Neurodegenerative Disorders and Sleep

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KEYWORDS

• Parkinson disease • Alzheimer disease • Dementia • Rapid eye movement sleep behavior disorder • Sleep apnea • Insomnia • Circadian rhythm disorder • Restless legs syndrome

KEY POINTS

- Sleep disorders are common in neurodegenerative conditions.
- Certain sleep disorders are more common in specific neurodegenerative conditions. REM sleep behavior disorder is more commonly seen in Parkinson disease than in Alzheimer disease.
- Common sleep disorders that may occur in most neurodegenerative conditions include insomnia, sleep apnea, restless legs syndrome, and circadian rhythm disorders.

INTRODUCTION

Cerebral neurodegenerative disorders, such as Parkinson disease (PD) and dementia, are increasing in prevalence as the population ages. These disorders are characterized by neuronal cell loss and abnormal accumulation of protein in cells of the brain. Symptoms, such as tremor, muscle rigidity, imbalance, and impaired cognition, progressively worsen with time. Not only are there challenges in managing the primary symptoms of these conditions, but many of these patients also suffer from sleep complaints, such as insomnia or hypersomnia. Others may suffer from abnormal movements during sleep, known as rapid eye movement (REM) sleep behavior disorder (RBD). This disorder may be dangerous and disruptive to sleep, and can sometimes precede the development of other symptoms of neurodegenerative disorders by years or even decades. High rates of sleep disorders, such as insomnia, hypersomnia, sleep apnea, restless legs syndrome (RLS), and circadian rhythm disorders, in older adults with neurodegenerative disorders are likely caused by the underlying symptoms of the disease along with damage to sleep-controlling regions of the brain. It is important to recognize and properly manage these sleep disorders because treatment may improve symptoms of the neurodegenerative condition and improve quality of life.

PARKINSON DISEASE AND OTHER SYNUCLEINOPATHIES

PD is a progressive neurodegenerative condition that causes motor symptoms of bradykinesia, shuffling gait, tremor, and rigidity. It is the second most common neurodegenerative condition affecting more than 1% of the population older than 60 years of age.[1] Patients commonly present with postural instability and falls. The pathologic hallmark of PD is Lewy bodies, which are intraneuronal α-synuclein inclusions. Lewy bodies first involve lower brainstem areas before spreading next to the substantia nigra and eventually areas throughout the brain. Motor symptoms of PD typically respond well to dopamine therapy early in the course of the disease. There are a variety of nonmotor symptoms of PD, including autonomic, olfactory, and mood dysfunction, and poor sleep. Sleep disorders are seen in most patients with PD.[2] The most common sleep disorders are

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insomnia, periodic limb movement disorder, sleep-disordered breathing, and RBD. In addition to PD, other synucleinopathies (which are central nervous system degenerative conditions caused by abnormal α-synuclein accumulation) include Lewy body dementia and multiple system atrophy, which are also associated with high rates of the same sleep disorders typically seen in patients with PD.

Sleep is disrupted in PD and other synucleinopathies for numerous reasons. The motor and nonmotor symptoms described previously can lead to poor sleep at night. Many medications used for PD can have side effects of sleepiness and poor sleep. In addition, the sleep-controlling centers of the brain are also affected by the underlying neurodegenerative process in the brain. Involvement of the pedunculopontine nucleus, locus ceruleus, pontine ceruleus alpha nucleus, and raphe nuclei are implicated in disorders of REM sleep and slow wave sleep, and have been directly localized as areas of involvement in some animal models of PD.[3]

Insomnia

Insomnia is defined by a complaint of repeated difficulties with initiating sleep, maintaining sleep, or waking up earlier than desired that occurs despite adequate time and opportunity for sleep. The symptoms should result in some form of daytime impairment to meet criteria for this disorder.[4] Patients suffering from synucleinopathies, such as PD, commonly complain of insomnia. Patients with PD more commonly suffer from sleep maintenance insomnia as compared with sleep-onset insomnia. One study cites sleep problems in 60% of patients with PD, with 76% complaining of poor sleep.[2] Insomnia may occur from a variety of issues (**Box 1**). The motor symptoms of PD can cause issues with muscle cramps, stiffness, and difficulties with turning or rolling in bed. Nonmotor symptoms, such as autonomic dysfunction (which can lead to frequent nocturia) or mood disorders, also contribute to sleep disruption. Many medications used for PD can cause disrupted sleep at night or sleepiness during the daytime (causing less sleepiness overnight). Sleep-controlling areas of the brain may be damaged leading to insomnia. As the PD and nervous system degeneration progresses, insomnia also worsens in incidence and severity. Underlying mood disorders and worsening motor and nonmotor PD symptoms also contribute to worse insomnia later in the course of the disease. Polysomnography in patients with PD demonstrates prolonged sleep latency and fragmented sleep with reduced slow wave sleep and REM sleep. Insomnia may often result in subjective complaints of daytime fatigue, irritability, mood changes, poor attention, trouble with motor skills, and may result in decreased ability to function at baseline during waking hours.

Box 1
Common causes of insomnia in Parkinson disease

- Motor symptoms (cramps, stiffness, impaired turning in bed)
- Nocturia
- Depression and/or anxiety
- Medication side effect
- Inadequate sleep hygiene
- Restless legs syndrome
- Sleep apnea
- Circadian rhythm disorders

Diagnosis and evaluation of insomnia typically involves a good history of sleep habits, bedtimes, wake times, naps, and awakenings at night. Directed questions in regards to causes or exacerbating factors of insomnia, such as RLS, medications, motor symptoms of PD, sleep apnea, and circadian rhythm disorders, should be performed. Sleep logs, diaries, and sleep trackers, such as actigraphy or wearable devices, are helpful. Polysomnography may be necessary if insomnia is thought to be secondary to sleep apnea, periodic limb movement disorder, or parasomnias.

Management of insomnia includes identifying and addressing any underlying primary sleep disorders. In addition, good sleep habits and hygiene should be encouraged. Medications and their timing should be scrutinized and possibly altered. If motor symptoms of PD are keeping the patient up at night, dopamine therapy at night may be necessary to alleviate the symptoms to help induce and maintain sleep. Short-acting carbidopa/levodopa, long-acting carbidopa/levodopa, dopamine agonists, and transdermal dopamine (ie, rotigotine patch) have shown small benefits in motor symptoms during the night in small trials.[5] Sometimes the dopamine agent itself may be causing insomnia. A decrease in dose or change in timing of the doses may improve sleep.

Primary sleep disorders, such as RLS and circadian rhythm disturbances, need to be correctly identified as a cause of insomnia in patients with PD. RLS is seen in 15% to 20% of patients with PD.[6] RLS is difficult to distinguish from other causes of leg pain in this population, such as muscle spasms and arthritis. Serum ferritin and iron

studies should be evaluated in these patients and replaced if low (ie, ferritin <50). Other treatments for RLS include dopamine agonists, gabapentin, pregabalin, and opioids. Some patients who present with sleep maintenance insomnia or early morning awakenings may have a circadian rhythm disorder, such as advanced sleep-wake phase disorder. This condition is seen more commonly in the older population and in patients with neurodegenerative disorders. Delayed sleep-wake phase disorder is also seen in this population and may present with sleep-onset insomnia or difficulties awakening in the morning. Circadian rhythm disturbances have been described in patients with PD, including disruption of circadian markers, such as cortisol and melatonin levels.[7,8] Diagnosis should include a detailed history, sleep logs, and actigraphy. Patients with advanced sleep-wake phase disorder demonstrate evening sleepiness with difficulties in staying asleep. A prolonged sleep latency and later wake times are commonly reported in delayed sleep-wake phase disorder. Treatment of advanced sleep-wake phase disorder involves evening bright light therapy. Treatment of delayed sleep-wake phase disorder involves bright light on awakening in the morning along with evening melatonin several hours before desired bedtime.

Hypnotic medications should be used judiciously in this population because of concerns of causing falls, worsened balance, and impaired cognition. Potential benefits of therapies should be weighed against their risks. Hypnotics used in the general adult populations are the same agents typically used in patients with PD. There are limited studies evaluating use in this specific population. Studies have demonstrated effectiveness of eszopiclone and another with doxepin in improving subjective impression of sleep in patients with PD, but not objective measurements.[9,10] Sedating antidepressants have been used, but there should be caution because they may worsen RLS or periodic limb movements of sleep. As in the general population, cognitive behavioral therapy for insomnia is strongly suggested as first-line therapy for treatment of insomnia, although again evidence is scarce in relation to its effectiveness specifically in patients with PD.

Hypersomnia

Excessive daytime sleepiness is a common symptom in patients with PD. Because hypersomnia is a side effect of dopamine therapy, this may present early on in the disease process when dopamine therapy is initiated for motor symptoms.[11] However, this is not the only reason that excessive daytime sleepiness may present in this population (**Box 2**). Many wake-promoting regions in the brain are affected in PD, including the locus coeruleus, raphe nucleus, and hypocretin neurons, among other areas. One study suggests that hypersomnia precedes the development of other motor symptoms in PD, demonstrating sleepy adults had a three times higher risk of developing PD than non-sleepy adults.[12] Sleepiness may present with sleep attacks, or sudden onset sleep, which are more commonly reported in patients with PD (up to 14%) than age-matched control subjects.[13] Sleep attacks are 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. In PD and multiple system atrophy, there has been evidence of damage to hypocretin neurons in the hypothalamus, leading to a narcolepsy-like condition with related symptoms.[14] Low hypocretin levels have been measured in patients with PD with these symptoms.[15]

A careful interview and evaluation for primary sleep disorders (eg, sleep apnea, restless legs, insomnia) is an important first step. Sleepiness as a possible side effect of dopamine therapy must also be recognized in patients with PD presenting with hypersomnia. If these factors and other causes of hypersomnia have been addressed, then use of a wake-promoting agent can be considered. Agents used to treat hypersomnia and narcolepsy in the general population are the same ones used in patients with PD with hypersomnia. Caffeine, modafinil, and methylphenidate have all been shown to improve sleepiness in patients with PD.[16,17] One trial used sodium oxybate and demonstrated improvement in symptoms.[18] Given the age of the population, caution must be used when starting wake-promoting agents in patients with comorbid cardiac or

Box 2
Common causes of hypersomnia in Parkinson disease

- Sleep apnea
- Medication side effect
- Loss of hypocretin neurons (central nervous system hypersomnia)
- Insufficient sleep
- Circadian rhythm disorder
- REM sleep behavior disorder

psychiatric disorders, and adverse effects, such as hypertension, confusion, and agitation, should be monitored.

Sleep-Disordered Breathing

Sleep-disordered breathing in the form of central and obstructive sleep apnea is seen in a greater proportion of patients with PD than in age-matched control subjects, although some studies dispute this finding.[19] Polysomnography is the proper diagnostic test in this population, because typically there is also concern for RBD and periodic limb movement disorder, both of which are not able to be identified with home sleep apnea testing. A randomized placebo-controlled crossover study of patients with PD showed improvements in sleep architecture and objective measures in sleepiness in the patients treated with continuous positive airway pressure (CPAP).[20] As in the general population, positive airway pressure is typically effective in treating obstructive sleep apnea, but adherence remains a glaring challenge. Use of CPAP in patients with multiple system atrophy demonstrated that more than 66% discontinued CPAP after a year in one study.[21] In addition to typical obstructive sleep apnea symptoms, patients with multiple system atrophy may present with stridor and laryngeal dysfunction, which is a poor prognostic factor and requires treatment with positive airway pressure or other forms of nocturnal ventilation.[22]

Parasomnias

Patients with PD may complain of abnormal movements during sleep. This may be from a variety of conditions including sleep myoclonus, periodic limb movements of sleep, tremor, dystonia, or parasomnias. RBD is the most common parasomnia seen in patients with PD, seen in up to 60% of patients with PD. RBD is even more common in multiple-system atrophy and Lewy body dementia (75% or higher).[23] RBD involves repeated episodes of sleep-related vocalization and/or complex motor behaviors that occur during REM sleep. Motor activity can be reaching, grabbing, kicking, or other vigorous motor activity that could lead to injury of the patient or bed partner.[4] Nonviolent behaviors, such as smiling, laughing, or shouting, can also occur. The patient does not typically ambulate, with almost all motor activity occurring in or next to the bed. Eyes are typically closed and the patient does not interact with the environment. If awoken from the event, the patient returns to normal levels of consciousness, but may remember dream content related to the motor activity. Patients with PD with RBD have fewer tremors, more falls, more autonomic dysfunction, and more cognitive dysfunction than patients with PD who do not have RBD.[24] RBD has been shown to be a prodromal stage for PD and other synucleinopathies. Studies following patients with idiopathic RBD have demonstrated high rates of conversion to PD and other synucleinopathies, with a 45% rate of conversion at 5 years, 76% rate at 10 years, and more than 90% rate at 14 years.[25] These patients with RBD at high risk for central nervous degenerative disorders will likely be ideal candidates for neuroprotective therapy when they become available, although at this time no proven therapies of this kind exist. Patients with idiopathic RBD need to be counseled in regards to this risk and followed for early signs of cerebral neurodegenerative conditions, namely synucleinopathies. This follow-up may include questioning in regards to symptoms; serial neurologic examinations to look for early signs of disease; or more formal testing, such as neuropsychological testing or imaging of the brain.

RBD diagnosis requires not only a clinical history of dream enactment behavior, but also in the sleep laboratory, attended polysomnography demonstrating REM sleep without atonia.[4] In addition to standard chin and lower extremity surface electromyogram recording leads, additional upper extremity electromyogram leads in the arms or shoulders are used to increase sensitivity in identifying REM sleep without atonia.[26] Polysomnography is also useful in ensuring there are no other causes of abnormal movements during sleep, such as periodic limb movements of sleep or sleep-disordered breathing triggering increased muscle tone during REM sleep (pseudo-RBD).

Initial therapy for RBD includes securing the sleep environment and avoiding injury to the patient or bed partner. This includes removing sharp objects and weapons from the bedroom, possibly sleeping in separate beds, moving the bed away from windows, or placing the mattress on the floor. It is also necessary to educate the patient on possible triggers for RBD including medications and sleep deprivation. Treating any underlying primary sleep disorders, such as RLS or sleep-disordered breathing, should also be emphasized. Pharmacologic treatment of RBD includes two major therapies: clonazepam and melatonin.[27] Clonazepam was the first medication shown to be effective in treating RBD. The mechanism of action is unclear. Clonazepam is effective in improving RBD motor activity, but there are significant concerns in older adults in regards to possible side effects of cognitive impairments, sleepiness, and increased risk for falls. Melatonin at high doses has also been shown to improve

RBD symptoms, with less potential for side effects.[28] For refractory cases, combination of melatonin and clonazepam has been used along with a customized bed alarm. Cases series and other small studies demonstrate possible effectiveness of rivastigmine, dopamine agonists, desipramine, clozapine, and carbamazepine.[27]

ALZHEIMER DEMENTIA AND OTHER TAUOPATHIES

Dementia is defined as progressive memory decline and diminished cognition in at least one additional domain: aphasia, apraxia, agnosia, or executive dysfunction. These impairments impact social or occupational functioning. There were an estimated 24 million people in the world with dementia in 2001, with the number expected to double in the next 20 years because of the increase in life expectancy of the population.[29]

Alzheimer disease (AD) is a neurodegenerative condition that causes progressive memory decline and other cognitive deficits. AD is the most common cause of dementia worldwide, and represents approximately 50% to 70% of cases. The neuropathologic hallmark of AD is neuronal loss with cerebral atrophy, β-amyloid plaques, and neurofibrillary tangles composed of tau. There are other neurodegenerative disorders associated with abnormal buildup of tau, including progressive supranuclear palsy (PSP) and corticobasal degeneration. All of these tauopathies are commonly associated with sleep disorders. The same processes that damage areas of the brain causing dementia also cause dysfunction in control of sleep, alertness, and the circadian rhythm. Degeneration of neurons in brain areas, such as nucleus basalis of Meynert, pedunculopontine tegmental and laterodorsal tegmental nuclei, and noradrenergic neurons of the brainstem can lead to reduced REM sleep in AD. Unlike in PD (and other synucleinopathies), RBD is rarely seen in AD.

Degeneration of neurons of the suprachiasmatic nucleus and reduction in melatonin levels in patients with AD has been demonstrated.[30] Further reports suggest that this decrease in melatonin level and disruption of the circadian rhythm may appear early in the course of the disease, and may be potentially responsible for progression of the disease.[31] An interesting association has been reported between sleep disruption or deprivation and β-amyloid levels in normal control subjects, suggesting sleep disruption as an accelerating factor in the progression to AD.[32] One hypothesis is that sleep plays an important role in clearing toxic protein accumulation, such as β-amyloid, in the central nervous system.[33] Sleep changes are also prominent in patients with mild cognitive impairment (MCI), which is a prodromal phase of AD. Studies have shown that up to 60% of patients with MCI have sleep complaints.[34] Patients with MCI were found to have more arousals during slow wave sleep, prolonged REM sleep latency, and increased wake after sleep onset.[35]

Sleep disturbances in AD may also be caused by underlying psychiatric, medical, and primary sleep disturbances; medication-related effects; and insufficient light during the day or excessive light at night before bedtime. Polysomnography studies in patients with AD demonstrate decreased sleep efficiency, percentage slow wave sleep, and REM sleep, and prolonged REM sleep latency.[36] Although some of these may be age-related changes, the findings in AD are more prominent than in age-matched control subjects. Sleep spindles and K-complexes become poorly formed as the condition progresses, making distinction between stage N1 and N2 sleep more difficult in electroencephalography.[37]

Insomnia

Even early in the course of disease, patients with AD complain of disrupted sleep, insomnia, and frequent nighttime awakenings. The insomnia is multifactorial, likely caused by comorbid medical conditions and medication side effects, and damage to areas in the brain that control sleep, wakefulness, and the circadian rhythm. A different hypothesis suggests altered orexin levels in cerebrospinal fluid resulting in sleep dysregulation.[38] Circadian rhythm disorders are seen at higher rates in patients with dementia, because there have been studies demonstrating altered levels of melatonin in these patients and damage to the suprachiasmatic nucleus.[30] Patients generally present clinically with prolonged wakefulness during the night along with excessive sleepiness during the daytime in the forms of naps. This disrupted sleep pattern can cause worsening behavior, confusion, and agitation in the evening and nighttime, which has been called "sundowning." Environmental factors also play a role in exacerbating these symptoms, such as decreased physical exercise and decreased bright light exposure.[39] In patients with dementia in skilled nursing facilities, nocturnal awakenings are exacerbated by roommates, ambient noise, or bed-checks. In addition, exacerbation of any underlying medical issue (ie, infection, metabolic abnormality) can trigger sundowning or worsen sleep. This insomnia and sleep disruption can affect not only the patient, but also the caregiver's sleep and may lead to a visit to an emergency department or placement into a facility if the disruption persists.

Management of insomnia includes educating the patient and caregivers about good sleep hygiene and habits (**Box 3**). Circadian rhythm disorders in patients with AD are treated with properly timed bright light therapy and exogenous melatonin to reset the intrinsic clock to their desired bedtime and wake times. Both nighttime melatonin and morning light exposure for 1 hour improved daytime alertness and reduced sleep disruption in patients with AD.[40] Evidence demonstrates that melatonin at night in this population may improve sleep quality and daytime functioning.[41]

Hypnotics in patients with dementia should be used cautiously. Careful consideration of the benefits versus risks of the pharmacotherapy needs to be assessed. Possible side effects of hypnotics in this age group with dementia include risks of falls and worsened cognition. There are limited studies of hypnotics in patients with dementia, although in practice, many of the same hypnotics used in the general population are used in this specific patient population. These include zolpidem, eszopiclone, zaleplon, ramelteon, and triazolam. Trazodone in low doses is also commonly used and was shown to improve sleep in one small randomized, placebo-controlled study.[42] Melatonin (prolonged release) helped improve sleep in patients with mild to moderate AD in one randomized, placebo-controlled multicenter study.[43]

Obstructive Sleep Apnea

It is unclear if there is a higher incidence of sleep-disordered breathing in patients with AD as compared with age-matched control subjects, although there are numerous studies suggesting a higher risk.[44] The incidence of sleep-disordered breathing in older patients is higher than the general population. There is some evidence to suggest that obstructive sleep apnea may lead to a higher risk or earlier onset of dementia or MCI.[45,46] Diagnosis should be confirmed with objective testing in the form of an in-laboratory attended polysomnography or home sleep apnea test in appropriate patients. Treatment options remain the same as in the general population, including positive airway pressure, weight loss, positional therapy, and oral appliances. CPAP has been shown to reduce subjective daytime sleepiness in AD[47] and decrease arousals and increase stage N3 sleep.[48] CPAP as treatment in patients with AD with sleep apnea has demonstrated improved cognition and slowing of cognitive decline.[49,50] Adherence with CPAP therapy, which is already challenging in the general population, may be even more challenging in patients with dementia given their cognitive deficits and possibly worsening confusion at bedtime.

Box 3
Sleep hygiene recommendations

- Keep a regular bedtime and wake time throughout the week
- Engage in relaxing activities (winding down) before bedtime
- Limit liquids before bedtime
- Avoid caffeine, tobacco, and alcohol in the evening time
- Avoid long naps (>30 minutes) during the day
- Limit exposure to light before bedtime (including light from electronic devices)
- Make sure sleep environment is quiet and comfortable

PROGRESSIVE SUPRANUCLEAR PALSY

Patients suffering from PSP also have numerous sleep complaints. PSP is a neurodegenerative condition caused by abnormal accumulation of tau in the central nervous system. Symptoms include axial rigidity, postural instability, and a supranuclear gaze palsy. Patients with PSP commonly suffer from insomnia for similar reasons as other patients with dementia and neurodegenerative conditions mentioned previously (eg, damage to sleep-controlling areas of the brain, muscle spasms, medication side effects, mood disorder). Sleep studies in patients with PSP have demonstrated reduced REM sleep and spindle formation[51] and frequent arousals.[52] Patients with PSP also have more RLS, which may contribute to insomnia.[53] RBD is noted at high rates in PSP, but not as high as PD or other synucleinopathies.[54]

SUMMARY

Patients suffering from neurodegenerative conditions frequently report sleep complaints, such as insomnia and excessive daytime sleepiness. These symptoms are likely multifactorial, not only caused by their underlying neurologic disorder, but also by medications and other comorbidities associated with the progressive condition. A detailed history, and possibly sleep logs, actigraphy, or polysomnography, may be necessary to properly diagnosis and manage these patients. Improvement in sleep may result in improvement in neurologic symptoms and quality of life in this population. There is growing evidence that disrupted sleep may lead

to acceleration in the progression of the neurodegenerative disorder and may play a role in the pathogenesis. RBD may precede the development of clinical symptoms of synucleinopathies, such as PD by years or decades. An awareness of the high prevalence and consequences of sleep disturbance in older adults with neurodegenerative disorders is essential in the management of these important conditions.

REFERENCES

1. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 2006;5(6):525–35.
2. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 1998;13(6):895–9.
3. Takakusaki K, Saitoh K, Harada H, et al. Evidence for a role of basal ganglia in the regulation of rapid eye movement sleep by electrical and chemical stimulation for the pedunculopontine tegmental nucleus and the substantia nigra pars reticulata in decerebrate cats. Neuroscience 2004;124(1):207–20.
4. American Academy of Seep Medicine. International classification of sleep disorders, 3rd edition: diagnostic and coding manual. Westchester (IL): American Academy of Sleep Medicine; 2014.
5. Pierantozzi M, Placidi F, Liguori C, et al. Rotigotine may improve sleep architecture in Parkinson's disease: a double-blind, randomized, placebo-controlled polysomnographic study. Sleep Med 2016;21:140–4.
6. Ondo W, Vuong K, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. Arch Neurol 2002;59:421–4.
7. Breen DP, Vuono R, Nawarathna U, et al. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol 2014;71(5):589–95.
8. Videnovic A, Noble C, Reid KJ, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol 2014; 71(4):463–9.
9. Menza M, Dobkin RD, Marin H, et al. Treatment of insomnia in Parkinson's disease: a controlled trial of eszopiclone and placebo. Mov Disord 2010; 25(11):1708–14.
10. Rios Romenets S, Creti L, Fichten C, et al. Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease: a randomized study. Parkinsonism Relat Disord 2013;19(7):670–5.
11. Frucht S, Rogers JD, Greene PE, et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52: 1908–10.
12. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology 2005;65:1442–6.
13. Hobson D, Lang A, Wayne Martin W, et al. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease. A survey by the Canadian movement disorder group. JAMA 2002; 287:455–63.
14. Arnulf I. Excessive daytime sleepiness and parkinsonism. Sleep Med Rev 2005;9:185–200.
15. Wienecke M, Werth E, Poryazova R, et al. Progressive dopamine and hypocretin deficiencies in Parkinson's disease: is there an impact on sleep and wakefulness? J Sleep Res 2012;21(6):710–7.
16. Postuma RB, Lang AE, Munhoz RP, et al. Caffeine for treatment of Parkinson disease: a randomized controlled trial. Neurology 2012;79:651–8.
17. Ondo WG, Fayle R, Atassi F, et al. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry 2005;76:1636–9.
18. Ondo WG, Perkins T, Swick T, et al. Sodium oxybate for excessive daytime sleepiness in Parkinson disease: an open-label polysomnographic study. Arch Neurol 2008;65(10):1337–40.
19. Trotti LM, Bliwise DL. No increased risk of obstructive sleep apnea in Parkinson's disease. Mov Disord 2010;25(13):2246–9.
20. Neikrug AB, Liu L, Avanzino JA, et al. Continuous positive airway pressure improves sleep and daytime sleepiness in patients with Parkinson disease and sleep apnea. Sleep 2014;37(1):177–85.
21. Shimohata T, Nakayama H, Aizawa N, et al. Discontinuation of continuous positive airway pressure treatment in multiple system atrophy. Sleep Med 2014;15(9):1147–9.
22. Silber MH, Levine S. Stridor and death in multiple system atrophy. Mov Disord 2000;15(4):699–704.
23. Palma JA, Fernandez-Cordon C, Coon EA, et al. Prevalence of REM sleep behavior disorder in multiple system atrophy: a multicenter study and meta-analysis. Clin Auton Res 2015;25(1):69–75.
24. Sixel-Doring F, Trautmann F, Mollenhauer B, et al. Associated factors for REM sleep behavior disorder in Parkinson disease. Neurology 2011;77:1048–54.
25. Iranzo A, Fernandez-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 2014;9:e89741.
26. Frauscher B, Iranzo A, Hogl B, et al. Quantification of electromyographic activity during REM sleep in multiple muscles in REM sleep behavior disorder. Sleep 2008;31:724–31.
27. Aurora RN, Zak RS, Maganti RK, et al. Best practice guide for the treatment of REM sleep behavior disorder (RBD). J Clin Sleep Med 2010;6:85–95.
28. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. J Sleep Res 2010; 19:591–6.

29. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007;29(1–2):125–32.
30. Mishima K, Tozawa T, Satoh K, et al. Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep-waking. Biol Psychiatry 1999;45(4):417–21.
31. Bedrosian TA, Nelson RJ. Pro: Alzheimer's disease and circadian dysfunction: chicken or egg? Alzheimers Res Ther 2012;4(4):25.
32. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. JAMA Neurol 2013;70(12):1537–43.
33. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science 2013;342:373–7.
34. Beaulieu-Bonneau S, Hudon C. Sleep disturbances in older adults with mild cognitive impairment. Int Psychogeriatr 2009;21:654–66.
35. Westerberg CE, Mander BA, Florczak SM, et al. Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. J Int Neuropsychol Soc 2012;18:490–500.
36. Bliwise DL. Sleep in normal aging and dementia. Sleep 1993;16(1):40–81.
37. Ktonas PY, Golemati S, Xanthopoulos P, et al. Potential dementia biomarkers based on the time-varying microstructure of sleep EEG spindles. Conf Proc IEEE Eng Med Biol Soc 2007;2007:2464–7.
38. Liquori C, Romigi A, Nuccetelli M, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. JAMA Neurol 2014;71(12):1498–505.
39. Sullivan SC, Richards KC. Predictors of circadian sleep-wake rhythm maintenance in elders with dementia. Aging Ment Health 2004;8(2):143–52.
40. 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(2):239–46.
41. de Jonghe A, Korevaar JC, van Munster BC, et al. Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. Int J Geriatr Psychiatry 2010;25(12):1201–8.
42. Camargos EF, Louzada LL, Quintas JL, et al. Trazadone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo controlled study. Am J Geriatr Psychiatry 2014;22(12):1565–74.
43. Wade AG, Farmer M, Harari G, et al. Add-on prolonged release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6 month randomized, placebo-controlled, multicenter trial. Clin Interv Aging 2014;9:947–61.
44. Ancoli-Israel S, Klauber MR, Butters N, et al. Dementia in institutionalized elderly: relation to sleep apnea. J Am Geriatr Soc 1991;39(3):258–63.
45. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011;306(6):613–9.
46. Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. Neurology 2015;84(19):1964–71.
47. Chong MS, Ayalon L, Marler M, et al. Continuous positive airway pressure reduces subjective daytime sleepiness in patients with mild to moderate Alzheimer's disease with sleep disordered breathing. J Am Geriatr Soc 2006;54(5):777–81.
48. Cooke JR, Ancoli-Israel S, Liu L, et al. Continuous positive airway pressure deepens sleep in patients with Alzheimer's disease and obstructive sleep apnea. Sleep Med 2009;10(10):1101–6.
49. Troussiere AC, Monaca CC, Salleron J, et al. Treatment of sleep apnea syndrome decreases cognitive decline in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2014;85(12):1405–8.
50. 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):2076–81.
51. Petit D, Gagnon JF, Fantini ML, et al. Sleep and quantitative EEG in neurodegenerative disorders. J Psychosom Res 2004;56(5):487–96.
52. Aldrich MS, Foster NL, White RF, et al. Sleep abnormalities in progressive supranuclear palsy. Ann Neurol 1989;25(6):577–81.
53. Gama RL, Tavora DG, Bomfim RC, et al. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy: a comparative study. Parkinsonism Relat Disord 2010;16:275–9.
54. Sixel-Doring F, Schweitzer M, Mollenhauer B, et al. Polysomnographic findings, video-based sleep analysis and sleep perception in progressive supranuclear palsy. Sleep Med 2009;10(4):407–15.