

Sleep & Neurodegenerative Disease

Sleep problems are common and treatable in neurodegenerative disorders, and may also be a treatable risk factor and early biomarker.

By Raman K. Malhotra, MD



Introduction

Cerebral neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD) are increasing in prevalence as our population ages. In addition to progressively worsening neurologic symptoms such as gait abnormalities, tremor, spasticity, and memory deficits, many people with neurodegenerative disease also suffer from sleep complaints such as insomnia, excessive daytime sleepiness, or abnormal motor activity during sleep. The higher prevalence of sleep disorders in this population is not only secondary to the underlying neurologic symptoms, but also a consequence of damage to sleep-controlling regions of the brain, often affected in neurodegenerative disorders. For example, rapid eye movement (REM) sleep behavior disorder can present years or decades before any other neurologic symptoms or signs are present, and may serve as an early biomarker for neurodegenerative conditions such as PD or other synucleinopathies. Despite a growing appreciation of the significance of sleep in this population, sleep disorders frequently remain undiagnosed and untreated. It is important for clinicians to recognize and properly manage sleep disorders because treatment may improve neurodegenerative disease symptoms and quality of life for both the patient and their caregivers. Sleep may also play a key role in the onset and progression of neurodegeneration. For example, there is growing evidence that poor sleep can accelerate progression of neurodegenerative disorders, such as AD, and may play a role in pathogenesis of the disease.

Parkinson's Disease and Other Synucleinopathies Insomnia

Sleep disorders are seen in a large percentage of patients with PD and other synucleinopathies, with one of the most common disorders being insomnia.¹ Insomnia is defined by repeated difficulties with sleep initiation, maintenance, or quality that occur despite adequate time and opportunity for sleep. The prevalence of insomnia in patients with PD is reported to be as high as 60%.¹ Insomnia may be secondary

to the underlying symptoms of the condition, such as stiffness, difficulties turning in bed, pain, depression, or nocturia. Medications used to treat PD may cause excessive daytime sleepiness and napping during the day, leading to poor sleep at night as a result of dissipated homeostatic sleep drive. Insomnia can also result from damage to the sleep-controlling brain centers, and, as the underlying neurodegenerative condition progresses, sleep also deteriorates. Objectively, polysomnography in patients with PD shows a breakdown of sleep architecture manifesting in prolonged sleep latency, fragmented sleep, reduced slow-wave sleep, and reduced REM sleep.²

Evaluation of insomnia requires a thorough history of an individual's sleep schedule and bedtime habits. Using sleep logs, sleep diaries, or actigraphy can be helpful to collect this information. When insomnia causes daytime effects (eg, fatigue, irritability, mood changes, or worsening motor function), therapeutic intervention may be needed. Conversely, symptomatic treatment of motor and nonmotor symptoms in patients with PD improves sleep in this population.³ This can include treatments such as general optimization of the primary treatment regimen, or the addition of long-acting dopamine agonists (or transdermal preparations) before sleep.

Patients complaining of insomnia should be asked about symptoms of restless legs syndrome (RLS), as this occurs in up to 20% of patients with PD,⁴ and can be treated by supplementing iron if levels are low or plasma ferritin is low (< 50 ng/L). In patients with moderate to severe RLS, clinicians can consider initiating dopamine agonists (eg, pramipexole) or $\alpha 2\delta$ ligands (eg, gabapentin) to help improve symptoms.

Proper identification and treatment of any underlying circadian rhythm disorders are also important in improving sleep in this population. Circadian rhythm disorders are misalignment of the person's own internal clock and their desired bedtime and wake times. In the case of advanced sleep-wake phase disorder, which is commonly seen in elderly patients, it presents as patients having difficulties remaining awake in the late evening accompanied by early morning awakenings or sleep maintenance insomnia.⁵ Treatment of advanced sleep-wake phase

disorder involves evening bright light therapy to help realign (or delay) the person's internal clock with their desired sleep schedule (Figure). Moreover, the essential interaction between the dopamine system and the suprachiasmatic nucleus (SCN) underscores the progressive degeneration of the circadian rhythms, reflected in flattened diurnal activity patterns and reduced quiescence at night.⁶

Hypnotic medications may be necessary under certain circumstances but should be used cautiously in this population because of increased falls and impaired cognition associated with their use. As in the general population, cognitive behavioral therapy for insomnia (CBT-I) is strongly suggested as first-line therapy for treatment of insomnia, although evidence for efficacy in this population specifically is limited. Sufficient data is also lacking regarding safety and efficacy of hypnotics in patients with synucleinopathies. Some studies have shown effectiveness of eszopiclone or doxepin in improving subjective impressions of sleep in patients with PD, but not objective measures of sleep.^{7,8} Other sedating antidepressants have been used clinically as well, but there are again concerns regarding side effects as well as the potential for worsening RLS or periodic limb movements of sleep. As in all cases, benefits of therapies must be weighed against risks.

Hypersomnia

Excessive daytime sleepiness and sleep attacks (sudden-onset sleep) are common in patients with synucleinopathies due to a variety of pathobiologic mechanisms.⁹ Sleep attacks can be dangerous if they occur during driving, work, or other activities where a sudden change in alertness may be dangerous. Sleep attacks can also be a side effect of dopamine agonists commonly used as treatment in patients with PD. Narcolepsy can be seen in some individuals with PD or multiple system atrophy (MSA), with evidence of damage to hypocretin neurons in the hypothalamus reported in some cases.¹⁰ Sleep-disordered breathing in the form of obstructive sleep apnea (OSA) and central sleep apnea (CSA) is commonly seen in synucleinopathies, although it is unclear if prevalence truly exceeds that of age-matched controls.¹¹ Diagnosis of sleep apnea requires attended polysomnography (or home sleep apnea testing in the appropriate patient) to confirm the diagnosis in patients who have multiple symptoms or risk factors for sleep apnea. Continuous positive airway pressure (CPAP) has been shown to improve excessive daytime sleepiness in this population, although adherence remains a challenge, similar to the general population.¹² In addition to typical OSA symptoms, patients with MSA may present with stridor and laryngeal dysfunction which requires treatment with CPAP or other forms of nocturnal ventilation. If underlying sleep disorders and medication side effects are addressed, and hypersomnia remains a major issue, wake-promoting agents can be used to combat excessive daytime sleepiness and fatigue.

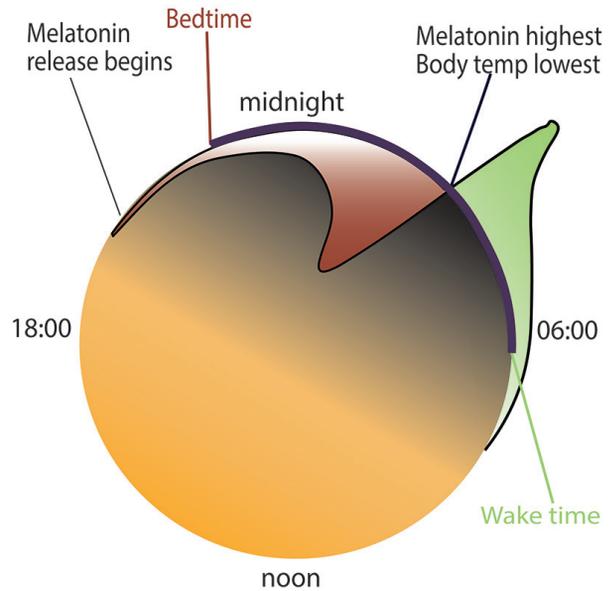


Figure. Properly timed bright, dim light, and melatonin can advance or delay a person's circadian rhythm. Light exposure in the green zone advances and locks in the sleep cycle. Light exposure in the red zone can disrupt the circadian system by suppressing melatonin and pushing the internal clock later.

Limited evidence in the literature demonstrates effectiveness of caffeine, modafinil, and methylphenidate in this population. Wake-promoting agents and stimulant medications should be used with caution in patients with comorbid cardiac or psychiatric disorders, which are commonly seen in this age group.¹³

Parasomnias

Patients with synucleinopathies may report abnormal movements during sleep, with REM-sleep-behavior disorder (RBD) being the most common parasomnia, occurring in up to 60% of patients with PD, or even higher in those with MSA or dementia with Lewy bodies (DLB). Consisting of complex motor behaviors, such as reaching, grabbing, kicking, or other vigorous motor activity that could lead to injury of the patient or bed partner, RBD occurs out of REM sleep. If awakened from the event, the patient will return to normal levels of consciousness, but may remember dream content related to the motor activity. In addition to a clinical history of dream-enactment behavior, RBD diagnosis requires attended polysomnography to demonstrate REM sleep without atonia, or increased muscle tone during REM sleep. Polysomnography is also helpful in this scenario to rule out other mimics (eg, periodic limb movements of sleep or sleep-disordered breathing) that can also cause movements during sleep.

Seen not only in patients with synucleinopathies, RBD may predate onset of other clinical symptoms of these diseases by years or even decades. Studies following patients with idiopathic RBD have demonstrated high rates of conversion to PD

and other synucleinopathies: 45% conversion rate at 5 years, 76% at 10 years, and over 90% at 14 years.¹⁴ Although the high risk of conversion to future neurodegenerative disorders is known, there is no proven neuroprotective therapy to delay or prevent onset or progression of these neurodegenerative diseases yet. Follow up typically involves a regular, detailed neurologic history and exam to look for early signs of disease.

Initial therapy for RBD includes patient education about securing the home and avoiding injury to the patient or bed partner during an episode (Box 1). Treating any underlying primary sleep disorders such as RLS or sleep-disordered breathing should also be emphasized in order to prevent arousals that could precipitate an RBD event. Pharmacologic treatment of RBD is clonazepam or melatonin.¹⁵ Melatonin at high doses (9 to 15 mg nightly) improves RBD symptoms, with less potential for side effects. However, given the potential danger of RBD events, in particularly refractory cases, alternative treatments, such as sodium oxybate, may be required (see *Update in Sleep Medicine Therapies* in this issue).

Alzheimer's Disease and Other Tauopathies

Insomnia

Neurodegenerative disorders associated with abnormal tau accumulation, including AD, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), are commonly associated with sleep disorders, mainly due to underlying damage to sleep-controlling brain regions but also to underlying psychiatric, medical, and primary sleep disturbances; medication-related effects; and insufficient light exposure and activity during the day. Polysomnography in patients with AD show decreased sleep efficiency, percentage of slow-wave sleep, and REM sleep, as well as prolonged REM-sleep latency, compared with age-matched controls.¹⁶

Insomnia and disrupted sleep at night are prominent features early on in AD. Some of these symptoms may be related to underlying circadian rhythm disorders that are caused by

degenerative changes to the suprachiasmatic nucleus (master clock), as well as changes in melatonin release.¹⁷ Patients with AD who have circadian rhythm disorders tend to have prolonged wakefulness at night and consequently have sleepiness and naps during the day. Sundowning, with worsening behavior, agitation, and confusion at night is known to occur in this population as well, and may reflect the degeneration of normal circadian rest-activity patterns.¹⁸ Lack of daytime light exposure and decreased physical and social activities during the day (common in patients in nursing homes) ultimately exacerbate the underlying physiologic problem.¹⁹ Moreover, disrupted sleep and insomnia not only cause worsening daytime symptoms of fatigue, sleepiness, and confusion during the day, resulting in perpetuation of the dysregulation and disrupted sleep for caregivers, which can contribute to burnout.

Safe and effective evidenced-based treatments for insomnia in patients with dementia are limited. Because of this, educating the patient and caregiver about good sleep hygiene and habits is an important first step to setting a strong biorhythm (Box 2). If a circadian rhythm disorder is suspected, properly timed bright-light therapy may be beneficial to entrain the internal clock (Figure). Melatonin at bedtime improves sleep quality and daytime functioning in patients with AD. In a study, both nighttime melatonin and morning light exposure for 1 hour improved daytime alertness and reduced sleep disruption in patients with AD.²⁰ The same hypnotics used in the general population including "Z-drugs" (eg, zolpidem) and benzodiazepines are also used in these patients. However, because of increased risk of falls in this population,²¹ and the possibility that these medications may worsen dementia,²² they should be avoided if possible. Judicious application of

▶▶▶ Box 1. Safety Precautions for REM Sleep Behavior Disorder

- Remove furniture with sharp edges or other sharp objects from the bedroom
- Remove weapons from the bedroom
- Move bed away from any windows
- Use heavy curtains or drapes
- Consider placing the mattress on the floor
- Put soft padding on any hard surfaces close to the bed
- Consider sleeping in separate beds to avoid injury
- Possibly add a bed alarm to awaken the patient or partner, or to pacify the patient

▶▶▶ Box 2. Healthy Sleep Habits

- Use light therapy (> 10,000 lux) throughout the day, with 30-60 min on awakening to time the internal clock
- Maintain regular activity throughout the day, with at least 30 minutes of exercise
- Avoid long naps (> 30 minutes) during the day, as this can cause problems with falling asleep at night
- Avoid large meals, caffeine (last consumption by 11:00 AM), alcohol, or tobacco within 4 hours of bedtime
- Avoid using electronics (tablets, smartphones, computers, television) 1 to 2 hours before bedtime, because this can suppress an already weak melatonin signal
- Establish a relaxing bedtime routine and avoid stressful activities before bedtime
- Set a regular bedtime and wake time and try to stick to this schedule every day
- Make sure bedroom is quiet, comfortable, and dark at night

a low-dose regimen within a defined time window may be appropriate. Comparatively, the antidepressant trazodone, in low doses, was shown to improve sleep in a small randomized, placebo-controlled study.²³

Sleep Apnea

Patients with AD commonly have OSA because incidence of sleep-disordered breathing increases with age. If patients report symptoms (eg, snoring, witnessed apneas, daytime sleepiness, or disrupted nighttime sleep), further evaluation with attended polysomnography (or home sleep apnea test in appropriate subgroups of patients) is needed to confirm the diagnosis and classify severity. Treatment options include CPAP, weight loss, positional therapy, and mandibular advancing oral appliances. It has been shown that CPAP reduces subjective daytime sleepiness, decreases arousals, and increases stage N3 sleep in patients with AD and sleep apnea.²⁴ Some studies show improved cognition and slowing of cognitive decline with use of CPAP in patients with AD.^{25,26} Adherence to CPAP therapy is the greatest challenge in patients with dementia given their cognitive deficits and confusion at night.

Emerging research suggests sleep disruption of untreated OSA may lead to higher risk, or earlier onset, of dementia or mild cognitive impairment (MCI). Other studies suggest sleep disruption from any cause increases β -amyloid levels in normal controls, suggesting this as a factor in the progression to AD.²⁷ This pathophysiologic link makes sense, because sleep may play a role in clearing toxic proteins from the brain. A majority (up to 60%) of patients with MCI have sleep complaints. Sleep studies in patients with MCI demonstrated more arousals during slow-wave sleep and increased wake after sleep onset.²⁸ More studies are necessary to better understand the role sleep plays in the onset and progression of AD, and more importantly how improving sleep can prevent or delay dementia.

Conclusion

Sleep disorders are commonly encountered in patients with neurodegenerative conditions, such as synucleinopathies and tauopathies. Sleep symptoms arise not only as consequences of damage to the central nervous system but also from medications used to treat the disease, and any comorbidities associated with these progressive conditions. Diagnosis and treatment of sleep disorders in this population may improve sleep, other symptoms from the underlying neurodegenerative condition, and quality of life. Sleep may also play a role in identifying patients at risk for future development of neurodegenerative disorders. For example, REM sleep behavior disorder may occur years to decades before other symptoms of PD. As we learn more about this patient population, there is hope that clinicians will have more tests available to better predict phenocconversion, and better yet, have agents to slow progression of the disease. Patients who are at high risk for

synucleinopathies serve as an ideal patient population to learn more about how to prevent or delay disease onset. Similarly, in patients with AD, disrupted sleep may play a role in the early degenerative process or lead to acceleration of abnormal protein deposition in the central nervous system. As we continue to learn about the complex relationship between sleep and neurodegeneration, it may be that treating sleep disorders earlier in life may ultimately prevent onset of some neurodegenerative disorders later in life. ■

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Raman K. Malhotra, MD

Associate Professor

Department of Neurology

Washington University School of Medicine in St. Louis

St. Louis, MO