Sleep Disorders & Dementia

Sleep disorders are emerging as a biomarker for prodromal dementia.

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As people age, their sleep patterns change. In cognitively normal elderly people, they can develop advanced sleep phase, with longer sleep latency and shorter total sleep time. There is also an increase in sleep fragmentation, with lighter and more fragile sleep, reduced deeper sleep, and increased time awake after sleep onset. Rapid eye movement (REM) sleep duration decreases, usually after age 80. People are also more affected by chronic medical conditions as they age, including sleep, psychiatric and neurologic conditions, and medication use. In individuals with dementia, these changes can be exacerbated.

Sleep disturbances are common in people with dementia, including insomnia, sleep disordered breathing (SDB), excessive daytime sleepiness (EDS), REM sleep behavior disorder (RBD), restless leg syndrome (RLS)-Willis Ekbom disease, periodic limb movements of sleep, circadian rhythm disorders, and other nonspecific sleep problems. In a multicenter study of persons with mild cognitive impairment (MCI) or dementia, over 60% reported 1 or more sleep disturbances. The most frequent sleep disorder was SDB (60%), followed by EDS (50.1%), insomnia (49.9%), RBD (22.6%), and RLS (6.1%).

Different neurodegenerative disorders can present with different sleep disturbances. This article reviews the more common types of sleep disturbances and their association with dementias.

Excessive Daytime Sleepiness

Frequently seen in neurodegenerative disorders, EDS may occur with or without nighttime sleep problems. Individuals with EDS normally take multiple short daytime naps. Treatment of EDS depends on etiologies, which may be environmental (eg, lack of activity or limited light exposure), from comorbid conditions (eg, depression, sleep disorders, stroke, neurodegenerative disorders, heart disease, or head injury), or medication use. Obtaining a detailed history is most important in evaluating EDS. Actigraphy is a helpful objective measurement of sleep-wake disturbances, that might lead to EDS, especially for people from whom reliable information can be difficult to obtain. Polysomnography (PSG) can be used to evaluate for SDB; however, PSG can be challenging for people with more advanced dementia. It is preferable to have a caregiver stay with an individual with dementia during a sleep study, because confusion and disorientation may interfere with obtaining accurate results.

Medication is a major cause of EDS in people over age 55, because sedating medications are commonly used in this population (eg, sleep aids, pain control, mood disorders, and more). Important side effects with these medications are worsening cognitive functions and increased fall risk, which in turn, can also contribute to worsening EDS.

An analysis of anticholinergic effects of commonly prescribed medications for people over age 55 evaluated 122 drugs, finding that half could induce cognitive impairment to some degree via their anticholinergic effects (Table). A number of medications could not be classified because of insufficient information. When a person with dementia reports EDS, review of medications is pertinent. For a person with hypersomnia due to, for example, Parkinson’s disease dementia (PDD) or Lewy body disease (LBD), low doses of psychostimulants may be helpful but with caution in those of advanced age or cardiovascular comorbidities.

Insomnia

Insomnia symptoms are reported by 50% of adults over age 60, and diagnosis of insomnia is present in 49.9% of patients with MCI or dementia. Insomnia is associated with increased risk of Alzheimer’s disease in a bidirectional manner, postulated to be caused by increases in inflammatory response, that can in turn increase β amyloid production. Sleep is involved in clearance of β amyloid, especially in slow-wave sleep. Increase in wake time and decrease in sleep time may affect β amyloid clearance, increasing AD risk.

Insomnia is characterized as persistent difficulty with sleep initiation and/or sleep maintenance that occurs despite ample opportunity and circumstances for sleep and results in complaints during the day that affect daily functioning. Insomnia can be caused by medical and psychiatric comorbidities, medication use, age-related changes in circadian rhythm, behavioral or environmental factors, or primary sleep disorders, which increase with age.
Treatment of insomnia should focus on evaluating medical and psychiatric comorbidities and resolving environmental disturbances. It is also important to distinguish between difficulties with sleep onset or sleep maintenance. If sleep maintenance is the issue, a person should be evaluated for SDB and medications that can precipitate SDB. Pharmacotherapy is for short-term relief and needs to be frequently reviewed. Nonbenzodiazepines and melatonin receptor agonists appear safest and most efficacious.

Behavioral treatment and cognitive behavioral therapy (CBT-I) which combines cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation is effective for treating insomnia and considered first-line treatment, although delivery can be expensive and may be challenging for those with progressive decline. Some sleep-hygiene recommendations include keeping a regular sleep-wake time, engaging in relaxing activities and limiting light exposure (eg, electronic devices) prior to bed time, keeping the sleep environment quiet and comfortable, and avoiding caffeine, tobacco, and alcohol in the evening and naps longer than 30 minutes during the day. Morning light exposure and nighttime melatonin can help with sleep disruption and daytime sleepiness. Drugs that are activating or can cause disruption in sleep (eg, diuretics, bronchodilators, corticosteroids, H₂ blockers, or cardiovascular agents) can be administered in the morning, or at least 6 to 8 hours before bedtime, to allow less interruption in sleep. Mindfulness-based stress reduction therapy (MBSR) and mindfulness-based therapy for insomnia (MBTI) have also been effective in treatment of insomnia. When insomnia is associated with agitation, confabulations, and misperception, however, atypical antipsychotics may be suggested if the affected patient or others are at risk. Low dose antidepressants may be helpful for people with AD, but they can exacerbate RLS.

Individuals with dementia can present with irregular sleep-wake rhythm disorder (ISWRD), which can be multifactorial. In neurodegenerative disorders, circadian rhythm may be impaired by abnormal melatonin secretion, damaging the central clock, the suprachiasmatic nucleus, or desynchronizing central and peripheral clocks in the body. Circadian rhythm can also be affected by impaired visual input (eg, those with macular degeneration, glaucoma, altered environment without a clear day-night pattern, as in a nursing home). People with ISWRD usually have irregular sleep and wake episodes, presenting with insomnia or EDS, or both. There is no major sleep displayed on actigraphy monitoring, but at least 3 or more irregular sleep bouts during a period of 24 hours. This can cause worsening of behavior, confusion, and agitation, usually in the evening and nighttime, in the form of “sundowning.” Factors that worsen sundowning include exhaustion, reduced light and increased shadows, new environment, and changes in caregivers or shift in hospital or facility. Any underlying medical condition (eg, infection or metabolic derangements) can also trigger sundowning.

**REM Sleep Behavior Disorder**

A parasomnia, RBD is characterized by repeated episodes of vocalization and/or complex movements during
sleep. The behaviors are either documented on PSG during REM sleep, or based on clinical history and presumed to occur during REM sleep. People with RBD may act out their dreams, and these behaviors can sometimes be violent, resulting in injuries to the individual and/or their sleep partners. Confirmation with PSG is important to rule out other causes of abnormal movements during sleep (e.g., periodic limb movements of sleep, SDB-induced movements, increases in muscle tone during REM sleep, nonREM parasomnias, or nocturnal seizures). Symptoms of RBD may also be seen during alcohol and barbiturate withdrawal. When PSG cannot be obtained in an individual with cognitive impairment because of intolerance to PSG, the Mayo Sleep Questionnaire is a validated tool to assess people with dementia for RBD.10

The prevalence of RBD is approximately 1%,11 and it occurs in 5% to 13% of community-dwelling adults age 60 to 99. In people with psychiatric diagnoses, RBD is 10 times more common and in those taking antidepressants, RBD is 5 times more common.12 Considered a prodromal biomarker for α-synucleinopathies, RBD is a harbinger for Parkinson’s disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). A meta-analysis13 showed that the risk of developing neurodegenerative diseases in people with RBD was 33.5% in 5 years, 82.4% in 10.5 years, and 96.6% in 14 years, with the majority developing PD (43%), followed by LBD (25%), and MSA (5%). A multicenter study found that conversion rate from idiopathic RBD to overt neurodegenerative syndrome was 6.3% per year, and 73.5% after 12 years of follow up. The phenoconversion rate significantly increases when coupled with a number of other biomarkers.14 Because most people with RBD eventually develop a neurodegenerative disorder with such a long prodromal interval, RBD diagnosis provides a unique opportunity to study early neuroprotective therapy before development of overt neurologic symptoms.

Characterized by sustained muscle activity on chin EMG and/or excessive transient muscle activity in chin/limb EMG during REM sleep, REM sleep without atonia (RSWA) is among required criteria for diagnosis of RBD. In persons with a history of RBD, RSWA can be observed during PSG, and is proposed as a precursor for RBD.15 In a study of individuals with isolated RSWA, but not clinical RBD, 70% had at least 1 neurodegenerative biomarker (e.g., hyposmia, orofacial dyskinesia, cognitive impairment, finger speed deficit, impaired color vision, or substantia nigra hyperechogenicity), and 7% subsequently developed RBD,16 suggesting that isolated RSWA could be an even earlier objective prodrome. If confirmed in larger cohorts, this could move the time line for initiating neuroprotective trials even earlier.

Initial treatment of RBD is to ensure safety to the individual and any sleep partners. Sharp objects or weapons should be removed from the bedroom, and night stands with pointed corners moved away from the bed or padded. The bed should be away from windows or the mattress placed on the floor. Pharmacotherapy is considered when RBD becomes potentially injurious. First-line agents include clonazepam (0.5-1.0 mg) and melatonin (3-12 mg). Clonazepam is a concern when used in patients with advanced age because it can induce sleepiness, increase fall risk, and worsen cognitive functions. Melatonin is not regulated by the Food and Drug Administration (FDA), and formulations may vary in quality and dose. Some agents with limited efficacy include rivastigmine, donepezil, and quetiapine. Sleep deprivation and medications can trigger RBD, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, tricyclic and tetracyclic antidepressant, and monoamine oxidase inhibitors (MAOIs).

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is characterized by repeated breathing cessation and/or reduction of airflow caused by partial or complete obstruction of the upper respiratory airway during sleep. This leads to intermittent hypoxia, with microarousals or awakenings, causing sleep fragmentation and EDS. Inflammation and endothelial dysfunction may ensue and reduce vascular elasticity and increase coagulation predisposing individuals to atherosclerosis, which, along with reduced oxygenation, may cause heart and brain damage.

Age over 60 is associated with significantly higher prevalence of moderate to severe OSA, because of higher airway resistance, decreased pharyngeal diameter, increased pharyngeal fat deposits, and sleep-induced upper airway muscle activity changes. Individuals with AD have a fivefold increased risk of OSA compared with age-matched controls.17

In a population-based study of people age 40 to 85, prevalence of moderate to severe OSA was 23.4% in women, and 49.7% in men, higher when over age 60, although individuals over age 60 did not report EDS as often as younger subjects implying that reliance on subjective complaints of EDS may lead to underdiagnosis of OSA in this age group.18

Prevalence of OSA in people with AD is estimated to be as much as 50% with a strong positive correlation between severity of OSA and dementia.17 In a multicenter study, when risk of sleep apnea was assessed by the Berlin Questionnaire, it was reported in 53.9% of people with AD, 58.7% of those with MCI, 74.4% of those with vascular dementia, 68% of people with frontotemporal dementia, and 76% of those with DLB/PDD.2 There is a bidirectional link between OSA and AD pathology,5,19 with patients who have OSA demonstrating higher risk of AD.20 A 3-year pilot study demonstrated significantly less cognitive decline in
individuals with AD and OSA who were treated with continuous positive airway pressure (CPAP) compared to those whose OSA was untreated.21

The increased risk of AD in people with OSA may be due to processes including oxidative stress and inflammatory immune responses through intermittent hypoxia, sleep structure changes, and disruption of slow-wave and REM sleep causing increases in β amyloid, total tau and phosphorylated tau production,7 and decreased glymphatic clearance due to high pressure changes during obstructive events.6 The increase in oxidative stress can also lead to endothelial damage and increased cardiovascular and cerebrovascular disease. It is believed there is a bidirectional relationship between sleep loss and β amyloid aggregation, with sleep loss increasing β amyloid aggregation that further fragments and decreases nonREM sleep (Figure).5,19

Treatments for OSA include surgical procedures, oral appliances, positional therapy, and hypoglossal nerve stimulation. The primary treatment however, is CPAP. Adherence to CPAP in people with AD is unknown but studies of CPAP in the general populations show adherence rates of 40% to 60% and significant numbers of people do not seek further treatment when they find CPAP intolerable. Medicare guidelines recommended use of 4 hours or more per night; however, an observational study of people with both OSA and memory impairment showed CPAP use for 6 hours per night 3 months treatment was required to normalize memory performance.22 Not all cognitive deficits can be normalized with CPAP usage, implying that OSA can lead to some degree of permanent damage to cortical functions.21

Nevertheless, treatment of OSA in AD patients is beneficial, well established, and may delay onset of cognitive decline.24 Longitudinal studies showed that sustained 1- and 3-year use of CPAP in people with AD and OSA had positive benefits on cognition and mood compared with those with AD and untreated OSA, making OSA a possible modifiable risk factor for AD.21,25

**Key Points**

- Patients with sleep disturbances have a higher risk of all-cause dementia, AD, and vascular dementia.
- Sleep disturbances are associated with worsening neuropsychiatric symptoms in dementia, which in turn are associated with higher medical cost, increased risk of nursing home placement, and reduced quality of life

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**Figure 1.** Association between obstructive sleep apnea and insomnia with Alzheimer’s disease and vascular dementia. Abbreviation: Aβ42, amyloid-β42.
for both caregiver and patient.

- Sleep disorders have emerged as prodromal biomarkers for dementia and may be therapeutic and preventive targets for dementia.
- Medical providers should be diligent in diagnosing and treating sleep disorders.

22. Baiker J, Weaver TE, Parthasarathy S, Alija HS. Adherence to CPAP: what should we be aiming for, and how can we get there? Chest. 2019. Published online ahead of print January 23.