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Sleep Disturbance, Cognitive Decline, and Dementia: A Review

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Abstract

Approximately half of older people report sleep disturbances, which are associated with various health conditions, including neurodegenerative disease and dementia. Indeed, 60 to 70% of people with cognitive impairment or dementia have sleep disturbances, which are linked to poorer disease prognosis. Sleep disturbances in people with dementia have long been recognized and studied; however, in the past 10 years, researchers have begun to study disturbed sleep, including sleep fragmentation, abnormal sleep duration, and sleep disorders, as risk factors for dementia. In this review the authors summarize evidence linking sleep disturbance and dementia. They describe how specific aspects of sleep (e.g., quality, duration) and the prevalence of clinical sleep disorders (e.g., sleep-disordered breathing, rapid eye movement sleep behavior disorder) change with age; how sleep parameters and sleep disorders are associated with the risk of dementia; how sleep can be disturbed in dementia; and how disturbed sleep affects dementia prognosis. These findings highlight the potential importance of identifying and treating sleep problems and disorders in middle-aged and older adults as a strategy to prevent cognitive decline and dementia. The authors also review recent evidence linking sleep disturbances to the pathophysiology underlying dementing conditions, and briefly summarize available treatments for sleep disorders in people with dementia.

Keywords

Sleep; aging; dementia

Sleep changes across the adult life course and, in recent years, disturbed sleep has been linked with several diseases common in older adults, including neurodegenerative disease and dementia. Here, we review changes in sleep related to aging, sleep disturbances in persons with cognitive impairment and dementia in general (i.e., all-cause dementia) and

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with particular dementias—namely Alzheimer's disease (AD) and Parkinson's disease (PD). We also summarize findings from studies in the general population of older adults linking sleep disturbances to cognitive performance, decline, and dementia, and to the pathology underlying particular dementias. We close with a brief discussion of strategies for diagnosing and treating sleep problems in persons with dementia. Although there are still gaps in the literature, the available evidence suggests that the association between sleep disturbance and dementing illness is bidirectional, and that sleep disorders should be considered when treating older adults with dementia—and perhaps when developing strategies for reducing dementia risk.

Aging and Sleep

Studies in healthy individuals suggest that objectively measured total sleep time (TST), sleep latency (SL), slow wave sleep (SWS), wake after sleep onset (WASO), and rapid eye movement (REM) sleep decrease across adulthood, but that only sleep efficiency (SE; % of time in bed spent sleeping) continues to significantly decrease in adults aged 60 and older.[1] However, epidemiological evidence indicates that approximately half of the general population of older adults report disturbed sleep, including shorter TST, low SE, longer SL, and greater WASO, and that greater medical morbidity is associated with greater sleep disturbance.[2]

Sleep and circadian rhythms are complex processes, regulated by dynamic interactions among genes, neural circuits, and the environment. Briefly, sleep is classified into four stages: non-REM stages 1 to 3 and REM sleep.[3] Although multiple regions are involved in the regulation of sleep/wake states, two nuclei implicated in age- or dementia-related changes in sleep are the ventrolateral preoptic area (VLPO) in the anterior hypothalamus and the suprachiasmatic nucleus (SCN).[4] Galaninergic and GABAnergic neurons in the VLPO send inhibitory projections to arousal areas during sleep,[4] and evidence from animal models show that the VLPO promotes sleep maintenance, and that lesions in this area result in sleep fragmentation patterns similar to those observed in AD.[4,5] The SCN acts as the central circadian pacemaker, and is therefore critical to the timing of sleep. External cues or "zeitgebers" (primarily light) act through the SCN to entrain circadian rhythms in the central nervous system and peripheral tissues.[6] Older adults' circadian rhythms are not as strongly "entrained" as in younger people, meaning their diurnal sleep/wake patterns are not as tightly synchronized to external cues (typically light–dark cycles).[7] This has been attributed to declining eye lens opacity and clarity with age, reduced exposure to bright light, and degeneration of the SCN.[7] However, evidence also suggests that older adults have more fragmented endogenous circadian rhythms than younger people,[8] which may be associated with greater degeneration of the SCN.[9] Disrupted circadian rhythms, through their impact on sleep, mood, and memory, have been linked with poorer cognition and risk of cognitive impairment.[10]

Sleep and All-Cause Cognitive Decline and Dementia

Disturbances of sleep and wake are especially common among people with dementia. As many as 70% of patients in early-stage dementia have sleep disturbances.[11] Sleep

disturbance in people with dementia is predictive of poorer outcomes, including more severe cognitive and neuropsychiatric symptoms, and poorer quality of life.[11–18] Among institutionalized dementia patients, sleep–wake cycles can be so disrupted that they are neither continuously awake or asleep for a full hour during a 24-hour period.[19] Even among older women without dementia, declining cognition is associated with poorer objectively measured sleep quality at follow-up.[20]

In addition to being prevalent in persons with dementia, poor sleep and altered circadian rhythms are common in healthier older populations. Moreover, these disturbances are associated with an increased risk of adverse cognitive outcomes, suggesting a possible causal link from disturbed sleep to cognitive decline. Furthermore, short sleep duration,[21–27] long sleep duration,[21,23,24,26,28,29] and changes in sleep duration[30,31] have all been linked to poorer cognitive performance and risk of dementia. Overall, there appears to be a U-shaped association between sleep duration and cognitive impairment, whereby both short and long sleep are associated with poorer cognition.[32] Various mechanisms have been proposed to explain how short or insufficient sleep could lead to cognitive impairment and decline (see below), but it is unclear which physiological or biological mechanisms may be linking longer sleep duration to dementia risk. Longer sleep duration may be an early marker of dementia, with a confounder (e.g., apnea, depression) driving both development of cognitive impairment and an increased sleep need.[33] Importantly, both sleep duration and sleep quality in midlife have been linked to poorer cognitive function in later life,[34] although we do not currently know how the timing of poor sleep in the life course differentially affects cognitive outcomes.

Sleep disordered breathing (SDB), including obstructive sleep apnea (OSA), is among the most common clinical sleep disorders, affecting ~60% of older adults, with higher rates among men.[35–39] An estimated 70 to 80% of people with dementia may have sleep apnea, and SDB severity increases with dementia severity, raising the possibility of a positive-feedback loop in which dementing illnesses exacerbate SDB, and vice versa.[40] Obstructive sleep apnea is also linked with poorer attention, executive functioning, visuospatial and constructional abilities, and psychomotor speed in nondemented persons.[41–43] In prospective longitudinal studies, OSA has been associated with a 2 to 6 times greater risk of mild cognitive impairment (MCI) or dementia,[44,45] and earlier onset of MCI or dementia.[46] Moreover, subjectively measured excessive daytime sleepiness, a common symptom of SDB, has been associated with subsequent cognitive decline,[47] perhaps suggesting that complaints about sleep quality are an early marker of cognitive decline.

The association of sleep quality, quantity, and sleep-disordered breathing with all-cause cognitive impairment may be mediated by a range of processes. For example, sleep disturbances have been linked to cortical thinning, a marker of cortical atrophy found in many dementia subtypes.[48,49] In a cross-sectional study of 141 cognitively normal community-dwelling older adults (median age = 82.9 years), decreased cortical thickness in the lateral orbitofrontal cortex and inferior frontal gyrus was associated with increased sleep fragmentation as measured by an Actigraph (a wrist-worn device that records movement over several days that uses a polysomnographically validated algorithm to assess sleep–wake patterns).[50,51] Further, among older adults without cognitive impairment (mean age = 66.6

years at baseline), self-reported sleep duration, ≤ 6 hours or ≥ 8 hours (i.e., short or long sleep duration) was associated with more rapid subsequent cortical thinning in frontotemporal regions over an average of 8 years.[52] Shorter sleep duration has been associated with a greater rate of ventricular enlargement, which similarly reflects loss of brain volume.[53] Shorter sleep duration may also contribute to cognitive decline via degeneration of the hippocampus through multiple pathways, including changes in neuronal excitability, decreasing synaptic plasticity, and decreasing neurogenesis.[54,55]

Similarly, sleep apnea has been associated with multiple brain changes, including magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) measures of loss of regional volume and white matter integrity in the hippocampus, cingulate cortex, and some cerebellar regions.[56–60] Sleep disordered breathing is also associated with a greater risk of developing cerebrovascular pathology. Specifically, moderate-to-severe OSA is associated with twice the risk of white matter hyperintensities (WHMs), and a greater apnea–hypopnea index has been positively correlated with the severity of WHM burden.[60,61] Even among younger adults, OSA was associated with greater fractional anisotropy (FA) in subcortical tracts of the superior and inferior parietal lobe, measured by DTI, suggesting reduced white matter integrity.[62] Obstructive sleep apnea is also a risk factor for stroke, bradycardia, supraventricular tachycardia, ventricular tachycardia, and atrial fibrillation,[63–66] all of which are risk factors for dementia.[67]

In summary, sleep disruption, sleep duration, and sleep disorders—specifically SDB—all may increase the risk of all-cause cognitive decline and dementia. Conversely, populations with clinical levels of cognitive decline, including AD, exhibit an elevated rate of sleep disturbances. A bidirectional link appears to exist between disturbed sleep and dementia.[68]

Disturbed Sleep and Dementia Subtypes

In addition to the associations with all-cause cognitive decline and dementia described above, poor sleep and sleep disorders (e.g., insomnia, SDB, REM sleep behavior disorder [RBD]) have been identified in relation to particular dementia subtypes. Here, we review two: AD- and PD-related dementias.

Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia, accounting for ~80% of all cases.[69] Alzheimer's disease is characterized by progressive memory loss particularly in the domain of episodic recall, often accompanied by decline in other cognitive domains, and eventual functional decline and death.[69] Its primary neuropathological features are amyloid-β (Aβ) plaques, neurofibrillary tangles, and subsequent neurodegeneration.[70] Approximately two-thirds of persons with AD have sleep-related problems,[40,71] such as frequent daytime napping, nighttime wakefulness, and sundowning (i.e., agitation and disruptive behaviors that occur in the evening or night).[72] Among AD patients, disrupted sleep is associated with poorer daily functioning, aggression, and agitation, even in those with mild severity of AD.[73] Actigraphy studies in community-dwelling persons with AD show deterioration of rest-activity cycles begins early in dementia and progresses with the disease course.[74]

Conversely, disturbed sleep parameters have also been linked to an increased risk of subsequently developing AD. Self-report of shorter sleep duration (≤ 5 hours) is associated with 2.4 times the odds of AD, and self-reported longer sleep duration (≥ 9 hours) is associated with 2.8 times the odds of AD.[75] Further, in a community-based sample, greater actigraphic-measured sleep fragmentation was associated with a greater risk of incident AD over approximately 3 years, and that those with the most sleep fragmentation had a 50% greater risk of developing AD compared with those with the least fragmentation.[76] Additionally, it was found that more consolidated (i.e., less fragmented) sleep decreased the elevated risk of developing AD attributable to the APOE ε4 allele over an average of 3 years.[77] Insomnia symptoms have also been associated with an increased risk of MCI or AD, with rates ranging from approximately 2 to 3 times above older adults without insomnia.[78,79] Although these studies show altered sleep duration, sleep fragmentation, and insomnia precede MCI or AD diagnosis, these sleep disturbances may be an early marker of cognitive impairment, especially because AD pathology can develop decades prior to diagnosis.[70] These findings suggest that disturbed sleep may causally promote development of AD or may be an early marker of the disease. Importantly, they also suggest that good sleep may protect against AD.

Some of the associations between sleep and dementia discussed above in the Sleep and All-Cause Cognitive Decline and Dementia section may be explained by studies that show mechanistic links between sleep and AD-related pathology. For instance, sleep disturbances have been robustly associated with Aβ dynamics and deposition. In a study by Kang et al, levels of Aβ in brain interstitial fluid (ISF) were positively correlated with the amount of time spent awake, but negatively correlated with the amount of time spent asleep in a transgenic mouse model of AD; moreover, humans exhibited a similar fluctuation of cerebrospinal fluid (CSF) Aβ levels.[80] Attenuated Aβ diurnal patterns were also observed in the CSF of young adult human participants with presenilin mutations.[81] The connection between sleep and Aβ has also been supported by community-based cohort studies showing that both self-reported and objectively measured sleep disturbances are associated with greater cerebral Aβ deposition, as measured by [^{11}C] –Pittsburgh compound B-positron emission tomography (PiB-PET)[82] and lower CSF Aβ levels (which is generally associated with greater brain burden of Aβ[83]), respectively.[68] Findings from *Drosophila* models show sleep deprivation causes excessive neuronal excitability, which results in greater Aβ accumulation,[84] implicating neuronal excitability in the pathogenesis of AD.[85]

Alternatively, it has been suggested that the association between sleep and Aβ is driven by dysfunction of the recently discovered “glymphatic system.” The glymphatic system is a macroscopic waste clearance system that functions through the exchange of CSF and ISF through channels formed by astroglial cells.[86,87] It is thought that this system may be important for removing toxic aggregates associated with neurodegenerative disease, such as Aβ, from the brain.[88] Glymphatic system function decreases by as much as 80 to 90% in aged mice compared with young mice.[89] This further implicates the glymphatic system in neurodegenerative disease development because age is the strongest risk factor for neurodegenerative disease.[86,87] Importantly, the activity of the glymphatic system increases substantially during sleep, likely because interstitial space increases by 10% during sleep, potentially due to shrinkage of astroglial cells.[90] This suggests that sleep could be central to

preventing Aβ accumulation, and possibly AD and other neurodegenerative diseases. For an excellent, more detailed review of how sleep disruption may promote the development of AD, please see the recent publication by Mander and colleagues.[91]

Evidence has also indicated that changes in circadian rhythms are associated with AD. People with AD, as compared with nondemented older adults, have disrupted circadian rhythms as evidenced by greater nighttime activity,[92,93] a phase delay,[93,94] and disrupted endogenous core body temperature rhythms.[92,95] Moreover, disrupted circadian rhythmicity, measured over a 72-hour period prior to death, has been linked to greater SCN degeneration.[96] Additionally, people with AD have been shown to have greater SCN degeneration on autopsy compared with cognitively intact elderly, supporting the notion that disrupted circadian rhythms are the result of SCN degeneration in AD.[96] Relatedly, among people with AD, greater actigraphically measured sleep fragmentation has been associated with a decreased number of galanin-immunoreactive neurons in the VLPO on autopsy.[97] Although it remains unclear whether circadian rhythms are disrupted due to neurodegeneration of the SCN and/or VLPO or due to disrupted processing of endogenous cues (e.g., limited bright light exposure), circadian rhythm disruption has a negative impact on sleep and function in people with AD and may put cognitively normal people at risk for developing dementia.[98]

Finally, the high prevalence of OSA among people with AD[99] and evidence linking OSA with Alzheimer's pathology suggests that OSA may affect core AD mechanisms. Indeed, the strength of the association and mechanistic links between OSA and AD has even caused some researchers to identify OSA as a prodromal stage of AD.[100] Specifically, hypoxia has been associated with AD pathology. In cellular and murine models, chronic hypoxia increases Aβ plaque formation,[101] and acute hypoxia has been shown to increase tau phosphorylation.[102] In cognitively normal adults, OSA has been associated with lower CSF levels of Aβ and tau;[103] however, others have shown that this association was significant only among those with the APOE ε3 allele.[104] Further, a pilot study that measured cerebral Aβ deposition using PiB-PET imaging found that SDB was associated with greater Aβ burden only among participants with MCI.[105] More research, particularly prospective research, is needed to better understand the association between SDB and AD-associated pathology.

Parkinson's Disease and Related Conditions

Parkinson's disease is a neurodegenerative disease defined by dopamine deficiency. Parkinson's disease affects ~2% of adults over age 65,[106] and is characterized by bradykinesia, rigidity, tremor, and disrupted gait. Several nonmotor symptoms are also common in PD, including neuropsychiatric symptoms, fatigue, gastrointestinal symptoms, and cognitive decline.[107,108] Approximately 50 to 80% of PD patients will develop PD dementia (PDD).[106] Parkinson's disease dementia is caused by the aggregation of the protein α-synuclein, deposits of which are known as Lewy bodies (DLBs).[106]

Sleep problems are also very common in PD, affecting 60 to 95% of patients,[109–111] and are associated with longer disease duration and severity.[112–114] Excessive daytime sleepiness, insomnia, and REM sleep behavioral disturbances are some of the most common complaints.[115] Sleep disturbances in PD are strongly linked with nonmotor and motor

symptoms alike. Cross-sectional evidence has shown that among people with PD, excessive daytime sleepiness is associated with poorer cognition and pupillomotor disorders,[116,117] whereas nighttime sleep problems have been associated with thermoregulatory symptoms.[117] Both daytime sleepiness and nighttime disturbances are associated with fatigue, depression, urinary tract infections, cardiovascular conditions, and dopamine agonist treatment. These findings support evidence from other cross-sectional studies investigating insomnia in PD.[117–122] One recent longitudinal study among 421 people with PD found that, over an average of 4.6 years, insomnia was more common with longer duration of PD and in women.[123] Further, depressive symptoms and dopamine agonists were risk factors for developing insomnia; motor symptoms and sleep medication use were associated with more severe insomnia. Because in PD sleep problems may perpetuate other PD symptoms and vice versa, identifying and addressing sleep disturbances can be critical for patient quality of life and, potentially, prognosis.

Perhaps unsurprisingly, motor-related sleep disorders are among the most common frank disorders in PD. For instance, restless leg syndrome (RLS) is prevalent among 15% of people with PD.[115] In untreated PD, RLS prevalence rates are similar to those in the general population; however, due to augmentation of RLS symptoms by PD medications, prevalence rates are higher in treated PD, with some studies suggesting nearly a fourfold increase.[124] It has been hypothesized that dopamine agonist treatment is associated with RLS through overstimulation of dopamine receptors.[125] Sleep disordered breathing is also common in PD patients, with prevalence estimates ranging from 20% to nearly 70%.[126] People with PD and OSA have been shown to have poorer cognitive function than people with PD without OSA.[127] Findings that OSA is common in PD are not unexpected given that upper airway and pulmonary obstruction are often observed in PD.[128,129]

Rapid eye movement sleep behavioral disorder is strongly associated with PD and dementia with DLBs. People with RBD have impaired skeletal muscle atonia, resulting in significant motor activity (i.e., acting out violent dreams) during REM sleep.[130,131] Epidemiological studies on RBD prevalence are lacking, but current estimates suggest prevalence is ~0.5%.[132] It is most commonly diagnosed between ages 40 to 70,[133,134] is strongly associated with PD-related disorders (i.e., PD, multiple systems atrophy [MSA]), and may be a prodrome of those diseases.[130] In retrospective studies, 50 to 80% of people with DLBs had RBD,[135] 30 to 60% of people with PD had RBD,[136,137] and 80 to 95% of those with MSA had RBD prior to diagnosis with these neurodegenerative conditions.[138,139] Prospectively, RBD is associated with a 20% 5-year, 40% 10-year, and 52% 12-year risk of developing a neurodegenerative disease.[134] Notably, RBD is also commonly diagnosed after the onset of PD, and is prevalent in both early and later stages of PD.[140,141] Though the mechanisms linking RBD and DLB have not yet been fully elucidated, patients with RBD without dementia should be monitored for signs of DLBs and PD-related disorders.[130,142] Further details about RBD are available in reviews from Jennum and colleagues[142] and Boeve.[130]

Beyond the proposed mechanistic link between RBD and DLBs, other pathological facets of PD are implicated in sleep disturbances. Alpha-synuclein aggregation, in addition to its role in RBD, may decrease neuronal firing in the SCN, reducing its ability to regulate circadian rhythms and thereby affecting sleep.[143] Further, degeneration of the hypothalamus is also

observed in PD,[144] and may disrupt SCN functionality and decrease melatonin production,[145,146] which is more disrupted in PD patients with excessive daytime sleepiness.[147] Multiple areas affecting sleep–wake regulation (e.g., cholinergic pedunculopontine nucleus, serotonergic tegmental area, nucleus magnocellularis, and noradrenergic locus coeruleus) are also deteriorated in PD and may also contribute to sleep problems.[148,149] Finally, dopamine is key for maintaining wakefulness and regulating sleep homeostasis,[150] and mediates circadian signals via the SCN.[151,152] Therefore, the characteristic decline in dopaminergic neurotransmission in PD is thought to be a cause of many sleep problems associated with the disease.

Assessment and Treatment of Sleep Disorders in Dementia

Diagnosing sleep problems in people with dementia can be difficult due to impaired memory and lack of insight.[69,153] Therefore, it is important to interview both patients and caregivers.[154] During these interviews, bed and wake times and bedtime routines should be reviewed. It should also be noted that sleep problems in people with dementia are associated with burden in caregivers of persons with dementia, in particular spousal caregivers.[11,155] Indeed, sleep disruption in dementia patients relating to caregiver burden has been found to be a primary reason for placing people with dementia in nursing homes,[155,156] so identifying and treating sleep disruption in dementia can be crucial to the well-being of patients and caregivers. We have summarized our recommendations in ►Table 1 and for more details, see a recent extensive review by Ooms and Ju.[157]

Treating Insomnia

Although both pharmacological and nonpharmacological interventions are widely used in clinical practice to treat insomnia in dementia, there are few rigorous clinical trials to inform clinicians' choices. The most important consideration in pharmacological interventions is to balance the considerable risks of psychotropic medications in demented patients. For example, many of the Food and Drug Administration-approved medications for insomnia are benzodiazepines. These drugs have many risks for adverse effects in dementia, including addiction, gait instability, worsening cognition, and drug–drug interactions, and their use is generally discouraged. A newer class of related drugs (zaleplon, zolpidem, and zopiclone) has not been studied in dementias, nor has the orexin antagonist suvorexant. The most commonly used drug for insomnia is AD is trazodone, an older antidepressant that may improve sleep onset at low doses through its sedative effect. Adverse effects from trazodone (including priapism, sedation, and orthostatic hypotension) are not common at low doses (25–50 mg) in demented patients, and there is no apparent risk of addiction. Trazodone may improve circadian cycle and sleep parameters in AD, and given its benign adverse event profile it is widely used.[158,159] There is evidence for sleep improvement in AD with the use of the second-generation antipsychotic risperidone.[160–162] However, the use of antipsychotics in AD is quite controversial due to increased mortality risk, and their use is necessarily limited.[163,164] Another medication is the antidepressant mirtazapine, which has been reported to benefit sleep in AD as a secondary outcome of an randomized controlled trial targeting depression.[165]

The agent melatonin is available over-the-counter and noted to have minimal adverse events in older adults. A recent meta-analysis of randomized controlled trials of melatonin use in people with dementia found that, compared with placebo, melatonin improved SE, TST, and global cognitive performance, and that very few adverse events occurred.[166] However, others have reported null effects,[167,168] perhaps due to the significant reduction of melatonin receptors in the SCN among people with dementia.[169] It should be noted that exogenous melatonin is a chronobiotic agent that alters circadian phase, and not a pharmaceutical developed specifically for the treatment of insomnia.[170]

Although many nonpharmacological treatments for insomnia in dementia have been investigated, bright-light therapy may be especially important because older adults with dementia have very little bright light exposure.[171] Lack of bright light exposure negatively impacts sleep and circadian rhythms, and is linked with other negative outcomes (e.g., poorer cognition, neuropsychiatric symptoms).[172] People with dementia who have insomnia or insomnia symptoms may also benefit from reducing or eliminating caffeine and alcohol consumption, refraining from drinking near bedtime (to avoid or reduce nighttime trips to the bathroom), maintaining a dark and quiet bedroom, and avoiding napping during the day.[153,173] Physical activity regimens have also been shown to improve sleep in people with dementia-causing diseases.[174,175] Among persons with PD, deep brain stimulation, a common treatment for motor symptoms in PD, has also been shown to improve subjective and objective sleep quality, RLS, and SDB.[176] These findings suggest nonpharmacological approaches are effective and safe, with few studies reporting adverse events; therefore, they should be considered for management of both daytime and nighttime disturbances.

Treating Daytime Sleepiness

Similar to treatment for insomnia, melatonin has also been shown to improve daytime sleepiness and increase daytime activity.[177–180] Daytime sleepiness may also be alleviated by changing medication type and dosing.[154] Daytime sleepiness is common among people with dementia and is a particular problem in PD. A recent meta-analysis found that physical activity may improve daytime sleepiness, as well as several other symptoms (e.g., depression and cognition) thought to be associated with sleep disturbance in PD.[174] Evidence from studies investigating the impact of pharmacological treatments suggests that modafinil, and to a lesser extent caffeine and atomoxetine, can improve excessive daytime sleepiness in PD.[181] Overall, daytime sleepiness and nighttime sleep problems are often cyclically linked, with one problem exacerbating the other, so strategies aimed at addressing either problem may help alleviate the other as well.

Treating Sleep Disordered Breathing in Dementia

Sleep disordered breathing is generally treated with continuous positive airway pressure (CPAP) therapy. Persons with dementia who have SDB seem to tolerate CPAP at the same rate as nondemented SBD patients;[127,182] however, people with dementia with more neuropsychiatric syndromes may not tolerate CPAP as well.[36,127,182] Two smaller studies suggest that among people with AD and SDB, CPAP use may help improve cognition, mood, and sleepiness.[36,183] Additionally, CPAP has been shown to lead to increases in

hippocampal and cortical volume and blood oxygenation level-dependent signals in the prefrontal cortex and subcortical regions,[184–187] which could potentially improve cognition.

Treating REM Sleep Behavior Disorder

The most common and effective treatments for RBD include melatonin and/or clonazepam.[188–191] However, clonazepam may cause side effects (e.g., sedation, memory impairment, confusion), and should be used with caution, particularly in patients with cognitive impairment or OSA.[192] It is also important to remove potentially injurious objects from the bedroom, set alarms to be alerted if the patient opens a door or window, and create barriers to keep patients and their bed partners safe. People with RBD should consider avoiding substances and medications (e.g., some antidepressants, caffeine, and chocolate) that may exacerbate the condition. In particular, selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors have been shown to cause or exacerbate RBD in some patients.[193,194] Further details on RBD management strategies are available elsewhere.[130]

Limitations and Suggestions for Future Directions

Although the field of research investigating the links between sleep and dementia has grown substantially in the past 20 years, future studies are needed to further probe these relationships. First, there is a paucity of longitudinal evidence examining the association between sleep and dementia. In this review, of the studies conducted in humans assessing risk factors or potential therapies for sleep disorders, fewer than half of the studies had a longitudinal design. Therefore, it is difficult to make conclusions about the potential for disturbed sleep to cause or promote dementia pathology or vice versa—though likely both are true. Future studies with prospective longitudinal designs should investigate (1) how sleep impacts risk of incident dementia of specific subtypes, (2) how co-occurring sleep problems and dementia impact trajectories of sleep and dementia, and (3) whether treating sleep problems reduces dementia risk.

Recent research has begun to focus on the pathophysiological links between sleep and dementia (e.g., Mander et al, 2016[91]). These studies are crucial for understanding both the etiological contribution that sleep makes in the development of dementia, as well as how sleep disturbance may be a prognostic marker for trajectories of cognitive impairment and dementia. Additional studies focusing on the pathophysiology and biomarkers linking sleep and clinical dementia will be important for enhancing both our understanding of the association and potential interventions for sleep disorders and dementia. Furthermore, few studies have investigated the association between sleep and frontotemporal dementia (FTD) or vascular dementia (VaD). Frontotemporal dementia affects ~0.02% of the population,[195] and the few studies that have been conducted suggest that people with FTD exhibit a phase delay and decreased TST and SE.[196] Vascular dementia is the second most common cause of dementia, affecting 10 to 15% of adults over 65.[197,198] Vascular dementia and AD pathology often present together,[199] suggesting that any links between sleep and AD may also be pertinent to persons with clinically diagnosed VaD. Additionally, white matter hyperintensities, a pathological hallmark of VaD, have been associated with disrupted circadian rhythms.[200] Finally, some studies have found that after adjusting for depressive

symptoms, there is no longer an association between sleep and cognition.[201] Therefore, it is also important for studies to consider potential confounders in the association between sleep and dementia. In particular, depression, polypharmacy, and undiagnosed comorbid medical conditions may drive observed associations between sleep and dementia and have important implications for treatment and perhaps prevention.

Conclusion

The association between sleep and dementia is complex and likely bidirectional. There are multiple ways in which sleep and dementia are linked. Brain pathology underlying dementia may lead to disturbed sleep, sleep disturbance may contribute to the development of dementia, and co-occurring sleep disturbances and dementia may lead to a more rapid decline. The majority of the research that has been conducted has been cross-sectional and has focused on sleep as a risk factor for and within the context of AD.[78,79,202–204] Identifying and treating disturbed sleep in persons with dementia may ameliorate multiple outcomes, including dementia course and caregiver burden.[155,156] Because sleep is a modifiable behavior, it is also an important potential target for intervention on cognitive decline and dementia. Disturbed sleep as early as in middle-age may increase the risk of dementia; this could have significant implications for AD prevention. Indeed, sleep may have to be targeted in midlife, like other AD risk factors (e.g., type II diabetes mellitus), to prevent AD. However, more research in this area is needed. Moving forward, sleep research has the potential to determine trajectories of dementia, improve patient prognosis, and reduce the risk of poor clinical outcomes, including dementia itself.

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References

1. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep. 2004; 27(07):1255–1273. [PubMed: 15586779]
2. Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res. 2004; 56(05):497–502. [PubMed: 15172205]
3. Berry, RB., Brooks, R., Gamaldo, CE., et al. The AASM Manual for the Scoring of Sleep and Associated Events. Vol. 2. Darien, IL: American Academy of Sleep Medicine; 2015.
4. Sherin JE, Shiromani PJ, McCarley RW, Saper CB. Activation of ventrolateral preoptic neurons during sleep. Science. 1996; 271(5246):216–219. [PubMed: 8539624]
5. Lu J, Greco MA, Shiromani P, Saper CB. Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. J Neurosci. 2000; 20(10):3830–3842. [PubMed: 10804223]
6. Buijs RM, Kalsbeek A. Hypothalamic integration of central and peripheral clocks. Nat Rev Neurosci. 2001; 2(07):521–526. [PubMed: 11433377]
7. Hofman MA, Swaab DF. Living by the clock: the circadian pacemaker in older people. Ageing Res Rev. 2006; 5(01):33–51. [PubMed: 16126012]

8. Yoon IY, Kripke DF, Elliott JA, Youngstedt SD, Rex KM, Hauger RL. Age-related changes of circadian rhythms and sleep-wake cycles. J Am Geriatr Soc. 2003; 51(08):1085–1091. [PubMed: 12890070]
9. Wang JL, Lim AS, Chiang WY, et al. Suprachiasmatic neuron numbers and rest-activity circadian rhythms in older humans. Ann Neurol. 2015; 78(02):317–322. [PubMed: 25921596]
10. Kondratova AA, Kondratov RV. The circadian clock and pathology of the ageing brain. Nat Rev Neurosci. 2012; 13(05):325–335. [PubMed: 22395806]
11. Rongve A, Boeve BF, Aarsland D. Frequency and correlates of caregiver-reported sleep disturbances in a sample of persons with early dementia. J Am Geriatr Soc. 2010; 58(03):480–486. [PubMed: 20398116]
12. Gagnon JF, Petit D, Latreille V, Montplaisir J. Neurobiology of sleep disturbances in neurodegenerative disorders. Curr Pharm Des. 2008; 14(32):3430–3445. [PubMed: 19075719]
13. Marion MH, Qurashi M, Marshall G, Foster O. Is REM sleep behaviour disorder (RBD) a risk factor of dementia in idiopathic Parkinson's disease? J Neurol. 2008; 255(02):192–196. [PubMed: 18217187]
14. Naismith SL, Glozier N, Burke D, Carter PE, Scott E, Hickie IB. Early intervention for cognitive decline: is there a role for multiple medical or behavioural interventions? Early Interv Psychiatry. 2009; 3(01):19–27. [PubMed: 21352171]
15. Naismith SL, Norrie L, Lewis SJ, Rogers NL, Scott EM, Hickie IB. Does sleep disturbance mediate neuropsychological functioning in older people with depression? J Affect Disord. 2009; 116(1–2):139–143. [PubMed: 19128840]
16. Vendette M, Gagnon JF, Décary A, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. Neurology. 2007; 69(19):1843–1849. [PubMed: 17984452]
17. Naismith SL, Hickie IB, Lewis SJ. The role of mild depression in sleep disturbance and quality of life in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2010; 22(04):384–389. [PubMed: 21037122]
18. Naismith SL, Rogers NL, Lewis SJ, et al. Sleep disturbance relates to neuropsychological functioning in late-life depression. J Affect Disord. 2011; 132(1–2):139–145. [PubMed: 21435728]
19. Pat-Horenczyk R, Klauber MR, Shochat T, Ancoli-Israel S. Hourly profiles of sleep and wakefulness in severely versus mild-moderately demented nursing home patients. Aging (Milano). 1998; 10(04):308–315. [PubMed: 9825022]
20. Yaffe K, Blackwell T, Barnes DE, Ancoli-Israel S, Stone KL, Study of Osteoporotic Fractures Group. Preclinical cognitive decline and subsequent sleep disturbance in older women. Neurology. 2007; 69(03):237–242. [PubMed: 17636060]
21. Kronholm E, Sallinen M, Suutama T, Sulkava R, Era P, Partonen T. Self-reported sleep duration and cognitive functioning in the general population. J Sleep Res. 2009; 18(04):436–446. [PubMed: 19732318]
22. Ohayon MM, Vecchierini MF. Daytime sleepiness and cognitive impairment in the elderly population. Arch Intern Med. 2002; 162(02):201–208. [PubMed: 11802754]
23. Schmutte T, Harris S, Levin R, Zweig R, Katz M, Lipton R. The relation between cognitive functioning and self-reported sleep complaints in nondemented older adults: results from the Bronx aging study. Behav Sleep Med. 2007; 5(01):39–56. [PubMed: 17313323]
24. Sternberg DA, Ballard K, Hardy JL, Katz B, Doraiswamy PM, Scanlon M. The largest human cognitive performance dataset reveals insights into the effects of lifestyle factors and aging. Front Hum Neurosci. 2013; 7:292. [PubMed: 23801955]
25. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. Alzheimer Dis Assoc Disord. 2006; 20(01):41–48. [PubMed: 16493235]
26. Xu L, Jiang CQ, Lam TH, et al. Short or long sleep duration is associated with memory impairment in older Chinese: the Guangzhou Biobank Cohort Study. Sleep. 2011; 34(05):575–580. [PubMed: 21532950]

27. Ohayon MM, Vecchierini MF. Normative sleep data, cognitive function and daily living activities in older adults in the community. Sleep. 2005; 28(08):981–989. [PubMed: 16218081]
28. Faubel R, López-García E, Guallar-Castillón P, Graciani A, Banegas JR, Rodríguez-Artalejo F. Usual sleep duration and cognitive function in older adults in Spain. J Sleep Res. 2009; 18(04): 427–435. [PubMed: 19691473]
29. Ramos AR, Dong C, Elkind MS, et al. Association between sleep duration and the mini-mental score: the Northern Manhattan study. J Clin Sleep Med. 2013; 9(07):669–673. [PubMed: 23853560]
30. Ferrie JE, Shipley MJ, Akbaraly TN, Marmot MG, Kivimäki M, Singh-Manoux A. Change in sleep duration and cognitive function: findings from the Whitehall II Study. Sleep. 2011; 34(05): 565–573. [PubMed: 21532949]
31. Loerbroks A, Debling D, Amelang M, Stürmer T. Nocturnal sleep duration and cognitive impairment in a population-based study of older adults. Int J Geriatr Psychiatry. 2010; 25(01):100–109. [PubMed: 19548221]
32. Lo JC, Groeger JA, Cheng GH, Dijk DJ, Chee MW. Self-reported sleep duration and cognitive performance in older adults: a systematic review and meta-analysis. Sleep Med. 2016; 17:87–98. [PubMed: 26847980]
33. Benito-León J, Louis ED, Bermejo-Pareja F. Cognitive decline in short and long sleepers: a prospective population-based study (NEDICES). J Psychiatr Res. 2013; 47(12):1998–2003. [PubMed: 24094933]
34. Virta JJ, Heikkilä K, Perola M, et al. Midlife sleep characteristics associated with late life cognitive function. Sleep. 2013; 36(10):1533–1541. 1541A. [PubMed: 24082313]
35. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. Sleep. 1991; 14(06):486–495. [PubMed: 1798880]
36. Ancoli-Israel S, Palmer BW, Cooke JR, et al. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J Am Geriatr Soc. 2008; 56(11):2076–2081. [PubMed: 18795985]
37. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med. 2001; 163(3 Pt 1):608–613. [PubMed: 11254512]
38. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med. 1998; 157(01):144–148. [PubMed: 9445292]
39. Young T, Shahar E, Nieto FJ, et al. Sleep Heart Health Study Research Group. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002; 162(08):893–900. [PubMed: 11966340]
40. Ancoli-Israel S, Klauber MR, Butters N, Parker L, Kripke DF. Dementia in institutionalized elderly: relation to sleep apnea. J Am Geriatr Soc. 1991; 39(03):258–263. [PubMed: 2005339]
41. Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. Respirology. 2013; 18(01):61–70. [PubMed: 22913604]
42. Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. Sleep. 2013; 36(02): 203–220. [PubMed: 23372268]
43. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc. 2004; 10(05):772–785. [PubMed: 15327723]
44. 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(06):613–619. [PubMed: 21828324]
45. Chang WP, Liu ME, Chang WC, et al. Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. PLoS One. 2013; 8(10):e78655. [PubMed: 24205289]
46. Osorio RS, Gumb T, Pirraglia E, et al. Alzheimer's Disease Neuroimaging Initiative. Sleep-disordered breathing advances cognitive decline in the elderly. Neurology. 2015; 84(19):1964–1971. [PubMed: 25878183]
47. Jaussent I, Bouyer J, Ancelin ML, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep. 2012; 35(09):1201–1207. [PubMed: 22942498]

48. Möller C, Hafkemeijer A, Pijnenburg YAL, et al. Different patterns of cortical gray matter loss over time in behavioral variant frontotemporal dementia and Alzheimer's disease. Neurobiol Aging. 2016; 38:21–31. [PubMed: 26827640]
49. Zarei M, Ibarretxe-Bilbao N, Compta Y, et al. Cortical thinning is associated with disease stages and dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2013; 84(08):875–881. [PubMed: 23463873]
50. Lim AS, Fleischman DA, Dawe RJ, et al. Regional neocortical gray matter structure and sleep fragmentation in older adults. Sleep. 2016; 39(01):227–235. [PubMed: 26350471]
51. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003; 26(03):342–392. [PubMed: 12749557]
52. Spira AP, Gonzalez CE, Venkatraman VK, et al. Sleep duration and subsequent cortical thinning in cognitively normal older adults. Sleep. 2016; 39(05):1121–1128. [PubMed: 26951390]
53. Lo JC, Loh KK, Zheng H, Sim SK, Chee MW. Sleep duration and age-related changes in brain structure and cognitive performance. Sleep. 2014; 37(07):1171–1178. [PubMed: 25061245]
54. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron. 2014; 81(01):12–34. [PubMed: 24411729]
55. Kreutzmann JC, Havekes R, Abel T, Meerlo P. Sleep deprivation and hippocampal vulnerability: changes in neuronal plasticity, neurogenesis and cognitive function. Neuroscience. 2015; 309:173–190. [PubMed: 25937398]
56. Joo EY, Jeon S, Kim ST, Lee JM, Hong SB. Localized cortical thinning in patients with obstructive sleep apnea syndrome. Sleep. 2013; 36(08):1153–1162. [PubMed: 23904675]
57. Kumar R, Birrer BV, Macey PM, et al. Reduced mammillary body volume in patients with obstructive sleep apnea. Neurosci Lett. 2008; 438(03):330–334. [PubMed: 18486338]
58. Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM. Brain structural changes in obstructive sleep apnea. Sleep. 2008; 31(07):967–977. [PubMed: 18652092]
59. Zimmerman ME, Aloia MS. A review of neuroimaging in obstructive sleep apnea. J Clin Sleep Med. 2006; 2(04):461–471. [PubMed: 17557478]
60. Kim H, Yun CH, Thomas RJ, et al. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. Sleep. 2013; 36(05):709–715B. [PubMed: 23633753]
61. Cho ER, Kim H, Seo HS, Suh S, Lee SK, Shin C. Obstructive sleep apnea as a risk factor for silent cerebral infarction. J Sleep Res. 2013; 22(04):452–458. [PubMed: 23374054]
62. Castronovo V, Scifo P, Castellano A, et al. White matter integrity in obstructive sleep apnea before and after treatment. Sleep. 2014; 37(09):1465–1475. [PubMed: 25142557]
63. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med. 2005; 172(11):1447–1451. [PubMed: 16141444]
64. Hermann DM, Bassetti CL. Sleep-related breathing and sleep-wake disturbances in ischemic stroke. Neurology. 2009; 73(16):1313–1322. [PubMed: 19841384]
65. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005; 365(9464):1046–1053. [PubMed: 15781100]
66. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med. 2010; 182(02):269–277. [PubMed: 20339144]
67. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. J Intern Med. 2015; 277(04):406–425. [PubMed: 25041352]
68. Ju YE, McLeland JS, Toedebusch CD, et al. Sleep quality and preclinical Alzheimer disease. JAMA Neurol. 2013; 70(05):587–593. [PubMed: 23479184]
69. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. Alzheimers Dement. 2016; 12(04):459–509. [PubMed: 27570871]
70. Jack CR, Knopman DS, Jagust WJ, et al. Update on hypothetical model of Alzheimer's disease biomarkers. Lancet Neurol. 2013; 12(02):207–216. [PubMed: 23332364]

71. Guarnieri B, Adorni F, Musicco M, et al. Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders: a multicenter Italian clinical cross-sectional study on 431 patients. Dement Geriatr Cogn Disord. 2012; 33(01):50–58. [PubMed: 22415141]
72. Bliwise DL, Watts RL, Watts N, Rye DB, Irbe D, Hughes M. Disruptive nocturnal behavior in Parkinson's disease and Alzheimer's disease. J Geriatr Psychiatry Neurol. 1995; 8(02):107–110. [PubMed: 7794473]
73. Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. Sleep disturbance in mild to moderate Alzheimer's disease. Sleep Med. 2005; 6(04):347–352. [PubMed: 15978517]
74. Hatfield CF, Herbert J, van Someren EJ, Hodges JR, Hastings MH. Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. Brain. 2004; 127(Pt 5):1061–1074. [PubMed: 14998915]
75. Benito-León J, Bermejo-Pareja F, Vega S, Louis ED. Total daily sleep duration and the risk of dementia: a prospective population-based study. Eur J Neurol. 2009; 16(09):990–997. [PubMed: 19473367]
76. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. Sleep. 2013; 36(07):1027–1032. [PubMed: 23814339]
77. Lim AS, Yu L, Kowgier M, Schneider JA, Buchman AS, Bennett DA. Modification of the relationship of the apolipoprotein E ε4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. JAMA Neurol. 2013; 70(12):1544–1551. [PubMed: 24145819]
78. Osorio RS, Pirraglia E, Agüera-Ortiz LF, et al. Greater risk of Alzheimer's disease in older adults with insomnia. J Am Geriatr Soc. 2011; 59(03):559–562. [PubMed: 21391952]
79. Lobo A, López-Antón R, de-la-Cámara C, Quintanilla MA, Campayo A, Saz P, ZARADEMP Workgroup. Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type. Neurotox Res. 2008; 14(2–3):263–272. [PubMed: 19073431]
80. 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]
81. Roh JH, Huang Y, Bero AW, et al. Disruption of the sleep-wake cycle and diurnal fluctuation of β-amyloid in mice with Alzheimer's disease pathology. Sci Transl Med. 2012; 4(150):150ra122.
82. Spira AP, An Y, Resnick SM. Self-reported sleep and β-amyloid deposition in older adults-reply. JAMA Neurol. 2014; 71(05):651–652.
83. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol. 2006; 59(03):512–519. [PubMed: 16372280]
84. Tabuchi M, Lone SR, Liu S, et al. Sleep interacts with aβ to modulate intrinsic neuronal excitability. Curr Biol. 2015; 25(06):702–712. [PubMed: 25754641]
85. Palop JJ, Mucke L, Roberson ED. Quantifying biomarkers of cognitive dysfunction and neuronal network hyperexcitability in mouse models of Alzheimer's disease: depletion of calcium-dependent proteins and inhibitory hippocampal remodeling. Methods Mol Biol. 2011; 670:245–262. [PubMed: 20967595]
86. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. Neurochem Res. 2015; 40(12):2583–2599. [PubMed: 25947369]
87. Mendelsohn AR, Larrick JW. Sleep facilitates clearance of metabolites from the brain: glymphatic function in aging and neurodegenerative diseases. Rejuvenation Res. 2013; 16(06):518–523. [PubMed: 24199995]
88. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med. 2012; 4(147):147ra111.
89. Kress BT, Iliff JJ, Xia M, et al. Impairment of paravascular clearance pathways in the aging brain. Ann Neurol. 2014; 76(06):845–861. [PubMed: 25204284]
90. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013; 342(6156):373–377. [PubMed: 24136970]

91. Mander BA, Winer JR, Jagust WJ, Walker MP. Sleep: a novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease? Trends Neurosci. 2016; 39(08):552–566. [PubMed: 27325209]
92. Mishima K, Okawa M, Satoh K, Shimizu T, Hozumi S, Hishikawa Y. Different manifestations of circadian rhythms in senile dementia of Alzheimer's type and multi-infarct dementia. Neurobiol Aging. 1997; 18(01):105–109. [PubMed: 8983038]
93. Satlin A, Volicer L, Stopa EG, Harper D. Circadian locomotor activity and core-body temperature rhythms in Alzheimer's disease. Neurobiol Aging. 1995; 16(05):765–771. [PubMed: 8532109]
94. Ancoli-Israel S, Klauber MR, Jones DW, et al. Variations in circadian rhythms of activity, sleep, and light exposure related to dementia in nursing-home patients. Sleep. 1997; 20(01):18–23. [PubMed: 9130329]
95. Harper DG, Volicer L, Stopa EG, McKee AC, Nitta M, Satlin A. Disturbance of endogenous circadian rhythm in aging and Alzheimer disease. Am J Geriatr Psychiatry. 2005; 13(05):359–368. [PubMed: 15879584]
96. Harper DG, Stopa EG, Kuo-Leblanc V, et al. Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. Brain. 2008; 131(Pt 6):1609–1617. [PubMed: 18372313]
97. Lim AS, Ellison BA, Wang JL, et al. Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer's disease. Brain. 2014; 137(Pt 10):2847–2861. [PubMed: 25142380]
98. Tranah GJ, Blackwell T, Stone KL, et al. SOF Research Group. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann Neurol. 2011; 70(05): 722–732. [PubMed: 22162057]
99. Emamian F, Khazaie H, Tahmasian M, et al. The association between obstructive sleep apnea and Alzheimer's disease: a meta-analysis perspective. Front Aging Neurosci. 2016; 8:78. [PubMed: 27148046]
100. Daulatzai MA. Death by a thousand cuts in Alzheimer's disease: hypoxia–the prodrome. Neurotox Res. 2013; 24(02):216–243. [PubMed: 23400634]
101. Li L, Zhang X, Yang D, Luo G, Chen S, Le W. Hypoxia increases Abeta generation by altering beta- and gamma-cleavage of APP. Neurobiol Aging. 2009; 30(07):1091–1098. [PubMed: 18063223]
102. Fang H, Zhang LF, Meng FT, Du X, Zhou JN. Acute hypoxia promote the phosphorylation of tau via ERK pathway. Neurosci Lett. 2010; 474(03):173–177. [PubMed: 20304032]
103. Ju YE, Finn MB, Sutphen CL, et al. Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. Ann Neurol. 2016; 80(01):154–159. [PubMed: 27129429]
104. Osorio RS, Ayappa I, Mantua J, et al. Interaction between sleep-disordered breathing and apolipoprotein E genotype on cerebrospinal fluid biomarkers for Alzheimer's disease in cognitively normal elderly individuals. Neurobiol Aging. 2014; 35(06):1318–1324. [PubMed: 24439479]
105. Spira AP, Yager C, Brandt J, et al. Objectively measured sleep and β-amyloid burden in older adults: a pilot study. SAGE Open Med. 2014; 2:2.
106. Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. N Engl J Med. 2003; 348(14):1356–1364. [PubMed: 12672864]
107. Bassetti CL. Nonmotor disturbances in Parkinson's disease. Neurodegener Dis. 2011; 8(03):95–108. [PubMed: 21196687]
108. Simuni T, Sethi K. Nonmotor manifestations of Parkinson's disease. Ann Neurol. 2008; 64(Suppl 2):S65–S80. [PubMed: 19127582]
109. Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. Mov Disord. 1990; 5(04):280–285. [PubMed: 2259351]
110. Lees AJ, Blackburn NA, Campbell VL. The nighttime problems of Parkinson's disease. Clin Neuropharmacol. 1988; 11(06):512–519. [PubMed: 3233589]
111. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord. 1998; 13(06):895–899. [PubMed: 9827612]

112. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology. 2006; 67(05):853–858. [PubMed: 16966550]
113. Svensson E, Beiske AG, Loge JH, Beiske KK, Sivertsen B. Sleep problems in Parkinson's disease: a community-based study in Norway. BMC Neurol. 2012; 12:71. [PubMed: 22883600]
114. Zoccolella S, Savarese M, Lamberti P, Manni R, Pacchetti C, Logroscino G. Sleep disorders and the natural history of Parkinson's disease: the contribution of epidemiological studies. Sleep Med Rev. 2011; 15(01):41–50. [PubMed: 20634113]
115. Barone P, Antonini A, Colosimo C, et al. PRIAMO study group. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009; 24(11):1641–1649. [PubMed: 19514014]
116. Bjørnarå KA, Dietrichs E, Toft M. Clinical features associated with sleep disturbances in Parkinson's disease. Clin Neurol Neurosurg. 2014; 124:37–43. [PubMed: 25016237]
117. Kurtis MM, Rodriguez-Blazquez C, Martinez-Martin P, ELEP Group. Relationship between sleep disorders and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2013; 19(12):1152–1155. [PubMed: 23953775]
118. Borek LL, Kohn R, Friedman JH. Mood and sleep in Parkinson's disease. J Clin Psychiatry. 2006; 67(06):958–963. [PubMed: 16848656]
119. Chahine LM, Daley J, Horn S, et al. Association between dopaminergic medications and nocturnal sleep in early-stage Parkinson's disease. Parkinsonism Relat Disord. 2013; 19(10):859–863. [PubMed: 23751512]
120. Happe S, Lüdemann P, Berger K, FAQT study investigators. The association between disease severity and sleep-related problems in patients with Parkinson's disease. Neuropsychobiology. 2002; 46(02):90–96. [PubMed: 12378126]
121. Scullin MK, Sollinger AB, Land J, et al. Sleep and impulsivity in Parkinson's disease. Parkinsonism Relat Disord. 2013; 19(11):991–994. [PubMed: 23880026]
122. Verbaan D, van Rooden SM, Visser M, Marinus J, van Hilten JJ. Nighttime sleep problems and daytime sleepiness in Parkinson's disease. Mov Disord. 2008; 23(01):35–41. [PubMed: 17960797]
123. Zhu K, van Hilten JJ, Marinus J. The course of insomnia in Parkinson's disease. Parkinsonism Relat Disord. 2016; 33:51–57. [PubMed: 27639814]
124. Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: a systematic review and new concept. Neurology. 2016; 86(14):1336–1343. [PubMed: 26944272]
125. Rijsman RM, Schoolderman LF, Rundervoort RS, Louter M. Restless legs syndrome in Parkinson's disease. Parkinsonism Relat Disord. 2014; 20(Suppl 1):S5–S9. [PubMed: 24262188]
126. da Silva-Júnior FP Jr, do Prado GF, Barbosa ER, Tufik S, Togeiro SM. Sleep disordered breathing in Parkinson's disease: a critical appraisal. Sleep Med Rev. 2014; 18(02):173–178. [PubMed: 23886661]
127. Harmell AL, Neikrug AB, Palmer BW, et al. Obstructive sleep apnea and cognition in Parkinson's disease. Sleep Med. 2016; 21:28–34. [PubMed: 27448468]
128. Herer B, Arnulf I, Housset B. Effects of levodopa on pulmonary function in Parkinson's disease. Chest. 2001; 119(02):387–393. [PubMed: 11171713]
129. Hovestadt A, Bogaard JM, Meerwaldt JD, van der Meché FG, Stigt J. Pulmonary function in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1989; 52(03):329–333. [PubMed: 2926415]
130. Boeve BF. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. Ann N Y Acad Sci. 2010; 1184:15–54. [PubMed: 20146689]
131. Schenck CH, Mahowald MW. Rapid eye movement sleep parasomnias. Neurol Clin. 2005; 23(04):1107–1126. [PubMed: 16243618]
132. Ohayon MM, Caulet M, Priest RG. Violent behavior during sleep. J Clin Psychiatry. 1997; 58(08):369–376. quiz 377. [PubMed: 9515980]

133. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology. 2010; 75(06):494–499. [PubMed: 20668263]
134. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology. 1996; 46(02):388–393. [PubMed: 8614500]
135. Boeve BF, Silber MH, Ferman TJ. REM sleep behavior disorder in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol. 2004; 17(03):146–157. [PubMed: 15312278]
136. Comella CL, Nardine TM, Diederich NJ, Stebbins GT. Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. Neurology. 1998; 51(02):526–529. [PubMed: 9710029]
137. Gagnon JF, Bédard MA, Fantini ML, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology. 2002; 59(04):585–589. [PubMed: 12196654]
138. Plazzi G, Corsini R, Provini F, et al. REM sleep behavior disorders in multiple system atrophy. Neurology. 1997; 48(04):1094–1097. [PubMed: 9109907]
139. Tachibana N, Oka Y. Longitudinal change in REM sleep components in a patient with multiple system atrophy associated with REM sleep behavior disorder: paradoxical improvement of nocturnal behaviors in a progressive neurodegenerative disease. Sleep Med. 2004; 5(02):155–158. [PubMed: 15033136]
140. Silber MH, Ahlskog JE. REM sleep behavior disorder in Parkinsonian syndromes. Sleep Res. 1992; 21:313.
141. Silber MH, Dexter DD, Ahlskog JE, Hauri PJ, Shepard JW. Abnormal REM sleep motor activity in untreated Parkinson's disease. Sleep Res. 1993; 22:274.
142. Jennum P, Christensen JA, Zoetmulder M. Neurophysiological basis of rapid eye movement sleep behavior disorder: informing future drug development. Nat Sci Sleep. 2016; 8:107–120. [PubMed: 27186147]
143. Kudo T, Loh DH, Truong D, Wu Y, Colwell CS. Circadian dysfunction in a mouse model of Parkinson's disease. Exp Neurol. 2011; 232(01):66–75. [PubMed: 21864527]
144. Politis M, Piccini P, Pavese N, Koh SB, Brooks DJ. Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: an in vivo 11C-raclopride PET study. Exp Neurol. 2008; 214(01):112–116. [PubMed: 18723016]
145. Nakamura TJ, Nakamura W, Yamazaki S, et al. Age-related decline in circadian output. J Neurosci. 2011; 31(28):10201–10205. [PubMed: 21752996]
146. Wu YH, Swaab DF. The human pineal gland and melatonin in aging and Alzheimer's disease. J Pineal Res. 2005; 38(03):145–152. [PubMed: 15725334]
147. Videnovic A, Noble C, Reid KJ, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 2014; 71(04):463–469. [PubMed: 24566763]
148. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003; 24(02):197–211. [PubMed: 12498954]
149. Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 2001; 24(12):726–731. [PubMed: 11718878]
150. Trotti, LM., Rye, DB. Neurobiology of sleep: the role of dopamine in Parkinson's disease. In: Chaudruri, KR.Tolosa, E.Scapira, A., Poewe, W., editors. Nonmotor symptoms in Parkinson's disease. New York, NY: Oxford University Press; 2009. p. 165-176.
151. Jackson CR, Chaurasia SS, Hwang CK, Iuvone PM. Dopamine D_4 receptor activation controls circadian timing of the adenylyl cyclase 1/cyclic AMP signaling system in mouse retina. Eur J Neurosci. 2011; 34(01):57–64. [PubMed: 21676039]
152. Witkovsky P. Dopamine and retinal function. Doc Ophthalmol. 2004; 108(01):17–40. [PubMed: 15104164]
153. Roth HL. Dementia and sleep. Neurol Clin. 2012; 30(04):1213–1248. [PubMed: 23099135]
154. Urrestarazu E, Iriarte J. Clinical management of sleep disturbances in Alzheimer's disease: current and emerging strategies. Nat Sci Sleep. 2016; 8:21–33. [PubMed: 26834500]

155. Etters L, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: a review of the literature. J Am Acad Nurse Pract. 2008; 20(08):423–428. [PubMed: 18786017]
156. Pollak CP, Perlick D. Sleep problems and institutionalization of the elderly. J Geriatr Psychiatry Neurol. 1991; 4(04):204–210. [PubMed: 1789908]
157. Ooms S, Ju YE. Treatment of sleep disorders in dementia. Curr Treat Options Neurol. 2016; 18(09):40. [PubMed: 27476067]
158. Camargos EF, Louzada LL, Quintas JL, Naves JO, Louzada FM, Nóbrega OT. Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study. Am J Geriatr Psychiatry. 2014; 22(12):1565–1574. [PubMed: 24495406]
159. Grippe TC, Gonçalves BS, Louzada LL, et al. Circadian rhythm in Alzheimer disease after trazodone use. Chronobiol Int. 2015; 32(09):1311–1314. [PubMed: 26376345]
160. Meguro K, Meguro M, Tanaka Y, Akanuma K, Yamaguchi K, Itoh M. Risperidone is effective for wandering and disturbed sleep/wake patterns in Alzheimer's disease. J Geriatr Psychiatry Neurol. 2004; 17(02):61–67. [PubMed: 15157345]
161. Ruths S, Straand J, Nygaard HA, Bjorvatn B, Pallesen S. Effect of antipsychotic withdrawal on behavior and sleep/wake activity in nursing home residents with dementia: a randomized, placebo-controlled, double-blinded study. The Bergen District Nursing Home Study. J Am Geriatr Soc. 2004; 52(10):1737–1743. [PubMed: 15450054]
162. Yin Y, Liu Y, Zhuang J, et al. Low-dose atypical antipsychotic risperidone improves the 5-year outcome in Alzheimer's disease patients with sleep disturbances. Pharmacology. 2015; 96(3–4): 155–162. [PubMed: 26279176]
163. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry. 2015; 72(05):438–445. [PubMed: 25786075]
164. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005; 294(15):1934–1943. [PubMed: 16234500]
165. Romeo R, Knapp M, Hellier J, et al. Cost-effectiveness analyses for mirtazapine and sertraline in dementia: randomised controlled trial. Br J Psychiatry. 2013; 202:121–128. [PubMed: 23258767]
166. Xu J, Wang LL, Dammer EB, et al. Melatonin for sleep disorders and cognition in dementia: a meta-analysis of randomized controlled trials. Am J Alzheimers Dis Other Demen. 2015; 30(05): 439–447. [PubMed: 25614508]
167. Gehrman PR, Connor DJ, Martin JL, Shochat T, Corey-Bloom J, Ancoli-Israel S. Melatonin fails to improve sleep or agitation in double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer disease. Am J Geriatr Psychiatry. 2009; 17(02):166–169. [PubMed: 19155748]
168. Trotti LM, Karroum EG. Melatonin for sleep disorders in patients with neurodegenerative diseases. Curr Neurol Neurosci Rep. 2016; 16(07):63. [PubMed: 27180068]
169. Wu YH, Zhou JN, Van Heerikhuize J, Jockers R, Swaab DF. Decreased MT1 melatonin receptor expression in the suprachiasmatic nucleus in aging and Alzheimer's disease. Neurobiol Aging. 2007; 28(08):1239–1247. [PubMed: 16837102]
170. Golombek DA, Pandi-Perumal SR, Brown GM, Cardinali DP. Some implications of melatonin use in chronopharmacology of insomnia. Eur J Pharmacol. 2015; 762:42–48. [PubMed: 26004526]
171. Shochat T, Martin J, Marler M, Ancoli-Israel S. Illumination levels in nursing home patients: effects on sleep and activity rhythms. J Sleep Res. 2000; 9(04):373–379. [PubMed: 11386204]
172. Forbes D, Blake CM, Thiessen EJ, Peacock S, Hawranik P. Light therapy for improving cognition, activities of daily living, sleep, challenging behaviour, and psychiatric disturbances in dementia. Cochrane Database Syst Rev. 2014; (02):CD003946. [PubMed: 24574061]
173. Naismith SL, Lewis SJ, Rogers NL. Sleep-wake changes and cognition in neurodegenerative disease. Prog Brain Res. 2011; 190:21–52. [PubMed: 21531243]

174. Cusso ME, Donald KJ, Khoo TK. The impact of physical activity on non-motor symptoms in Parkinson's disease: a systematic review. Front Med (Lausanne). 2016; 3:35. [PubMed: 27583249]

175. McCurry SM, Pike KC, Vitiello MV, Logsdon RG, Larson EB, Teri L. Increasing walking and bright light exposure to improve sleep in community-dwelling persons with Alzheimer's disease: results of a randomized, controlled trial. J Am Geriatr Soc. 2011; 59(08):1393–1402. [PubMed: 21797835]

176. Eugster L, Bargiotas P, Bassetti CL, Michael Schuepbach WM. Deep brain stimulation and sleep-wake functions in Parkinson's disease: a systematic review. Parkinsonism Relat Disord. 2016; 32:12–19. [PubMed: 27605426]

177. Cohen-Mansfield J, Garfinkel D, Lipson S. Melatonin for treatment of sundowning in elderly persons with dementia - a preliminary study. Arch Gerontol Geriatr. 2000; 31(01):65–76. [PubMed: 10989165]

178. Mishima K, Okawa M, Hozumi S, Hishikawa Y. Supplementary administration of artificial bright light and melatonin as potent treatment for disorganized circadian rest-activity and dysfunctional autonomic and neuroendocrine systems in institutionalized demented elderly persons. Chronobiol Int. 2000; 17(03):419–432. [PubMed: 10841214]

179. Brusco LI, Márquez M, Cardinali DP. Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer's disease. Neuroendocrinol Lett. 2000; 21(01):39–42. [PubMed: 11455329]

180. Dowling GA, Burr RL, Van Someren EJ, et al. Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. J Am Geriatr Soc. 2008; 56(02):239–246. [PubMed: 18070004]

181. Rodrigues TM, Castro Caldas A, Ferreira JJ. Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson's disease: systematic review and meta-analysis. Parkinsonism Relat Disord. 2016; 27:25–34. [PubMed: 27010071]

182. Ayalon L, Ancoli-Israel S, Stepnowsky C, et al. Adherence to continuous positive airway pressure treatment in patients with Alzheimer's disease and obstructive sleep apnea. Am J Geriatr Psychiatry. 2006; 14(02):176–180. [PubMed: 16473983]

183. Cooke JR, Ayalon L, Palmer BW, et al. Sustained use of CPAP slows deterioration of cognition, sleep, and mood in patients with Alzheimer's disease and obstructive sleep apnea: a preliminary study. J Clin Sleep Med. 2009; 5(04):305–309. [PubMed: 19968005]

184. Archbold KH, Borghesani PR, Mahurin RK, Kapur VK, Landis CA. Neural activation patterns during working memory tasks and OSA disease severity: preliminary findings. J Clin Sleep Med. 2009; 5(01):21–27. [PubMed: 19317377]

185. Ayalon L, Ancoli-Israel S, Klemfuss Z, Shalauta MD, Drummond SP. Increased brain activation during verbal learning in obstructive sleep apnea. Neuroimage. 2006; 31(04):1817–1825. [PubMed: 16626972]

186. Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK. Functional imaging of working memory in obstructive sleep-disordered breathing. J Appl Physiol (1985). 2005; 98(06):2226–2234. [PubMed: 15677733]

187. Zhang X, Ma L, Li S, Wang Y, Wang L. A functional MRI evaluation of frontal dysfunction in patients with severe obstructive sleep apnea. Sleep Med. 2011; 12(04):335–340. [PubMed: 21398177]

188. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003; 4(04):281–284. [PubMed: 14592300]

189. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. Mov Disord. 1999; 14(03):507–511. [PubMed: 10348479]

190. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain. 2000; 123(Pt 2):331–339. [PubMed: 10648440]

191. Schenck CH, Mahowald MW. A polysomnographic, neurologic, psychiatric and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. Cleve Clin J Med. 1990; 57(supplement):10–24.

192. Aurora RN, Zak RS, Maganti RK, et al. Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of REM sleep behavior disorder (RBD). J Clin Sleep Med. 2010; 6(01):85–95. [PubMed: 20191945]

193. Onofrj M, Luciano AL, Thomas A, Iacono D, D'Andreamatteo G. Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. Neurology. 2003; 60(01):113–115. [PubMed: 12525729]

194. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep. 2004; 27(02):317–321. [PubMed: 15124729]

195. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry. 2013; 25(02):130–137. [PubMed: 23611343]

196. Anderson KN, Hatfield C, Kipps C, Hastings M, Hodges JR. Disrupted sleep and circadian patterns in frontotemporal dementia. Eur J Neurol. 2009; 16(03):317–323. [PubMed: 19170747]

197. Gorelick PB, Scuteri A, Black SE, et al. American Heart Association Stroke Council, Council on Epidemiology and Prevention Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42(09):2672–2713. [PubMed: 21778438]

198. Kalaria RN. Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. Stroke. 2012; 43(09):2526–2534. [PubMed: 22879100]

199. Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimer Dis Assoc Disord. 1999; 13(Suppl 3):S115–S123. [PubMed: 10609690]

200. Oosterman J, van Harten B, Vogels R, et al. Distortions in rest-activity rhythm in aging relate to white matter hyperintensities. Neurobiol Aging. 2008; 29(08):1265–1271. [PubMed: 17368870]

201. Foley D, Monjan A, Masaki K, et al. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. J Am Geriatr Soc. 2001; 49(12):1628–1632. [PubMed: 11843995]

202. Cooke JR, Liu L, Natarajan L, et al. The effect of sleep-disordered breathing on stages of sleep in patients with Alzheimer's disease. Behav Sleep Med. 2006; 4(04):219–227. [PubMed: 17083302]

203. Cricco M, Simonsick EM, Foley DJ. The impact of insomnia on cognitive functioning in older adults. J Am Geriatr Soc. 2001; 49(09):1185–1189. [PubMed: 11559377]

204. Talarico G, Canevelli M, Tosto G, et al. Restless legs syndrome in a group of patients with Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2013; 28(02):165–170. [PubMed: 23264651]

Table 1

Recommended treatments for dementia patients with sleep problems

Sleep problem	Recommended pharmaceutical approach	Recommended nonpharmaceutical approach
Insomnia	Low dose (25–50 mg) trazodone; mirtazapine; melatonin	Bright light therapy; reducing or eliminating caffeine and alcohol; dark and quiet bedroom; not drinking near bedtime; avoid daytime napping; daytime physical activity
Daytime sleepiness	Melatonin; changing current medication type and dosing; modafinil (in PD patients)	Daytime physical activity
SDB	Consider discontinuation of medications that may worsen SDB (e.g., benzodiazepines, opioids, testosterone)	CPAP
RBD	Melatonin; clonazepam (with caution)	Remove potentially injurious objects from bedroom; create barriers; avoid antidepressants, caffeine, chocolate

Abbreviations: CPAP, continuous positive airway pressure; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder; SDB, sleep disordered breathing.