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Targeting sleep and circadian function in the prevention of Alzheimer Disease

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State of the field

The accelerating pace of research on the link between sleep or circadian function and Alzheimer Disease (AD) has raised the possibility of targeting sleep or circadian behaviors to mitigate AD risk. Sleep and circadian functions are separate but intertwined, in that circadian mechanisms coordinate physiological functions to the 24-hour clock for optimal function, including sleep-wake state. Accumulating data support a bi-directional relationship between AD pathology and sleep-circadian function. Even during the 15+ year "preclinical" pre-symptomatic stage of AD, decreased sleep quality and fragmented circadian rhythms are associated with AD pathology.[1,2] Conversely, sleep-circadian dysfunction, particularly slow-wave sleep disruption, elevates levels of amyloid-beta (Aβ) and tau.[3–5] Large longitudinal studies show that obstructive sleep apnea and insufficient sleep increase risk of cognitive impairment.[6,7] Given the high prevalence of sleep-circadian dysfunction—an estimated 1 billion individuals have OSA, and 40% in a large survey reported insufficient sleep[7,8]—sleep-circadian function may be a high-impact target for intervention as a modifiable AD risk factor.

Despite the clear clinical need for therapeutic strategies to address sleep-circadian dysfunction, at the bedside we are stymied by lack of screening tools, prognostic markers, and most importantly, treatments to offer patients. In mice, orexin (hypocretin) receptor antagonists mitigated amyloid plaque formation,[4] and while these medications are FDA-approved for insomnia, there have been no trials examining the effects of these or any other sleep-circadian therapies on AD biomarkers and outcomes. Treatment with positive airway pressure (PAP) for OSA has shown only very modest effect on neurocognitive function in cognitively-normal or -impaired individuals.[9,10] Otherwise, there is a wide gap between bench and bedside. Here, we provide recommendations for advancing and translating sleep-circadian science into new strategies for AD prevention and treatment.

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Basic Research

Major basic science questions remain unanswered regarding the interactions between sleep and AD pathogenesis. Sleep deprivation increases amyloid and tau pathology in mice, but it remains uncertain if sleep alters brain *production* or *clearance* of Aβ and tau, or both.[11–13] Sleep-circadian dysfunction may impact other pathways that contribute to AD, including neuroinflammation, proteostasis, and synaptic health, but exact mechanisms are unknown. It is also unclear which aspect of sleep, such as sleep duration, specific sleep stage(s), consolidation/timing of sleep, slow wave sleep, or other variables are most critical in AD pathogenesis. Understanding molecular mechanisms by which OSA contributes to AD might also facilitate molecular therapies which could be used in combination or in lieu of PAP. Finally, therapies directly targeting circadian functions require development and translation. Ideally, future therapies would directly target or augment sleep/circadian-mediated mechanisms, without necessarily inducing sleep.

Clinical Research

Clinical studies need to account for the bi-directional nature of AD pathology and sleep-circadian function, and the long preclinical stage of AD. To demonstrate a causal relationship between sleep-circadian dysfunction and AD, studies must either 1) assess sleep-circadian phenotypes 20+ years prior to cognitive symptom onset; or 2) detect preclinical AD using biomarkers in longitudinal studies that include sleep-circadian measures. One study reported that insufficient sleep during midlife increased risk of AD up to 25 years later, suggesting that sleep problems contribute to AD pathogenesis,[7] otherwise, there are no published studies appropriately-designed to determine causality. Certainly, sleep-circadian measures should be added to existing longitudinal studies of aging and dementia, and studies should aim to enroll diverse cohorts, to asses for any racial/ethnic effects on the sleep-AD relationship.

Methods for sleep-circadian measurement require further development, validation, and consensus. A shift away from subjective questionnaires and toward objective measures is needed, though gold-standard methods such as polysomnography and dim light melatonin onset are cumbersome to implement. Actigraphy is an attractive option, as it is easy to deploy in larger populations and provides data on both sleep and circadian rhythms, though it does not directly measure either. Emerging technologies such as home electroencephalography, wearables, home OSA diagnosis, and “smart” devices hold great promise. However, all of these methods need thorough validation across diverse populations. Open and consistent data access, formats, and analysis methods are also needed to facilitate pooling and sharing of data across studies. The lack of biologically-based biomarkers for sleep-circadian functions hampers research by forcing reliance on direct measurement, and a critical need exists for development of such biomarkers, including transcriptomic and proteomic approaches. Finally, genetic approaches such as Mendelian Randomization have potential to identify causative genetic links between sleep and AD risk.

Clinical Trials and Implementation

While the therapeutic pipeline targeting sleep/circadian mechanisms is growing, such as orexin antagonists or slow-wave sleep enhancement, no human studies have examined the effect on AD-related biomarkers, disease risk, or progression of cognitive symptoms and functional status. For circadian disorders, melatonin (and its agonists) and light exposure are currently mainstays of therapy but have limited effect in symptomatic AD. Trials assessing the impact of these and other more traditional sleep-circadian therapies (such as CBT for insomnia or CPAP for OSA) on AD-related outcomes could be done immediately and have immense clinical impact. Sleep-circadian disturbance in dementia is extremely challenging to treat, particularly balancing effective treatment of insomnia without daytime sedation. The recent approval of suvorexant for insomnia in AD is a step forward, but further drug development in this area is needed.

Greater implementation efforts are required to take the emerging science on the sleep-circadian and AD relationship to benefit at the societal level. Hospitals and other institutions need to promote policies to promote sleep-circadian health, such as optimizing light exposure and limiting disturbances during sleep. For neurologists seeing patients with memory concerns, it is vital to assess for sleep hygiene habits (including use of antihistamines or alcohol for self-medication of insomnia) and OSA that may be contributory. The absence of effective screening measures for sleep-circadian dysfunction is a problem, and in parallel, educational messaging is needed to publicize a normal/optimal range for sleep behaviors: as consumer-targeted sleep wearables have gained traction, orthosomnia (an unhealthy preoccupation with sleep) has emerged as a new source of sleep disruption. Expert, evidence-based guidelines for sleep-circadian health behaviors, screening, treatment, and monitoring are needed, with attention to effectively communicating with the layperson, who will ultimately be responsible for their daily (or nightly) sleep practice.

Summary

A growing body of evidence supports the link between sleep-circadian function and AD risk. A “tsunami” of AD looms in the coming 20–30 years, and sleep-circadian therapies that reduce AD risk would monumentally benefit societal health. To achieve such a goal, researchers in this area must intentionally adopt strategies to translate science efficiently and collaboratively into clinical trials and public implementation.

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References

1. Ju YE, McLeland JS, Toedebusch CD, et al. Sleep quality and preclinical Alzheimer disease. JAMA Neurol. 2013;70(5):587–593. doi:10.1001/jamaneurol.2013.2334 [PubMed: 23479184]
2. Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju YE. Circadian Rest-Activity Pattern Changes in Aging and Preclinical Alzheimer Disease. JAMA Neurol. 2018;75(5):582–590. doi:10.1001/jamaneurol.2017.4719 [PubMed: 29379963]
3. Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science. 2019;363(6429):880–884. doi:10.1126/science.aav2546 [PubMed: 30679382]
4. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science. 2009;326(5955):1005–1007. [PubMed: 19779148]
5. Ju YS, Ooms SJ, Sutphen CL, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-beta levels. Brain. 2017. doi:doi: 10.1093/brain/awx148
6. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011;306(6):613–619. doi:10.1001/jama.2011.1115 [PubMed: 21828324]
7. Sabia S, Fayosse A, Dumurgier J, et al. Association of sleep duration in middle and old age with incidence of dementia. Nat Commun. 2021;12(1):2289. doi:10.1038/s41467-021-22354-2 [PubMed: 33879784]
8. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin JL, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019 Aug;7(8):687–698. doi: 10.1016/S2213-2600(19)30198-5. Epub 2019 Jul 9. PMID: 31300334; PMCID: PMC7007763. [PubMed: 31300334]
9. Kushida CA, Nichols DA, Holmes TH, Quan SF, Walsh JK, Gottlieb DJ, Simon RD Jr, Guilleminault C, White DP, Goodwin JL, Schweitzer PK, Leary EB, Hyde PR, Hirshkowitz M, Green S, McEvoy LK, Chan C, Gevins A, Kay GG, Bloch DA, Crabtree T, Dement WC. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep. 2012 Dec 1;35(12):1593–602. doi: 10.5665/sleep.2226. Erratum in: Sleep. 2016 Jul 1;39(7):1483. PMID: 23204602; PMCID: PMC3490352. [PubMed: 23204602]
10. Richards KC, Gooneratne N, Dicicco B, Hanlon A, Moelter S, Onen F, Wang Y, Sawyer A, Weaver T, Lozano A, Carter P, Johnson J. CPAP Adherence May Slow 1-Year Cognitive Decline in Older Adults with Mild Cognitive Impairment and Apnea. J Am Geriatr Soc. 2019 Mar;67(3):558–564. doi: 10.1111/jgs.15758. Epub 2019 Feb 6. PMID: 30724333; PMCID: PMC6402995. [PubMed: 30724333]
11. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013;342(6156):373–377. doi:10.1126/science.1241224 [PubMed: 24136970]
12. Lucey BP, Hicks TJ, McLeland JS, et al. Effect of sleep on overnight CSF amyloid-beta kinetics. Ann Neurol. 2017. doi:10.1002/ana.25117
13. Eide PK, Vinje V, Pripp AH, Mardal KA, Ringstad G. Sleep deprivation impairs molecular clearance from the human brain. Brain. 2021;144(3):863–874. doi:10.1093/brain/awaa443 [PubMed: 33829232]

Table 1:

Recommendations for sleep and circadian research aimed at the prevention or treatment of Alzheimer Disease (AD)

	No AD pathology	Preclinical (asymptomatic) AD	Symptomatic AD
Basic research	Identify mechanisms linking sleep to Aβ/tau production/ clearance	Examine effect of different sleep/circadian-promoting drugs or interventions on tau aggregation, inflammation, synaptic function, other degenerative processes in preclinical models.	
Clinical research	Longitudinal (20 + years) followup studies	AD biomarker assessment regardless of cognitive status	Test effect of existing treatments on cognitive outcomes, with specific attention to safety & tolerability
	Objective measures of sleep and circadian function	Objective measures of sleep and circadian function	
	Analytic methods for non-linear risk factors (e.g. sleep time)	Assess for obstructive sleep apnea and other sleep disorders	Identify and test new non-sedating therapies for sleep-circadian disruption in dementia patients
	Assess for obstructive sleep apnea and other sleep disorders	Test effect of existing treatments (ex: PAP for OSA; medication for insomnia) on AD markers	
	Genetic, race/ethnicity	Genetic, race/ethnicity	
	Sleep-circadian biomarkers		
Trials and implementation	Screening measures for abnormal sleep/circadian function		
	Tractable markers of abnormal sleep/circadian dysfunction		
	Determination of a goal range.		
	Education and outreach		