Sleep Changes in Normal Aging

From early brain development to senescence, sleep is a dynamic and evolving state that changes dramatically as we age. In order to better understand the relationship of cognitive impairment and sleep, it is important to first review the changes that occur during the normal aging process. In reviewing the basic sleep stages that constitute a night of sleep, the vast majority of age-dependent changes in sleep architecture occur well before the age of 60.\(^1\) For example, in late adolescence and early adulthood, slow-wave sleep declines, while in middle age and beyond the proportion of stage 1 nonrapid eye movement (NREM) sleep may
increase slightly, while rapid eye movement (REM) sleep decreases. Among the elderly, there are few significant changes in sleep architecture, with only slight increases in stage 1 NREM sleep and more wakefulness occurring after sleep onset.

Insomnia and excessive daytime sleepiness are common in elderly individuals. The Established Populations for Epidemiologic Studies of the Elderly (EPESE) evaluated 9000 participants and found that 29% of those older than age 65 had difficulty maintaining sleep. It is speculated that a reduced homeostatic sleep drive may contribute to more frequent awakenings, especially from stage 2 NREM sleep, and lead to more fragmented sleep. In addition, obstructive sleep apnea (OSA) may lead to both nocturnal awakenings and excessive daytime sleepiness, and increases with age.

Aging may also impact the circadian rhythm, a complementary alerting signal that directly affects the timing of optimal sleep and wakefulness. There is evidence that aging contributes to decreased amplitude of the sleep–wake rhythm and core body temperature. The endogenous system may become less responsive to phase shifting due to impairment of the suprachiasmatic nucleus (SCN), the body’s circadian pacemaker. In addition, visual impairment, such as that caused by cataracts or macular degeneration, may affect the retinal ganglia cells that project to the SCN, further exacerbating the problem. In one study, elderly subjects with impaired vision were 30–60% more likely to have disturbed night time sleep when compared to age-matched controls. Without light input to reset the innate circadian rhythm, misalignment may occur and contribute to both insomnia and daytime sleepiness.

When considering poor sleep among the elderly, there is an extensive list of potential causes, including primary sleep disorders, comorbid medical and psychiatric illnesses, medications, lifestyle choices, and environmental considerations (Table 4.1).

Regardless of the cause, poor sleep can have significant impacts on quality of life and overall health. Both depression and anxiety are associated with poor sleep, and poor sleep is a risk factor for depression among the elderly. In particular, there seems to be a negative association between poor sleep and cognitive function. Women may be particularly susceptible to impaired cognition in the context of poor sleep. In the Study of Osteoporotic Fractures, older women scored lower on the Mini Mental State Examination (MMSE) and took more time to complete Trail Making Tests as sleep efficiency decreased and sleep onset latency increased. Cognitive decline over 15 years was more likely to occur when sleep efficiency was less than 70% in the same population. Another cohort, the participants in the Nurses’ Health Study, demonstrated worse cognitive performance, including memory and attention, with sleep durations of less than 5 h. Moreover, sleep-disordered breathing appears to contribute to neurocognitive decline, especially among women.

**SLEEP IN DEMENTIA**

Dementia is defined as a disorder that includes cognitive or behavioral impairment that represents a decline from prior functioning and causes impairment in occupational or social functioning. The impairment must not be better explained by delirium, substance or toxin exposure, or another medical or psychiatric condition. The global prevalence of dementia is estimated to be more than 24 million, mostly constituting Alzheimer’s disease (AD), and is expected to double every 20 years through 2040. The criteria used to define these disorders
continue to evolve as the scientific understanding of the various etiologies advances. This section will review the sleep characteristics associated with eight of the major subtypes of dementia, some of which are associated with other medical disorders (Table 4.2).

**Alzheimer’s Disease**

AD is a progressive neurodegenerative disorder characterized by decline in episodic memory, language, visuospatial function, and executive function. The pathology of the disease is...
characterized by the deposition of neurofibrillary tangles and neuritic plaques, the accumulation of which leads to the dysfunction and loss of healthy neurons. Ultimately, widespread structural degeneration can include the entorhinal cortex, hippocampus, amygdala, nucleus basalis of Meynert, suprachiasmatic nucleus, intralaminar nuclei of the thalamus, locus coeruleus, raphe nuclei, central autonomic regulators, and finally cortex. These abnormalities can have profound effects on sleep.

In mild to moderate AD, sleep disturbances occur in 25% of patients; in advanced stages, more than 50% are impacted. Symptoms include excessive daytime sleepiness (often manifesting as naps), insomnia, frequent nocturnal awakenings and early morning awakenings, and may gradually lead to greater functional impairment. There are specific sleep state changes noted on polysomnography (PSG) and characteristic electroencephalographic (EEG) abnormalities in wakefulness with AD. The proportion of stage 1 NREM increases with more frequent awakenings, with a corresponding decrease in slow-wave sleep. The K-complexes of stage 2 sleep become less frequent and poorly formed, of lower amplitude, shorter duration, and lower frequency. The density of delta waves in stage NREM 3 sleep is also reduced. Episodes of REM sleep are of shorter duration, perhaps due to degeneration of the cholinergic nucleus basalis of Meynert. Normally, this structure inhibits the nucleus reticularis of the thalamus, which generates NREM sleep. With the loss of this inhibition, NREM sleep constitutes more of the total sleep time. In wakefulness, slowing of the dominant occipital rhythm occurs with increased theta and delta intrusion. REM sleep behavior disorder (RBD) rarely occurs in Alzheimer’s disease and if present may suggest an alternate or comorbid diagnosis, such as dementia with Lewy bodies (DLB).

Structural changes of the hippocampus occur with disrupted sleep. As measured by volumetric MRI, reduced sleep efficiency (time asleep/time in bed) leads to reduced hippocampal volumes over time. Reduced sleep efficiency may occur in the setting of insomnia and OSA as well. Growing evidence suggests treatment of the latter condition with continuous positive airway pressure (CPAP) may help reverse these morphological changes.

There appears to be a bidirectional relationship between amyloid-β(Aβ) plaque formation and compromised sleep. Levels of Aβ are regulated by neuronal synaptic activity and the sleep–wake cycle. Sleep deprivation increases Aβ deposition, while sleep recovery decreases Aβ. This process can be potentiated by orexin, a wake-promoting neurotransmitter. Amyloid deposition in cognitively normal individuals, a preclinical stage of Alzheimer’s disease, is associated with poor sleep quality. Following plaque formation, the sleep–wake cycle degenerates in mice models and the normal diurnal fluctuation is lost. Artificial dissolution of these plaques normalizes the sleep–wake cycles. The circadian rhythm disturbances often occur early in the course of the disease and impairment of circadian clocks at the cellular level may have a role in the neurodegenerative process by contributing to oxidative stress (Fig. 4.1).

These neuropathological observations have important clinical implications. Chronic sleep deprivation, due to either restricted quantity with failure to meet sleep needs, or undermined quality due to other sleep disorders like sleep apnea, are risk factors that may contribute to these pathological changes. Moreover, loss of normal sleep–wake cycles may lead to the type of circadian disruption and sleep irregularities frequently seen in dementia.

Beyond the electrical, imaging, and pathological changes, important clinical consequences occur as AD progresses. The most disruptive phenomenon may be the circadian
occurrence of sundowning, a delirium-like state that includes nocturnal agitation and wandering behaviors. The nucleus basalis of Meynert also modulates the SCN and its degeneration may contribute to altered sleep–wake rhythms and melatonin production. One manifestation of these circadian changes is the development of an irregular sleep–wake rhythm disorder (ISWRD). This condition is characterized by chronic patterns of irregular sleep and wake episodes throughout the 24-h period, with insomnia at night and excessive daytime sleepiness (with napping) during the daytime. Instead of a major period of sleep lasting 6 or more hours and occurring overnight, multiple irregular sleep bouts occur throughout the day and night. The longest period of sleep typically lasts less than 4 h. Despite the disorganization and variability in the timing of sleep, the total amount of sleep obtained may be normal for age. ISWRD may be exacerbated by institutionalization, with a lack of exposure to synchronizing factors such as natural light and regular social schedules. Beyond the safety concerns associated with wandering and falls, the condition is highly disruptive to the sleep of caregivers and this may lead to higher rates of placement in assisted living.

Despite the high incidence of insomnia, the use of hypnotics as first-line treatment among this population is discouraged. The use of sedative-hypnotics may exacerbate the development of delirium, worsen cognition, and may be associated with a higher incidence of falls and hip fractures. Over-the-counter agents containing diphenhydramine are associated with an exceptionally high risk of delirium in this patient population due to anticholinergic side effects. Though there may be modest improvements in total sleep time with the use of zolpidem or zaleplon (averaging about 25 min), research indicates that the associated risks for altered cognition (odds ratio 4.78) and daytime fatigue or sleepiness (odds ratio 3.82) are

substantial. One retrospective case-control study found the associated risk of a hip fracture doubled with the use of zolpidem in the elderly population. It should be noted that insomnia itself, especially when occurring in the context of nocturia and daytime sleepiness, seems to be independently associated with an increased likelihood of falling.

Alternatively, efforts to reinforce the circadian rhythm through preservation of zeitgebers (time-givers), such as properly timed light exposure and efforts to minimize napping, may be helpful. It is highly important to educate caregivers and to engage them actively in the intervention. Although 15–30 min of natural sunlight exposure upon awakening is preferred, the use of a light box may be considered. Research has shown that sleep duration improves by about 15 min with both morning and all-day exposures to 2500 lux of artificial light. By combining light exposure with efforts to limit time in bed during the day, increased daytime physical activity, and reduced noise and light at night, dramatic reductions in daytime sleep have been noted in nursing home patients. There was no significant change in hours of night time sleep or number of awakenings, however. The exposure to light may have further impacts on mood and cognition.

There is little evidence that the use of oral melatonin improves on these effects.

Frontotemporal Dementia

Frontotemporal dementia (FTD) accounts for 5–15% of all dementias. FTD is characterized by early personality changes, executive dysfunction, and language difficulties. Behavioral changes may manifest as disinhibition, loss of insight, hyperorality, lack of social awareness, and apathy. It is estimated that up to 75% of patients with FTD have sleep disturbances. The sleep–wake rhythm is disturbed, but with less marked changes compared to AD. These rhythms may be highly fragmented with phase advancement of the overnight sleep epoch, resulting in an earlier onset and offset of sleep relative to conventional sleep timing. EEG may demonstrate generalized slowing with increased theta and delta activity in the frontotemporal regions, corresponding with the areas of degeneration.

Parkinson’s Disease

Parkinson’s disease (PD) is a neurodegenerative disease with distinctive motor features of rigidity, bradykinesia, and tremor. Cognitively, patients may have mild cognitive impairment affecting executive and visuospatial function. About 80% of patients with PD will go on to develop dementia within 8 years. Pathologically, Lewy bodies, eosinophilic spherical cytoplasmic inclusions with dense cores and peripheral halo, are present and may be indistinguishable from those of Lewy body disease. Dopaminergic medications used to treat PD may exacerbate confusion and hallucinations, which may actually represent the intrusion of REM elements into wakefulness. In one study that reviewed the EEG findings of patients with PD, electrocortical slowing was noted in up to one third of patients, predominately in the temporal, occipital and frontal regions. In addition, patients with RBD have been observed to have EEG slowing of the dominant occipital frequency, along with higher theta power during wakefulness in all regions of the brain.

There is substantial evidence that RBD is an early manifestation of neurodegenerative disorders of alpha-synucleinopathy deposition [PD, DLB, and multiple system atrophy (MSA)],
sometimes preceding these diagnoses by decades. Clinically, RBD can interrupt sleep for the patient and caregiver, leading to impaired cognition and fatigue, and may result in injury to the patient or bed partner. For a more thorough review of this topic, the reader is directed to the movement disorders chapter of this text.

### Lewy Body Dementia

DLB is second only to AD in terms of prevalence, affecting an estimated 1–5% of the population. Compared to patients with AD, patients with DLB more frequently complain of sleep disturbances, abnormal nocturnal movements, and excessive sleepiness, with approximately 50% reporting elevated Epworth sleepiness scales. PSG may demonstrate reduced sleep efficiency, respiratory disturbances consistent with obstructive sleep apnea in 88%, and periodic limb movements of sleep (PLMs) associated with arousals in 74%. The latter finding may represent an increased incidence of restless legs syndrome in this population, which by itself can contribute to sleep fragmentation, nocturnal awakenings, and insomnia. One study found that 75% of patients who underwent PSG had arousals unrelated to movement or breathing abnormalities, and that these arousals were not entirely accounted for by a primary sleep disorder. This same study found that 96% of patients reported RBD, and this was confirmed by PSG in over 80%. Another study found 12 of 15 patients with RBD and a neurodegenerative disease had limbic or neocortical Lewy body disease at autopsy; consequently, RBD is a supportive feature in the diagnostic criteria. The awake EEG may demonstrate generalized slowing with loss of alpha and increased theta activity, correlating with the severity of the disease. Transient sharp waves may be noted in the temporal regions. Frontal intermittent rhythmic delta activity (FIRDA) has also been reported. The degree of fluctuation in cognition seems to be reflected by variability in the mean EEG power. Reducing fluctuations in arousal with cholinesterase inhibitors not only improves cognition but may also treat the visual hallucinations that sometimes occur. The reduction in the psychiatric, sleep, and cognitive aspects of the disease can greatly improve the quality of life for these patients.

### Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is a dementia associated with degeneration of the frontosubcortical neural networks, often resulting in apathy, decreased executive function, or impulsivity. It is characterized by progressive axial rigidity, postural instability, and supranuclear gaze palsy, corresponding with impaired downward gaze. Pathologically, tau tangles are present along with gliosis and neuronal loss in the brainstem and basal ganglia. Patients with PSP complain of excessive daytime sleepiness and are noted to have a dramatic reduction in REM sleep. Cognitive decline is reflected by EEG slowing that predominates in the frontal regions during wakefulness. There is also evidence that CSF hypocretin 1 (orexin A) levels may be reduced in some patients, a finding common in narcolepsy, correlating with the duration of disease. REM without atonia has been reported, indicating a possible association with RBD. One study estimated that 28% of patients with PSP have loss of atonia and 13% have clinical RBD, confirmed by PSG.
Vascular Dementia

Vascular dementia is characterized by progressive cognitive impairment secondary to recurrent vascular injury. Sleep in vascular dementia is characterized by more disruption of the sleep–wake cycle and decreased sleep quality. The EEG demonstrates slowing of the dominant occipital rhythm, increased theta activity, and increased delta activity. In addition, there is more alpha activity noted anteriorly, which may correlate to diminished vigilance and fluctuating cognition.

Huntington’s Disease

Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder characterized by caudate atrophy. The pathophysiology involves expansion of a CAG trinucleotide repeat in the IT15 gene located on the short arm of chromosome four. Symptoms include choreiform movements, cognitive impairment with early executive dysfunction, and psychiatric manifestations such as depression. Dementia can occur as the disease progresses.

Degeneration affects the SCN, motor cortex, and striatum and the loss of SCN function leads to disruption of the circadian rhythm. As a result, sleep latency can increase, sleep efficiency and slow-wave sleep can decrease, and nocturnal awakenings occur more frequently. When HD progresses in severity, PLMs increase, although this may not necessarily translate to increased daytime sleepiness. Moreover, gradual slowing and reduction of the wake EEG amplitude is noted with increased theta and decreased alpha activities.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive dementia resulting from accumulation of misfolded prion proteins. Pathological findings include gliosis and vacuolation. CJD is associated with myoclonus and ataxia. Associated diagnostic findings include EEG sharp wave abnormalities, elevated CSF tau levels, and prion induction via real-time quaking-induced conversion (RT-QuIC). The disease is rapidly progressive, with a mean survival of 4–8 months, although 5–10% may survive 2 years or more.

More than half of patients experience sleep disturbances, mostly insomnia, and up to 15% present initially with sleep complaints. Aggressive behaviors and dream-reality confusion, in which it is hard to distinguish what occurs as part of dream mentation from real life events, may occur in sleep. Central or obstructive sleep apnea events are significantly elevated, although the exact prevalence of these conditions is not well studied.

PSG studies in CJD demonstrate disorganized sleep patterns with abrupt transitions between sleep stages, few sleep spindles and K-complexes, and a lower amount of REM sleep. During wakefulness, the EEG demonstrates hallmark periodic sharp wave complexes—biphasic, triphasic, or mixed spikes or slow waves—with a generalized slow background.
There is a growing body of literature that suggests that sleep deprivation and sleep disorders can independently contribute to the development of cognitive impairment and dementia. While the role of sleep in humans in not completely understood, it is clear that it serves at least several important restorative functions. Researchers in 2012 described the gliovascular clearance system, or “glymphatics,” a network of CSF-filled paravascular spaces that flush interneuronal debris from the brain parenchyma. Sleep is, at least in part, a process by which these metabolic waste products—including adenosine (a signal for sleepiness)—are removed from the brain. Slow-wave sleep seems to enhance the activity of the glymphatic system by approximately 60%.

As mentioned earlier, there may be a bidirectional relationship between Aβ plaque deposition and sleep changes. Mouse models demonstrate that plaque formation may lead to more fragmented sleep with a loss of the natural diurnal variation of Aβ, while dissolution of these plaques normalizes sleep–wake cycles. It is possible that disorders that disturb sleep quantity and quality may exacerbate neurodegeneration.

OSA has long been implicated as a potential contributing factor in the development of dementia. Sleep-disordered breathing occurs more frequently in Alzheimer’s disease than in age-matched controls, with prevalence estimates ranging from 40% to 50%, and its severity is correlated with the degree of cognitive impairment. Though a causal relationship is not yet established, it is hypothesized that both sleep fragmentation and intermittent hypoxia may contribute to neurodegenerative changes. Chronic and recurrent hypoxia may affect highly oxygen-dependent regions of the brain, including the hippocampus and neocortex, while secondary hypertension may exacerbate cognitive decline.

Elevated blood pressure during sleep may also play a direct role in Aβ deposition. The normal reduction in blood pressure that occurs during sleep is referred to as “dipping.” It has been demonstrated that “nondippers,” or those who do not exhibit this normal blood pressure reduction, have higher levels of Aβ deposition in the posterior cingulate region when compared to normal “dippers.” It has also been demonstrated that patients with both OSA and insomnia have a greater risk of nondipping during sleep. In addition, hypoxia can lead to endothelial dysfunction, inflammation, and oxidative stress in vulnerable cell populations. This cellular stress may become sufficient to impair cell–cell interactions, synaptic function, and neural circuitry. OSA also results in extensive sleep fragmentation, undermining sleep quality, which may further potentiate Aβ deposition. Individuals with Down syndrome serve as an interesting example as they have an increased incidence of both OSA, due to midface hypoplasia, and early-onset AD. Based on the available evidence, it is reasonable to assume that untreated OSA may lead to more rapid progression of dementia, and treatment with CPAP may delay the onset of the disease. Normalization of sleep should be a priority in managing those with dementia to optimize daily function and to protect remaining cognitive reserve.

Insomnia is very common in patients with dementia, and many of these patients take medication to help them fall asleep. Although there is some data to suggest that those taking over-the-counter and prescription sleeping pills have a greater risk of developing dementia,
direct link has not been established and there are likely several confounding variables at play. Anticholinergics\textsuperscript{108} and benzodiazepines\textsuperscript{109} have been demonstrated to worsen cognitive impairment. Limited research suggests that the most popular nonbenzodiazepine sleep aid, zolpidem, may increase the risk of dementia, although again this has not been firmly established and many confounding variables may be contributing.\textsuperscript{110} Interestingly, nocturnal awakenings and resulting insomnia commonly occur in untreated OSA. This might explain the increased association of dementia among the elderly population with comorbid hypertension, diabetes, and stroke—all conditions that are provoked by OSA. This might also explain the association between dementia and proton pump inhibitors, as OSA frequently incites symptoms of reflux due to the increase of negative intrathoracic pressure during apneic events.\textsuperscript{111} These medications may be used to treat symptoms that are actually the result of untreated OSA, chronically damaging vulnerable brain cell populations.

\section*{TREATMENT}

\subsection*{Insomnia}

Difficulty initiating or maintaining sleep may occur as part of insomnia and contribute to fragmented sleep and agitated behaviors. Insomnia may be exacerbated by irregular sleep habits, excessive daytime sleeping, pain, medication effects, poor sleep environment, and comorbid depression.\textsuperscript{112} Proper sleep hygiene includes a regular bedtime routine, avoidance of caffeine and alcohol in the hours preceding sleep, and increased activity during the day. As much as possible, benzodiazepine and anticholinergic medications should be avoided as they may contribute to confusion and cognitive decline.

\subsection*{Circadian Disorders}

Degeneration of the circadian rhythm via disruption of the SCN and pineal gland, or inadequate or improperly timed light exposure may contribute to sleep irregularities, resulting in insomnia and daytime sleepiness.\textsuperscript{113,114} Although some of these changes are irreparable due to the disease process itself, a regular sleep schedule and properly timed light exposure may still be helpful.\textsuperscript{115-117} In addition, low doses of melatonin may enhance the circadian signal and reduce sundowning phenomena without significant adverse effects, although the benefits may be modest compared to light exposure.\textsuperscript{118,119}

\subsection*{Obstructive Sleep Apnea}

As discussed, there is growing evidence that OSA may worsen cognitive decline and contribute to dementia.\textsuperscript{120} Untreated, the condition is associated with snoring, excessive daytime sleepiness, nocturia, nocturnal awakenings, bruxism, and mood complaints. A small percentage of dementia patients with comorbid OSA may experience cognitive benefit with CPAP treatment.\textsuperscript{121} Clinical experience demonstrates that CPAP is surprisingly well tolerated by those with dementia and caregivers may likewise benefit from improved sleep.
Restless Legs Syndrome and Periodic Limb Movements of Sleep

Restless legs syndrome (RLS), or Willis-Ekbom disease, is characterized by an uncomfortable feeling, often in the legs, associated with an urge to move, relieved by movement, that occurs more often in the evening and during periods of prolonged immobilization. It may trigger nocturnal wandering and be associated with periodic limb movements during sleep that lead to sleep fragmentation. The exact prevalence of these conditions among patients with dementia is difficult to determine and remains unknown. RLS does increase in incidence among older individuals, with a peak prevalence in older women (16.3% among those age 60–69) and late middle-aged men (7.8% among those age 50–59). Iron replacement when serum ferritin levels fall below 50 may be helpful. Dopamine agonists may also be an effective therapeutic option, though these medications may exacerbate hallucinations and psychosis among susceptible individuals. Therefore, they should be used with caution or not at all among patients with DLB. For a complete review of RLS including treatment options, the reader is directed to the movement disorders chapter in this text.

REM Behavior Disorder and Parasomnias

Dream-enactment behaviors such as kicking, hitting, and jumping out of bed may occur as part of RBD. These can be potentially harmful to both the patient and his or her bed partner. Therefore, safety precautions and protective measures are recommended with the removal of dangerous objects, clearing away bedside furniture, and lowering the mattress to the floor. Clonazepam and high-dose melatonin are effective in reducing these behaviors with few side effects. RBD and its association with neurodegenerative disease is also covered in detail in the movements disorders section of this text.

CONCLUSIONS

Sleep disorders are extremely common in patients with neurodegenerative disease. As the population ages, this will become an even greater issue. The interplay between sleep and cognition is complex and it is only recently that efforts have been made to systematically evaluate these connections; thus, much research is still needed. Sleep is an often-overlooked component of patients’ health, and the evaluation of any patient with cognitive symptoms should include a review of their sleep history. Treatment can be difficult, but if successful may slow progression of disease and lead to greater quality of life for both patients and caregivers.

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4. SLEEP AND COGNITIVE IMPAIRMENT


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