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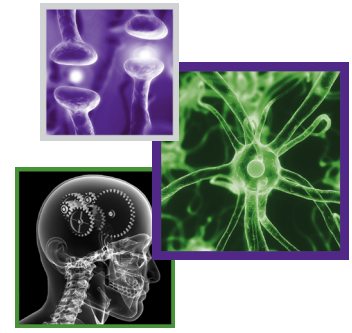
Neurodegenerative Disease Management



The sleep–wake cycle and Alzheimer's disease: what do we know?

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Practice points

- Sleep–wake disturbances are a common and often debilitating feature of Alzheimer's disease (AD).
- Sleep–wake disturbances may be one of the earliest symptoms in preclinical AD.
- Evidence from animal and human studies suggests that AD pathology disrupts the sleep–wake cycle, including increased sleep fragmentation and wakefulness, and decreased slow-wave sleep.
- Evidence from animal and human studies also suggests that prolonged wakefulness may increase levels of soluble amyloid-β in the brain, and may both exacerbate and accelerate the onset of AD pathology.
- We discuss possible mechanisms underlying the reciprocal relationship between the sleep–wake cycle and AD pathology and behavior.
- Current approaches to therapy for sleep disorders in AD are discussed, including nonpharmacological approaches to improve sleep hygiene, melatonin/bright light therapy, pharmacological treatments, and treatment of common underlying sleep disorders such as obstructive sleep apnea.

SUMMARY Sleep–wake disturbances are a highly prevalent and often disabling feature of Alzheimer's disease (AD). A cardinal feature of AD includes the formation of amyloid plaques, associated with the extracellular accumulation of the amyloid-β (Aβ) peptide. Evidence from animal and human studies suggests that Aβ pathology may disrupt the sleep–wake cycle, in that as Aβ accumulates, more sleep–wake fragmentation develops. Furthermore, recent research in animal and human studies suggests that the sleep–wake cycle itself may influence Alzheimer's disease onset and progression. Chronic sleep deprivation increases amyloid plaque deposition, and sleep extension results in fewer plaques in experimental models. In this review geared towards the practicing clinician, we discuss possible mechanisms underlying the reciprocal relationship between the sleep–wake cycle and AD pathology and behavior, and present current approaches to therapy for sleep disorders in AD.

Alzheimer's disease (AD) is the most common cause of dementia, yet causes and risk factors of AD are not well understood. While genetic factors such as *APOE* genotype, and mutations in APP, PS1 or PS2 have been identified in familial AD, sporadic AD is a multifactorial disease affected by many other, potentially modifiable factors. Aging is the major risk factor in sporadic AD, but other factors such as head trauma, the presence of *APOE4* alleles, and cardiovascular disease also

KEYWORDS
• Alzheimer's • amyloid • amyloid-β • circadian • EEG • glia • hypocretin • orexin • sleep • wake

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strongly increase an individual's future risk of developing sporadic AD [1]. Recently, evidence has implicated the sleep–wake cycle in the development of AD. The relationship between sleep and AD has important implications for the optimal clinical management and potential treatment strategies in patients with AD. This article highlights recent advances in our understanding of the reciprocal relationship between sleep and AD, and provides an overview of our current clinical practice guidelines.

AD is a neurodegenerative disease, which typically progresses from mild cognitive impairment to severe dementia over the course of many years. The mean time from onset of cognitive symptoms to death is approximately 10–12 years, but the course is variable. Importantly, the pathology of AD begins about 15 years before any cognitive symptoms appear. This period when AD pathology is accruing in the absence of detectable cognitive decline has been termed preclinical AD [2]. In the earliest stage of preclinical AD, amyloid plaques, derived from soluble monomeric forms of the peptide amyloid-β (Aβ) that are 40–42 amino acids in length, begin to deposit in an aggregated form. Reduction in cerebrospinal fluid (CSF) levels of the less soluble form of Aβ, or Aβ42, occurs around the same time as amyloid plaque formation, and together, have been proposed as biomarker evidence of preclinical AD [2–7]. Tau tangles, the other pathological hallmark of AD, develop later in the disease course [8]. While amyloid plaques and tau tangles initially form in specific, mostly nonoverlapping brain regions, they are eventually found throughout multiple brain regions with disease progression, including in brain regions critical for the sleep–wake cycle, such as the cerebral cortex, the basal forebrain, the locus coeruleus and the hypothalamus [9].

Changes in sleep appear to precede the onset of cognitive symptoms in patients with AD, and a strong association exists between disrupted sleep and the development of AD [10]. The gold standard for determining sleep staging involves polysomnography, which includes the electroencephalogram (EEG). Polysomnography in AD is associated with decreased slow-wave sleep and rapid eye movement (REM) sleep, prolonged REM latency, increased proportions of stages N1 and N2 non-REM (NREM) sleep, and increased sleep fragmentation, leading to an overall decrease in sleep duration [11,12]. During wakefulness, AD patients show a shift in the EEG power spectrum shift to lower frequencies and incoherent fast rhythms [13]. While these nonspecific EEG changes have also been described in other neurodegenerative diseases, newer quantitative EEG techniques may hold promise in distinguishing AD from other dementias early in the disease course [14–16]. Thus, early sleep assessment and EEG may provide more sensitive diagnostic tools for the preclinical detection of AD rather than more traditional cognitive testing [17].

Disturbances in sleep and the circadian rhythm are frequent and disabling features in individuals with AD, affecting approximately 25–60% of all patients [18–21]. The most common sleep-related complaints are insomnia, sleep fragmentation and excessive daytime sleepiness [22,23]. In addition to sleep complaints, AD is also associated with phase shifts in the normal circadian alertness profile, which likely contributes to 'sundowning' in later stages of disease [11,23]. Furthermore, sleep and circadian disturbances may worsen as AD progresses [12,24]. However, the mechanisms underlying poor sleep and disturbed circadian rhythms in AD are poorly understood.

Sleep itself appears to be critical for normal memory function and memory consolidation. Nocturnal sleep and daytime naps stabilize and enhance certain memory processes, and specific tasks appear to be enhanced by specific sleep stages. In general, declarative memories (i.e., memory for conscious events) are enhanced by NREM or slow wave sleep, whereas nondeclarative memories (i.e., learned skills/habits, procedural memories) are enhanced by REM sleep [25,26]. Poor sleep quality and sleep deprivation cause deficits in synaptic plasticity and memory processes [27–29]. Therefore, it stands to reason that poor sleep quality in AD likely also adversely affects cognition and memory.

In this Special Report, we discuss the evidence for a reciprocal relationship between AD and sleep, namely, the mechanisms by which AD pathology disrupts sleep, and also the specific role of the sleep–wake cycle in the pathogenesis of AD. We also review the evidence for current pharmacological and nonpharmacological therapeutic approaches to sleep disturbances in AD.

AD pathology disrupts sleep

• Animal studies

Animal models have provided a useful avenue in order to dissect the association between sleep disturbances and AD. Transgenic mouse models

– genetically engineered mice with mutations causing amyloid and/or tau aggregates in the brain – have been particularly revealing, and suggest a direct causal link between AD pathology and sleep disturbances. Although mice are nocturnal animals, and typically have shorter sleep bouts compared with humans, the neural circuits and neurotransmitters that regulate sleep and wakefulness and circadian biology are highly conserved between mammalian species. Therefore, much can be learned from these experimental models of sleep and AD.

In mice expressing the human amyloid precursor protein (APP) Swedish mutation (Tg2576 line), amyloid plaques accumulate within brain regions critical for the normal generation of sleep, including the brainstem region containing mesopontine cholinergic neurons involved in REM sleep, and these mice have prominent sleep and circadian abnormalities [30,31]. Triple-transgenic mice (3×Tg) harboring mutations for APP, PS1 and tau demonstrate age-related loss of noradrenergic neurons in the locus coeruleus, an area critical for maintaining normal wakefulness [32]. In the PLB1 triple-knock-in model, mice carry mutations in human APP, PS1 and tau transgenes, and exhibit decreased sleep, more sleep fragmentation and less robust circadian rhythms compared with nonmutant littermates [33]. These mice also show slower EEG frequencies during wakefulness, similar to that reported in human mild cognitive impairment and AD [13]. In another transgenic mouse model, in which mice overexpress APP and presenilin 1 (APP/PS1), which also develops Aβ plaques throughout the brain, significantly disrupted sleep–wake patterns including increased time awake and decreased sleep begins at the time of plaque deposition (6 months of age), and worsens with age as plaques become more widespread [34]. Notably, in these mice, immunization with Aβ, which is an experimental manipulation that prevents amyloid plaque formation, normalized sleep–wake patterns, which is the strongest evidence yet for a direct, causal relationship between amyloid plaque deposition and sleep–wake disturbances.

• Human studies

Several human studies suggest that AD brain pathology particularly targets circuits known to be important for normal sleep–wake behavior, thereby causing sleep–wake disturbances. Similar to the 3×Tg mouse model, a well-described early feature of human AD pathogenesis is degeneration of the locus coeruleus, the main source of norepinephrine to the cortex and a region critical for maintenance of normal wakefulness [35]. Deficits have also been identified in the wake-promoting molecule, orexin (also known as hypocretin), which is implicated in human narcolepsy: CSF orexin levels are significantly correlated with CSF Aβ42 levels in AD patients, suggesting decreased control of the sleep–wake cycle occurs with decreased Aβ42 levels (used as a surrogate marker for amyloid plaque deposition) [36]. Furthermore, CSF orexin levels have a significant correlation with tau and phosphorylated tau protein levels in the CSF of ten patients with AD compared with ten age-matched controls, indicating a relationship between sleep–wake molecules and tau pathology [37]. In accordance with these data, an autopsy study of ten AD and ten matched control brains demonstrated a significant 40% decrease in orexin neuron counts in advanced AD, providing a direct mechanism for sleep–wake dysfunction in late-stage AD [38]. Last, melatonin, which is a neurohormone critical for maintenance of normal circadian rhythms, has been reported to have a significantly advanced time of onset in mild AD patients compared with matched controls [39]. Other systems implicated in the control of sleep and wakefulness such as histamine, serotonin and GABAergic populations in the preoptic regions may also be involved in AD, but these findings have not been as robust [40].

Other human disorders involving amyloid and tau pathology also demonstrate sleep disturbances, lending credence to the notion that this pathology affects the sleep–wake cycle. For example, Down's syndrome, which involves trisomy of chromosome 21 in which APP resides, is associated with the characteristic amyloid deposition as well as neurofibrillary tangle development of AD by age 40 years. Affected individuals also exhibit profound sleep disturbances, among other neurological phenotypes [31]. Classic tauopathies such as progressive supranuclear palsy, frontotemporal dementia and corticobasal degeneration feature tau tangles in sleep–wake circuits of the brain and sleep disorders feature prominently [32]. Last, in traumatic brain injury and chronic traumatic encephalopathy, acquired amyloid and tau pathology, sleep disturbances are also commonly reported both in the acute phase as well as several years out from injury [33–35].

Normal aging is associated with more sleep fragmentation, insomnia and increased wakefulness [11,24,41]. Sleep disorders such as obstructive sleep apnea and restless legs syndrome become more common as we age, and these disorders can also contribute to sleep fragmentation, insomnia and daytime sleepiness. Medications for common comorbid medical problems such as depression and cardiac dysfunction often carry side effects that affect the sleep–wake cycle. Aging is also associated with circadian rhythm disturbances such as advanced sleep phase syndrome and irregular sleep–wake circadian disorder [11,24,41,42]. Less physical activity and inadequate light exposure can also disrupt circadian rhythms in the elderly, especially in those that are institutionalized [42]. Therefore, in addition to AD brain pathology, there are likely many other factors that contribute to poor sleep in patients with AD, thus setting up a perpetuating cycle of sleep–wake disturbances.

Sleep exacerbates AD pathology

While it has been known for decades that individuals with AD typically display sleep and circadian rhythm disturbances, only recently has evidence surfaced that directly implicates the sleep–wake cycle in the pathogenesis of AD itself.

• Animal studies

The strongest evidence for sleep–wake regulation of Aβ and amyloid plaque deposition, again, lies in animal models. The first study to demonstrate this used young Tg2576 mice to follow soluble, monomeric Aβ levels in the brain interstitial fluid across the sleep–wake cycle [43]. Kang *et al.* found approximately 25% higher levels of extracellular Aβ in these mice during wakefulness compared with sleep, and persistently elevated Aβ levels in conditions of sleep deprivation as well as during orexin infusion (which promotes wakefulness) [43]. Furthermore, chronic sleep restriction to 4 h daily for 21 days resulted in a twofold increase in amyloid plaque burden in both Tg2576 mice as well as an additional transgenic mouse model, the APP/PS1 mutant line [43]. Last, chronic sleep extension using a pharmacological manipulation daily for 8 weeks – intraperitoneal injections of the dual orexin receptor antagonist, almorexant, which increases total sleep time by approximately 10% – significantly reduced Aβ plaque burden compared with vehicle-injected mice [43]. These experimental manipulations suggest a direct role for sleep in modulating extracellular levels of soluble Aβ; and Aβ plaque deposition in mouse models of AD.

A similar study manipulating the sleep–wake cycle in mice was also performed with significant effects on tau metabolism. Using the 3×Tg mice that expresses both amyloid plaques and tau tangles, mice were moved from a 12:12 light:dark cycle to a 20:4 light:dark cycle for 8 weeks. Mice in the 20:4 light:dark cycle showed significantly increased insoluble tau, memory impairment and synaptic pathology compared with 12:12 controls [44]. While sleep and wakefulness were not directly manipulated nor examined in these mice, these data indicate the importance of the role of the circadian response to light in the course of AD pathology.

Another animal study examined the role of a wake-promoting region, the locus coeruleus, in the pathogenesis of AD [45]. It has been known for over 30 decades that loss of cortical noradrenergic innervation from LC degeneration is an early pathological hallmark of AD [46]. In this study, LC degeneration was induced in young mice transgenic for APP23 prior to developing amyloid plaques. Mice with early LC degeneration showed significantly more plaques, cognitive deficits, glial inflammation and neuronal loss compared with age-matched controls [45]. Since LC degeneration is known to affect the sleep–wake cycle, these results are consistent with the hypothesis that manipulation of sleep and wakefulness has direct and profound effects on the disease course of AD.

One caveat of using studies involving animal models of familial AD is that these models may not show the same sequence of events occurring in sporadic AD (which accounts for more than 95% of all AD cases). Thus, while these models may be useful in genetic mechanisms leading to neurodegeneration, findings may not always generalize to sporadic AD (reviewed in [47]). However, it should be noted that in at least one study wild-type mice who were subjected to sleep deprivation also showed acute increases in ISF Aβ levels, suggesting that similar pathological mechanisms may hold true in mice with normal physiology [43].

• Human studies

In human studies, the causal relationship between the sleep–wake cycle and the pathogenesis of AD is more difficult to prove due to obvious limitations in experimental design

that would allow a direct test of this hypothesis. However, correlational studies on this topic are compelling. Many of these studies utilize actigraphy (a noninvasive accelerometer, often embedded in a wristband, which monitors rest/activity cycles) as a surrogate to polysomnography to measure sleep and sleep fragmentation, which lacks EEG confirmation of sleep, but confers an advantage of multiple days to weeks of recording time per individual [48].

In normative populations, acute and chronic sleep disruption has deleterious effects on cognition and memory processes [49]. A natural extension of this phenomenon is also seen in the aged population, in which sleep disruption has been associated with more severe cognitive deficits [50,51]. These human studies suggest that one of the possible functions of sleep is a restorative one; although this may seem obvious, the notion is still somewhat controversial in the field.

Regarding human studies of AD, in short-term (i.e., 1–6 years) prospective studies, sleep disruption has been reported to increase the risk of incident dementia. A recent study of 737 community dwelling older adults examined sleep fragmentation as measured using of actigraphy, and found that a unit increase in their calculated sleep fragmentation index was associated with a 22% increase in the annual rate of cognitive decline relative to the average rate of decline [52]. Furthermore, individuals in the 90th percentile of sleep fragmentation had a 1.5-fold risk of developing AD compared with someone in the 10th percentile of sleep fragmentation [52]. A separate study from the same group found that each unit improvement in sleep consolidation significantly attenuated the *APOE4* genotype risk of incident AD to a hazard ratio of 0.67, compared with the average [53]. While still correlative in nature, these data establish a strong association between sleep fragmentation and incident dementia.

Several groups have established the utility of low CSF Aβ42 levels as a surrogate marker for amyloid plaque deposition in the *in vivo* human brain [4–6]. In a recent cross-sectional study of 145 cognitively normal individuals, of the 32 participants with low CSF Aβ42 levels, there was worse sleep quality and more frequent daytime napping compared with matched peers without evidence of preclinical AD [54]. Interestingly, human CSF Aβ levels fluctuate in a diurnal pattern similar to that observed in transgenic mouse studies [43,55]. Furthermore, individuals with amyloid plaques as detected by *in vivo* PET neuroimaging using the PIB compound show less diurnal variation in CSF Aβ, also a finding paralleled in mouse studies [34,55]. Therefore, we can conclude that CSF Aβ levels and the degree of CSF Aβ diurnal oscillation are predictive of amyloid plaque deposition and are associated with sleep disruption/loss.

A very recent, compelling study in The Netherlands found that a single night of sleep deprivation significantly increased CSF Aβ42 levels in a cohort of 26 healthy, cognitively normal men with an average age of 50 years old [56]. A night of unrestricted sleep was associated with a 6% decrease in CSF Aβ42 levels. One night of sleep deprivation counteracted this decrease, suggesting that prolonged wakefulness interferes with a physiologic sleep-related morning decrease in Aβ42 levels, thus elevating the risk of subsequent AD.

The striking similarity in extracellular Aβ physiology between mice and humans lends credence to the hypothesis that sleep/wake disturbances may directly impact AD pathology. However, long-term prospective studies are warranted, especially in the preclinical stage of AD. In addition, experimental manipulations in humans using either induced short-term sleep fragmentation and CSF Aβ measurements, coupled with long-term studies using experimentally induced sleep extension (i.e., hypnotics or other sleep-consolidating therapies) are needed before this hypothesis can be fully validated. For example, as a start, several commonly used medications are known to affect the distribution of sleep stages, which might provide opportunities for cross-sectional studies on pharmacologically induced sleep manipulations on incident dementia.

Possible mechanisms?

Although compelling, the hypothesis that AD pathology causes sleep–wake disturbances, and the reciprocal notion that sleep–wake disturbances accelerate AD pathology, still requires mechanistic support, particularly in humans. Several possible underlying mechanisms have been postulated that could explain the reciprocal relationship between the sleep–wake cycle and AD (schematized in **Figure 1**).

One possible mechanism is that slow-wave activity during NREM sleep leads to decreased neuronal activity, which is protective against rising extracellular Aβ levels and therefore amyloid

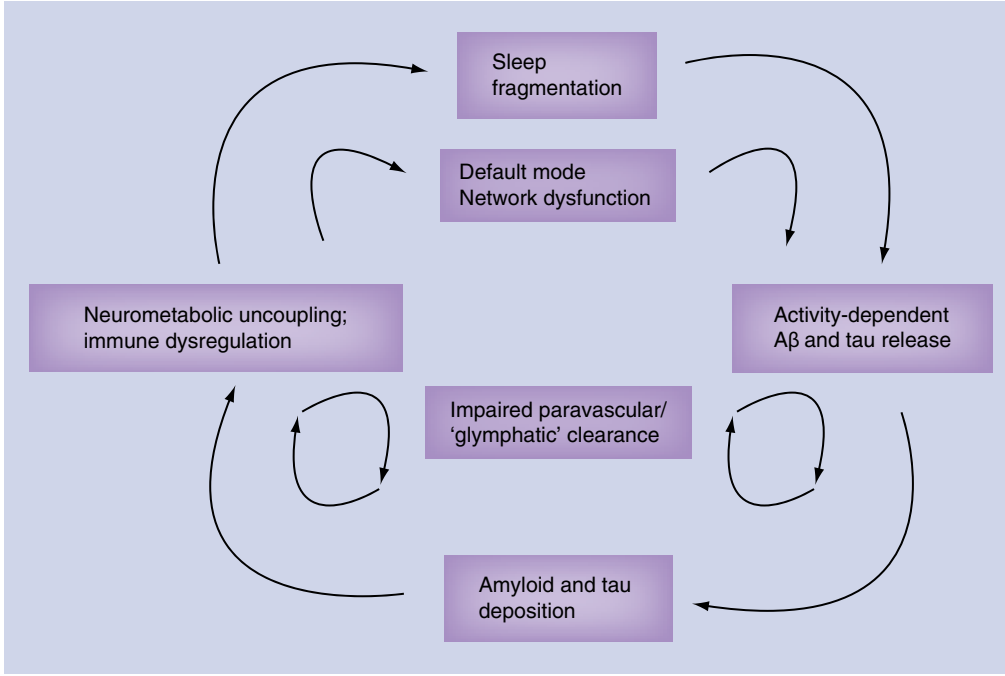

Figure 1. Schematic of possible mechanisms underlying the reciprocal relationship between sleep disturbances and Alzheimer's pathology. In summary, sleep disturbances lead to increased waking neuronal activity-dependent Aβ and tau release, resulting in greater amyloid plaque and tau tangle deposition. Pathological proteins lead to neurometabolic uncoupling of lactate metabolism with the sleep–wake cycle, causing further sleep disturbances. Alzheimer's disease pathology may also impact the immune system, continuing to feed forward alterations in sleep and subsequent pathology. Within the larger positive feedback cycle lies smaller positive cycles involving the default mode network, whose dysfunction exacerbates activity-dependent Aβ and tau, and impaired glia-lymphatic ('glymphatic') clearance of Aβ and tau, leading to increased Alzheimer's disease pathology and astrocytic metabolic dysfunction.
Aβ: Amyloid-β.

plaque formation [10]. In support of this are mouse studies showing that extracellular Aβ levels are tightly correlated with neuronal firing and wakefulness [57,58]. However, this hypothesis would predict that other sleep states such as REM sleep, which is associated with an increase in neuronal activity and metabolism, might exacerbate AD pathology [59]. The contribution of REM sleep to AD pathology remains to be tested. Furthermore, much remains to be determined regarding the translation of slow-wave sleep seen on aggregate scalp or skull-based EEG and neuronal activity at the single-cell or regional level.

A 'hypnic hypothesis' of AD has been proposed that involves altered function of brainstem neurotransmitter pathways associated with sleep, causing regionally specific disintegration within the 'default mode' brain network that is selectively vulnerable in AD [60,61]. The default mode network shows decreased functional connectivity during slow-wave or NREM sleep; thus, it follows that slow-wave sleep might be protective against the disintegration of the default mode network in AD [62–64]. Likewise, during wakefulness, although there is evidence that more frequent cognitive activity is related to slower cognitive decline in those without cognitive impairment, in patients with AD this appears to be the opposite in that more frequent cognitive activity leads to more rapid cognitive decline [65,66]. Central to this hypothesis is the idea that synaptic neurotransmission facilitates both the 'seeding' of local insoluble protein aggregates such as Aβ and the 'spread' of AD pathology (such as tau pathology) among functionally connected regions [67,68]. Although an intriguing concept, trans-synaptic transmission of AD pathology is still being tested [69,70].

A third possible mechanism focuses on the diurnal aspect of Aβ clearance, involving

neurometabolic coupling of lactate derived from astrocytes, a subtype of glial cell in the brain, and apolipoprotein E (ApoE), an astroglial-enriched protein associated with genetic risk for sporadic AD [71]. While the relationship between Aβ and ApoE is very complex, one intriguing mechanism is the binding of ApoE to Aβ to facilitate Aβ clearance and prevent Aβ aggregation in the brain [72]. Loss of diurnal Aβ oscillations in mice and humans upon insoluble Aβ aggregation is thought to contribute to progressive sleep loss through uncoupling of lactate metabolism [34]. The astrocyte-neuron lactate shuttle asserts that glutamate released by neurons is taken up by astrocytes and supplied back to neurons as fuel in the form of lactate [73]. Since wakefulness is associated with increased levels of extracellular glutamate and lactate [74], and extended wakefulness increases brain interstitial fluid Aβ levels [43], AD pathology may commence through dysfunction of astrocyte–ApoE Aβ clearance mechanisms tied to changes in sleep/wake-derived lactate metabolism [71]. Pharmacological treatments, such as bexarotene, which augment ApoE lipidation, have been shown to decrease interstitial Aβ, reduce Aβ aggregation and restore memory deficits [75,76]. While aspects of these findings have been controversial, bexarotene treatment still appears to reduce Aβ peptides and improve Aβ-induced cognitive deficits [77–81]. In addition to improved cognition and memory, bexarotene treatment has also been shown to suppress the relocation of astrocytes around amyloid plaques [75]. Therefore, Aβ aggregates would favor a localized astroglial response, preventing neurometabolic support coupled to glutamate release from neurons, setting up the vicious cycle: increased wakefulness increases glutamate and Aβ levels, these in turn prevent their own clearance and induce more wakefulness. This suggests that preventing localized astroglial response to Aβ aggregates would permit neurometabolic coupling to remain intact, and normal sleep/wake cycles would be permitted [71,82]. Whether pharmacological treatments that facilitate astrocyte–ApoE Aβ clearance mechanisms restore the sleep–wake cycle and neurometabolic lactate shuttle coupling remains to be examined.

A fourth possible mechanism stems from recent exciting data in a mouse model, which identified a novel pathway for the clearance of toxic proteins via glia-lymphatic ('glymphatic'), or paravascular pathways in the brain. Mice that were asleep or in the anesthetized state showed much faster clearance of exogenously applied Aβ from the interstitial space, compared with mice that were awake [83]. During sleep, and during the anesthetized state, there was a 60% increase in the interstitial space, resulting in a dramatic increase in convective exchange of CSF with the brain interstitial fluid. This increase in interstitial space was mimicked with noradrenergic receptor blockade, suggesting that locus coeruleus-derived noradrenergic signaling during wakefulness may be critical for the effect. However, several questions still remain to be determined, including the dynamics of clearance of endogenous Aβ and other proteins, as well as the distinction between sleep and the anesthetized state, which are very different brain states with previously reported contradictory effects on AD pathology [84,85].

A fifth possible mechanism, although much less developed, could involve the interaction between sleep, AD and the immune system. Sleep has well-documented effects on the immune system, in that sleep and sleep loss modulate optimal immune function, and certain cytokines and other immune modulators enhance or suppress sleep [86–88]. Glial, and particularly microglial, dysfunction has been described in aging and AD (reviewed in [89,90]). Perhaps not coincidentally, active and passive immunotherapy presents a promising approach to AD prevention and treatment (reviewed in [91]). Thus, although little direct evidence exists for this immune link between sleep and AD, it is conceivable that poor sleep could sufficiently alter immune function and affect the pathogenesis of AD [92].

Current therapies

Current pharmacological and nonpharmacological therapies for Alzheimer's patients suffering from sleep disturbances are unfortunately limited. Targeting the sleep–wake cycle may be an effective, low-risk, noninvasive intervention to ameliorate the symptoms of AD, although evidence is still needed to show that sleep interventions improve disease course.

Current behavioral practice relies on the use of 'sleep hygiene' in AD, including limiting caffeine and alcohol intake, avoiding evening light exposure from computers or the television, exercising regularly and keeping regular bed times and wake times with adequate light exposure upon waking. Adequate daytime light exposure is a critical issue in AD, especially

for institutionalized individuals. Studies have reported that median daily bright light exposure in nursing home residents with dementia was only 1 min on average, and 47% of demented residents were never exposed to light greater than 1000 lux (equivalent to an overcast day) [42,93]. More regular light exposure could help better entrain dysfunctional circadian rhythms in AD, and possibly decrease the incidence of 'sundowning'. Light exposure is an effective, low-risk, noninvasive intervention that would be relatively easy for most patients to implement.

Other nonpharmacological treatments for improving sleep in AD are promising. One recent large, prospective study from Italy examined acupressure effects on insomnia in 129 institutionalized patients with AD and found significant improved sleep by questionnaire/self-report [94]. To date, however, there are no other published interventions examining acupuncture, meditation or alternative therapies in improving sleep in AD, although arguably these interventions pose little harm and could potentially benefit individual patients.

Pharmacological treatments have been sought to alleviate sleep issues in AD, although practitioners have been reticent to prescribe traditional hypnotics in such populations at risk for confusion and falls such as AD. There are no published randomized controlled trials for drugs commonly prescribed for sleep problems including those in the benzodiazepine and nonbenzodiazepine hypnotic classes. As alternatives to traditional hypnotics, three drugs have been tested in randomized controlled trials with the primary aim of improving sleep in individuals with AD: melatonin, trazodone and ramelteon [95]. The melatonin and trazodone trials included patients with moderate-to-severe AD, whereas the ramelteon study included only mild-to-moderate AD. Melatonin has been tested in a number of clinical trials in AD. All primary sleep outcomes were measured using actigraphy. Although no serious adverse effects were reported, overall there was no evidence that melatonin or ramelteon improved sleep outcomes [96–100]. The small study using trazodone at 50 mg nightly for 2 weeks (n = 30 patients) showed modest improvements in total sleep time and sleep efficiency, but did not improve sleep fragmentation, daytime sleep, cognition or activities of daily living [101]. Clearly, there is a dearth of evidence to help guide pharmacological treatment of sleep disturbances in AD. This is an area of great need for more comprehensive clinical trials, and especially those trials that examine not only sleep outcomes, but also cognitive or pathological outcomes in AD.

Lastl, it is also generally recommended to treat any known underlying sleep disrupters comorbid with AD. These include common sleep disorders such as obstructive sleep apnea, restless legs syndrome and circadian phase shift disorders.

Continuous positive airway pressure (CPAP) is a safe and effective treatment for obstructive sleep apnea (OSA), a common disorder in aged individuals as well as in AD. Several studies, including a randomized controlled study, have shown significant cognitive benefit in AD with CPAP treatment of comorbid OSA, a disorder that causes sleep fragmentation [102–105]. These studies are consistent with the hypothesis that sleep–wake disturbances contribute to AD symptomatology, and that treatment of sleep disturbances may improve some features of AD, but much still remains to be determined regarding whether amyloid or tau pathology is affected, and whether long-term morbidity and mortality outcomes are improved with CPAP.

Conclusion & future perspective

In conclusion, sleep–wake disturbances, including reduced night-time sleep, sleep fragmentation, nocturnal wandering or 'sundowning', and excessive daytime sleepiness are common and often debilitating features in dementia due to AD. Sleep–wake disturbances may be one of the earliest symptoms in preclinical AD and often precede cognitive symptoms. Evidence from animal and human studies suggests that AD pathology itself, including the presence of amyloid plaques and tau tangles, disrupts the sleep–wake cycle. Evidence from animal and human studies also suggests that prolonged wakefulness may increase levels of soluble amyloid-β in the brain, and in turn, exacerbate AD pathology.

Possible mechanisms underlying the reciprocal relationship between the sleep–wake cycle and AD pathology and behavior include decreased neuronal activity during slow-wave sleep, deficits in resting state functional connectivity, glial-medicated circadian clearance of soluble Aβ, and sleep effects on the paravascular clearance of toxic proteins from the interstitial space, among other processes. However, many questions still remain with regard to the exact mechanisms underlying the relationship between sleep and AD.

Current approaches to therapy for sleep disorders are lacking in clear evidence-based clinical trials. Behavioral sleep practices such as sleep hygiene and bright light therapy, and the treatment of underlying comorbid sleep disrupters such as sleep apnea, restless legs syndrome and circadian phase shift disorders are recommended as a start.

In 5–10 years from now, we hope that there are more basic research studies elucidating the mechanisms for the direct effects of sleep disturbances on AD pathology, and randomized clinical trials in AD on commonly used drugs available for clinical sleep problems, with an emphasis on long-term cognitive and pathological outcomes. Rigorous scientific approaches to both the basic and clinical sides of the issue of sleep in AD will be essential to inform best clinical practices.

Financial & competing interests disclosure

This work is supported by the Portland VA Research Foundation and the American Sleep Medicine Foundation to MM Lim, NIH T32 HL007713 to JR Gerstner, and NIH 1P01NS074969-A1, P01 NS080675, PO1-AG03991, and an Ellison Medical Foundation Senior Scholar Award to DM Holtzman. MM Lim is a Staff Physician in the Department of Veterans Affairs and has also received support from the Research and Development Service at the Portland VA Medical Center. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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• of interest; •• of considerable interest.

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• **This seminal study was the first to measure production and clearance rates of amyloid-β *in vivo* in the human CNS, and set the stage for several subsequent studies examining the role of sleep on cerebrospinal fluid (CSF) amyloid-β levels in humans.**

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• **This study was the first to investigate the hypothesis that amyloid plaques act as an amyloid-β-42 'sink', and found that brain amyloid imaging (measured using PIB in PET) results in low CSF amyloid-β-42. Thus, amyloid imaging and CSF amyloid-β-42 may be reliable antecedent biomarkers of preclinical Alzheimer's disease (AD).**

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