT-like 1; PER, period; CRY, cryptochrome; ROR, retinoic acid receptor-related orphan receptor; REV-ERB, nuclear receptor subfamily 1 group D member; TTFL, transcription-translation feedback loop; RORE, ROR response elements.

2017). After receiving the input signal, the complex is transported into the nucleus (Saran *et al.* 2020) and binds to the E-box, involved in regulatory processes by modulating the activity of other pathways affected by ROR and REV-ERB proteins (Takahashi 2017; Cho *et al.* 2012). The complex binds to E-box elements in the promoter regions of target genes such as PER1, PER2, CRY1 and CRY2 to drive their transcription (Ruan *et al.* 2021). Meanwhile, ROR and REV-ERB proteins activate or repress BMAL1 transcription by binding to ROR elements, respectively, thus ensuring the balance of BMAL1 expression and maintaining the stability of the circadian cycle (Guillaumond *et al.* 2005). Subsequently, PER and CRY proteins form complexes in the cytoplasm and accumulate over time (Saran *et al.* 2020). During this period, ROR proteins promote the upregulation of BMAL1, whereas REV-ERB proteins act antagonistically to limit BMAL1 production, ensuring that BMAL1 levels oscillate in synchrony with other circadian regulators (Liu *et al.* 2008; Guillaumond *et al.* 2005). These complexes eventually migrate back to the nucleus where they inhibit BMAL1 activity and, as a result, their transcription is in a negative feedback loop (Waggoner 2020). This negative feedback mechanism is further regulated by the REV-ERB protein, which represses BMAL1 expression at specific times to ensure the accuracy of circadian rhythms (Guillaumond *et al.* 2005; Liu *et al.* 2008). The stability and turnover of PER and CRY proteins are tightly regulated by phosphorylation and ubiquitination (Ruan *et al.* 2021). The casein kinase CK1ε/δ phosphorylates PER protein and marks it for ubiquitination via the $SCF^{\beta\text{-}TrCP}$ complex, thereby allowing it to be degraded by the proteasome (Takahashi 2017). Similarly, CRY proteins are ubiquitinated and degraded, a process facilitated by the SCF^{FBXL3} complex (Takahashi 2017). In contrast, FBXL21 does not target CRY proteins for rapid degradation but ubiquitinates CRY proteins to protect them from immediate degradation (Yoo *et al.* 2013). This stabilizing effect helps maintain proper CRY protein levels in the cytoplasm during certain phases of the circadian rhythm (Yoo *et al.* 2013)

Mutations or polymorphisms in these genes are associated with circadian rhythm disturbances, such as advanced or delayed sleep phase syndromes (Patke *et al.* 2020). They are thought to contribute to the sleep disorders observed in AD (Phan & Malkani 2019). For example, the BMAL1 gene is a core component of the molecular clock and has been shown to regulate synaptic plasticity and cognitive function (Huang *et al.* 2012). In animal models, BMAL1 deficiency impairs the physiological oscillation of the circadian clock (De Virgiliis *et al.* 2023). Studies have shown that the knockdown of specific clock genes, such as BMAL1 and PER2, increases amyloid-β production and worsens

neurodegeneration (Lananna *et al.* 2020). Similarly, increased AD risk may be associated with polymorphisms in the PER gene by affecting sleep architecture and circadian regulation (Majcin Dorcikova *et al.* 2023). The connection between circadian dysfunction and AD is not solely due to behavioral factors but also involves molecular mechanisms (Trujillo-Rangel *et al.* 2024). Circadian clock genes such as BMAL1 and PER2 play crucial roles in regulating neuroprotective processes (Zhang *et al.* 2022a), and disruptions in these genes have been shown to exacerbate amyloid accumulation and impair the clearance of neurotoxic proteins (Fan *et al.* 2022).

AD-related Pathogenic Variants in SCRD

Genetic studies have identified several genes related to AD that might be implicated in SCRD (Yang *et al.* 2023). Among them, the apolipoprotein E gene (APOE) is best known in a few allelic forms (Yang *et al.* 2023). The APOEε4 allele is a recognized genetic risk factor for AD, and recent investigations have shown that carriers of the APOEε4 allele might be more vulnerable to circadian dysrhythmia and sleep disturbances that accelerate cognitive decline and amyloid-β accumulation (Koutsodendris *et al.* 2022). APOEε4 carriers show more fragmented sleep-wake cycles, less efficient sleep, and a different pattern of melatonin secretion than non-carriers (Koutsodendris *et al.* 2022) leading to accelerated cognitive decline.

In addition, SCRD may also be a potential risk factor for AD-related dementia as well as Parkinson's disease (Leng *et al.* 2019). However, most current studies rely on animal models, which limits the generalisation of these findings to human populations. Nevertheless, other genes associated with circadian rhythms, such as CRY1, may also be linked to AD in some way and deserve further exploration.

Evidence from AD Animal Models: APP/PS1

Animal models of AD include transgenic mice expressing amyloid precursor protein (APP) and presenilin-1 (PS1) mutations (Jankowsky & Zheng 2017). In app/ps1 mice, amyloid-β plaques began to accumulate as early as six months of age (Yokoyama *et al.* 2022), coinciding with the onset of circadian disruption (Carrero *et al.* 2023). They also exhibit hallmark features of AD, including amyloid β-plaque formation, neuroinflammation, and cognitive deficits (Jankowsky & Zheng 2017).

APP/PS1 mice have shown significant disruption of circadian rhythms in these animals, including sleep fragmentation and altered activity patterns (Yao *et al.* 2020). These circadian disruptions are thought to result from amyloid-β accumulation in brain regions that regulate the sleep-wake cycle, such as the SCN and basal forebrain (Niu *et al.* 2022). Moreover, APP/PS1 mice showed increased tau phosphorylation and neurofibrillary tangle formation in response to sleep deprivation, suggesting that SCRD accelerates AD pathological progression (Niu *et al.* 2022). Importantly, interventions aimed at restoring normal circadian rhythms, such as light therapy or pharmacologic manipulation of clock genes, have been shown to reduce β-amyloid-β levels and improve sleep in these models (Blackman *et al.* 2021).

PSG studies in APP/PS1 mice revealed several key abnormalities in sleep architecture, including decreased slow-wave activity and shortened rapid-eye-movement sleep (Zhang *et al.* 2022b). These findings mirror the sleep disturbances observed in human AD patients and further support the use of this model to investigate the mechanisms between SCRD and AD. Behavioural maps of APP/PS1 mice revealed disrupted activity rhythms, increased nighttime activity, and scattered daytime rest periods, mirroring patients with advanced AD (Yao *et al.* 2020).

Animal models like APP/PS1 offer insights into SCRD and AD but also have limitation. For instance, the gene mutations used in these models may not fully capture the complexity of sporadic AD observed in most human cases (Kelliny *et al.* 2021). Many animal studies overlook sex differences in SCRD and AD, a significant oversight since women are more susceptible to both (Sil *et al.* 2021). Future research may develop more sophisticated models that better replicate human AD pathology and include sex as a biological variable.

TARGETING SCRD FOR AD TREATMENT

Non-Pharmacological treatment

Cognitive behavioural therapy (CBTi) for insomnia has become the primary non-pharmacological treatment for SCRD patients (Alimoradi *et al.* 2022). CBTi, which focuses on changing behaviour and thought patterns that affect sleep, is a structured short-term therapy designed to improve sleep quality by addressing cognitive and behavioural factors that contribute to insomnia (Chan *et al.* 2021). Core elements of CBTi include sleep hygiene education, stimulus control, sleep restriction, and cognitive restructuring to counteract negative thoughts and beliefs about sleep (Perlis *et al.* 2022). CBTi improved sleep quality and daytime sleepiness in patients with insomnia, as well as comorbid conditions such as depression, anxiety, and schizophrenia (Perlis *et al.* 2022). However, data on the efficacy of CBTi in patients with mild AD is relatively scarce (Blackman *et al.* 2021). Thus, insufficient evidence exists to confirm that CBTi significantly impacts AD, necessitating further research.

Light therapy, for example, 40 Hz flickering light, has shown promise as a potential non-invasive treatment for AD. Mechanistically, the therapy targets gamma oscillations, which are critical for cognitive processes like memory and attention (Sahu & Tseng 2023). The 40 Hz stimulation aims to boost gamma-wave activity, which is often reduced in AD patients. Preclinical

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studies showed 40 Hz light exposure in AD mouse models reduced Aβ plaques and improved microglia function (Ismail *et al.* 2018). Induction with 40 Hz gamma oscillations enhanced microglial activity as microglia became more efficient at clearing Aβ deposits (Iaccarino *et al.* 2016). In addition, gamma stimulation can promote lymphatic clearance (Murdock *et al.* 2024). Thus, gamma-ray synchronization via phototherapy may provide a dual mechanism: improved synaptic connectivity while enhancing the brain's immune response. However, human studies have produced more mixed results. Some clinical studies found no significant reduction in amyloid load after a short-term 40 Hz light therapy regime in AD patients, suggesting that the human response may differ from that observed in animal models (Ismail *et al.* 2018), potentially requiring longer treatment durations or different protocols to achieve significant outcomes. More rigorous, long-term studies are required to understand the efficacy and mechanisms of light therapy in AD.

Pharmacological Regulation of Sleep in AD

Drugs targeting SCRD in AD patients have undergone clinical trials, including sedatives, such as suvorexant, benzodiazepines, etc., as well as melatonin, as summarized in Table 1.

Suvorexant exerts inhibitory effects on the orexin system, targeting the orexin receptors. The orexin system is essential for arousal. A randomized, double-blind clinical trial (ClinicalTrials.gov ID NCT02750306) found that suvorexant 10 mg for 4 weeks improved polysomnography-derived total sleep time (Suvorexant promotes sleep by inhibiting orexin receptors without the sedative effects of traditional sleep medications (Kuriyama & Tabata 2017).

Cholinesterase inhibitors target cholinesterase and are commonly used to treat cognitive symptoms of AD with benefits for sleep (Reeve *et al.* 2019). A naturalistic study (ClinicalTrials.gov ID NCT02187276) found that 5 mg of donepezil, rivastigmine, or galantamine improved cognitive function, assessed using the Mini Mental State Examination (MMSE), after 12 months of treatment. Responders at 3 months continue to respond at 12 months, with a 27.8% response rate. No correlation was found between response and APOE or CYP2D6 polymorphisms (Reeve *et al.* 2019).

Benzodiazepines and non-benzodiazepine hypnotics act on γ-aminobutyric acid (GABA) A receptors and are sometimes used to treat insomnia in Alzheimer's disease (AD) patients. A completed single-group clinical trial (ClinicalTrials.gov ID NCT04057807) investigated the effects of benzodiazepines on microglial activation in AD, finding that these drugs modulate microglial activity but present risks such as cognitive impairment and dependence. Another non-randomized study (ClinicalTrials.gov ID NCT02833272) examined the deprescription of both benzodiazepines and non-benzodiazepine hypnotics in elderly patients,

Tab. 1. Pharmacological Regulation of sleep on AD patients

Drug	Targets and Effects	Dosage and Duration	Observed Effects	Clinical Trials	References
Suvorexant	Orexin receptors (inhibitory effect on orexin system essential for arousal)	10 mg for 4 weeks	Improved total sleep time (TST) in AD patients; promotes sleep without sedative effects of traditional medications	NCT02750306	(Kuriyama & Tabata 2017)
Cholinesterase Inhibitors (Donepezil, Rivastigmine, Galantamine)	Cholinesterase (improves cognitive function and has benefits for sleep)	5 mg, assessed over 12 months	Improved cognitive function (assessed using MMSE); responders continued at 12 months with 27.8% response rate	NCT02187276	(Reeve et al. 2019)
Benzodiazepines and Non-Benzodiazepine Hypnotics	GABA A receptors (acts on receptors to treat insomnia, affects microglial activity)	Various doses, studied in different trials for effects on microglial activity	Modulates microglial activity; improves sleep but poses risks of cognitive impairment and dependence	NCT04057807, NCT02833272	(Markota et al. 2016)
Melatonin	Melatonin system (reduced production in AD patients, supplementation aims to improve sleep)	2.5 mg slow-release and 10 mg immediate-release over 8 weeks	Improved nocturnal sleep time, reduced time awake after sleep onset; effects on cognitive function inconsistent	NCT00000171	(Blackman et al. 2021; Chen et al. 2021)

aiming to reduce their inappropriate use. Both classes of drugs can improve sleep (Markota *et al.* 2016). However, these drugs may have significant side effects, including increased risk of falls, cognitive impairment, and dependence, and are therefore less suitable for long-term use (Markota *et al.* 2016; Kuriyama & Tabata 2017; Reeve *et al.* 2019).

Given that AD patients often exhibit reduced melatonin production (Song 2019), melatonin supplementation has also been explored as a treatment for SCRD in AD patients (Peter-Derex *et al.* 2015). A randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov ID NCT00000171) investigated the effects of melatonin on sleep disturbances in AD patients. The trial compared two doses of melatonin—2.5 mg slow-release and 10 mg immediate-release—over an 8-week period in 150 AD patients with documented sleep disruption. Results showed that melatonin improved nocturnal sleep time and reduced time awake after sleep onset, though its effects on cognitive function were inconsistent (Blackman *et al.* 2021). This discrepancy may result from differences in doses, preparations, and patient populations across studies.

Potential Drugs Modulating Circadian Rhythms

Emerging *in vitro* and *in vivo* research has identified several promising drug targets for treating SCRD in AD. Compounds that modulate circadian clock genes, such as BMAL1 and PER2, have shown the potential to restore normal circadian rhythms and reduce amyloid-β accumulation in animal models (Kress *et al.* 2018). Recent understanding of the glymphatic system has also opened new avenues for treatment. As mentioned, the lymphatic system clears metabolic waste products from the brain, including amyloid-β protein (Aβ) and tau (Feng *et al.* 2020). Thus, dysfunction in the glymphatic system leads to the accumulation of these proteins (Ding *et al.* 2023). Drugs such as Quercetagitrin, which is an inhibitor and targets tau phosphorylation (NF-κB), have also shown promise (Zhong *et al.* 2023). Research showed that quercetagitrin reduced tau tangles and improved cognitive function in AD mice (Zhong *et al.* 2023). Novel approaches to slow the AD progression may through enhanced lymph-like clearance of β-amyloid-β and tau during sleep. Several pharmacological agents aimed at boosting glymphatic function are currently under investigation, though clinical trials in humans are still in the early stages.

Most of the current research on AD treatment focuses on three targeting Aβ and γ or β-secretase enzymes responsible for cleaving APP. Although preclinical studies are promising, the effects of these drugs currently do not significantly improve AD, and translating to clinical use remains challenging (Briggs *et al.* 2016). In addition, most animal studies focus on early AD, whereas clinical trials involve advanced AD patients (Akhtar 2015). Evidence suggested that current animal models cannot accurately predict neurally related diseases (Akhtar 2015; Green 2015). This discrepancy highlights the need for more translational research to bridge the gap between animal models and patients.

FUTURE OUTLOOK

One of these therapeutic directions is the research and development of personalized treatments targeting specific genetic and molecular pathways involved in circadian disorders. For example, therapies that restore the normal functioning of circadian clock genes, enhance the ability of the glymphatic system to remove waste from the brain, or reduce neuroinflammation may offer more effective ways to manage SCRD and slow AD progression (Buccellato *et al.* 2022; Formolo *et al.* 2023; Wang & Li 2021). Preclinical studies suggest agents that improve perivascular AQP4 localization, such as certain omega-3 fatty acids and small molecule enhancers, significantly boost glymphatic clearance and subsequently reduce amyloid accumulation (Ren *et al.* 2017; Wen *et al.* 2024). Moreover, non-invasive neuromodulation techniques, such as transcranial ultrasound and gamma-frequency sensory stimulation (e.g., 40-Hz light flicker), have demonstrated efficacy in animal models by promoting glymphatic activity, enhancing cerebrospinal fluid circulation, and accelerating the removal of neurotoxic proteins from the brain (Murdock *et al.* 2024; Bae *et al.* 2024). Future clinical research is needed to develop and evaluate therapies targeting the glymphatic system.

Another promising direction is the use of wearable technology, such as actigraph devices, to monitor sleep and circadian rhythms in real-time (Lujan *et al.* 2021), provide early warning about SCRD, and allow timely intervention to delay symptoms.

More experiments are needed to confirm the safety and effectiveness of treatments like light therapy and melatonin. While they may delay Alzheimer's disease progression, their effectiveness varies by patient. More robust interventions for the underlying mechanisms of sleep disorders and circadian rhythm disruption remain to be explored. Future research should focus on personalized strategies based on genetic predispositions and explore new pharmacological agents targeting tau phosphorylation and amyloid-β production.

CONCLUSIONS

SCRD is not only a complication of AD but also a contributing factor. Disturbances in sleep and circadian rhythms disrupt memory consolidation as well as impair patients' behavioural and cognitive abilities and accelerate the accumulation of amyloid-β and tau protein pathology, driving further AD deterioration. Sleep disruption reduces the duration and quality of deep sleep, which reduces the adequate circulation of cerebrospinal fluid, leading to a decrease in

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the efficiency of amyloid-β and tau protein clearance. Moreover, SCRD may also affect the polar distribution of AQP4, which impairs the lymphoid system's clearance capacity. In contrast, the accumulation of amyloid-β leads to synaptic dysfunction and neurodegeneration. In addition, microglia activity is regulated by circadian rhythms. Circadian rhythm disruption leads to increased release of pro-inflammatory cytokines, which can further damage neurons, thereby exacerbating neuroinflammation. Therefore, targeting SCRD may become a therapeutic strategy to slow the progression of AD. Current non-pharmacological treatments for SCRD in AD patients can be treated with light therapy, while pharmacological treatments often involve the use of melatonin to alleviate the symptoms of AD, but these approaches are often insufficient to address the full range of sleep and circadian rhythm disturbances in AD patients. Emerging research in circadian gene modulation and tau-targeting drugs holds promise for more effective interventions in the future, slowing AD progression and improving the quality of life for dementia patients.

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