Sleep in Parkinson's Disease

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Anjali Gera and Cynthia Comella

Abstract

Parkinson's disease (PD) is a neurodegenerative condition that can present with a constellation of other symptoms that are defined as "non-motor." Sleep problems are one of the prominent and frequently (nearly 64%) reported non-motor symptoms. Sleep fragmentation may arise because of pain, dystonia, bradykinesia, and neurodegeneration. Similarly, excessive daytime sleepiness (EDS) can be multifactorial in etiology in PD, including being a result of sleep fragmentation at night and primary sleep disorders that are often seen in PD (including periodic limb movement, obstructive sleep apnea, and circadian rhythm disorders). Few genome-wide association studies have been done among patients with PD having sleep disorders. Thus far, there is no association for genetic predisposition to PD and OSA, EDS, and RLS or PLMS, although additional studies are needed. This chapter discusses these issues in detail along with management strategies for the sleep disorders in PD.

Keywords

Parkinson's disease · Pathophysiology · Insomnia · RLS · Genome-wide studies · OSA · Daytime sleepiness

A. Gera (✉)
Central Dupage Hospital—Northwestern Medicine, Winfield, IL, USA
e-mail: nm179628@nm.org

C. Comella
Leslie Nan Burridge Endowed Faculty Scholar, Rush University Medical Center, Chicago, IL, USA
e-mail: Cynthia_Comella@rush.edu

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31.1 Introduction

Parkinson's disease (PD) is a neurodegenerative condition which is diagnosed by its clinical presentation with bradykinesia as the key feature and including at least one of the following: tremor, rigidity, and postural instability. However, PD also includes—and can present with—a constellation of other symptoms that are defined as "non-motor." These include fatigue, anxiety, depression, constipation, pain, autonomic dysregulation, and disturbances in sleep. Some studies have suggested that the presenting symptoms of PD can be non-motor. Non-motor symptoms can present in the absence of the cardinal features of PD, and one study of 433 PD patients found that 21% of patients with PD presented with non-motor symptoms [1].

Disturbances of sleep in PD were first described by James Parkinson over 200 years ago. Sleep disturbances are now recognized as one of the most frequent non-motor symptoms of PD and can occur in up to 64% of patients with PD [2, 3]. Table 31.1 includes some of the sleep disorders that can be seen in PD. Sleep disorders, along with other non-motor symptoms, have the propensity to become increasingly disabling with a significant impact on quality of life with greater severity and duration of disease.

31.2 Sleep Fragmentation

Difficulty with sleep maintenance, or sleep fragmentation, is one of the most common problems with sleep in PD, occurring in 81% of PD patients in one study involving 689 participants [4]. The most common cause of sleep fragmentation in patients with PD is due to the motor and non-motor symptoms—which often increase in severity—at night. Patients can be awakened due to their tremors reappearing in the earlier stages of sleep. Bradykinesia and rigidity can make it very difficult for patients to turn in bed or get out of bed at night in particular, when their dopaminergic medications wear off a few hours after their last dose of the day. Pain can disrupt sleep, which is another non-motor symptom that can accompany motor symptoms of PD, including dyskinesias, dystonia, or be a result of rigidity, including shoulder pain due to chronically reduced arm swing and rigidity. Several

Table 31.1 Sleep disorders in PD

Sleep fragmentation
Excessive daytime sleepiness
Obstructive sleep apnea
REM sleep behavior disorder
Restless legs syndrome
Altered sleep-wake cycle
Periodic limb movements
Nocturia
Circadian rhythm disturbances

antiparkinsonian medications have stimulant properties which can contribute to sleep fragmentation, including the carbidopa-levodopa controlled-release formulation, intake of regular levodopa when nocturnal motor symptoms occur, dopamine receptor agonists, and the monoamine-oxidase type B inhibitor selegiline (which has a methamphetamine metabolite). Immediate release dopaminergic therapy should be avoided close to bedtime and selegiline should be given in the morning hours. Evidence regarding the impact of surgical options on sleep in Parkinson's disease patients, in particular deep brain stimulation of the subthalamic nucleus, is conflicting at this time.

Patients can also have disrupted sleep due to other non-motor symptoms that can be seen in PD, including anxiety and depression. Treatment of anxiety and depression as it contributes to sleep fragmentation in PD can include mirtazapine. In addition to treating anxiety and depression, mirtazapine has been reported to help parkinsonian symptoms including rest tremor and levodopa-induced dyskinesias, and can also help boost appetite, another non-motor symptom commonly seen in PD [5, 6].

Practicing good sleep hygiene and keeping an optimal sleeping environment are especially important for patients with PD. Exercise in the morning or late afternoon can help promote sleep, while vigorous exercise later in the day can disrupt sleep and should be avoided. Ensuring adequate exposure to light during the day, especially for elderly patients who may not be able to go outside on their own, is important for maintaining a healthy sleep-wake cycle. Television or use of electronic devices should be avoided prior to bedtime or when one has difficulty falling back asleep in the middle of the night, as the light from the screens can further disrupt the sleep-wake cycle. Light shining into the room (including from under the bedroom door or between the shades) and light from electronics must be minimized. This includes turning an alarm clock away from the face, turning off cell phones or placing them face down (with vibrations off), shutting off computers, and covering small but bright lights on surge protectors, fans, humidifiers, and air purifiers with dark tape or sticker scan all help darken the bedroom to optimize the sleep environment. If a caregiver or partner is working and waking up with an alarm before the patient, vibrating wristwatches can be used for silent alarms that will not also wake the patient. Sudden noises such as a semi or an ambulance passing by at night, or a snoring partner in bed can all be minimized with a white noise machine, a fan, or ear plugs. We also recommend to avoid taking naps during the day, exercising in the evening, or eating a heavy meal before bedtime. Caffeine, nicotine, and alcohol should also be avoided close to bedtime. If one has trouble falling back asleep for more than 20 min, then the patient should get out of bed and do a quiet, relaxing activity such as stretching or reading.

31.3 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) can be multifactorial in etiology in PD, including being a result of sleep fragmentation at night and primary sleep disorders that are often seen in PD (including periodic limb movement, obstructive sleep apnea, and circadian rhythm disorders). Patients with PD have been reported to have an increased need for sleep as well.

EDS can significantly impact quality of life for not only patients with PD but also their caregivers, as these patients are sleeping during the day and awake at night. EDS can be seen in about 16–55% of patients with PD [7], and its frequency increases with disease duration. In a study of 153 patients, the frequency of EDS increased from 12% at time of diagnosis to 23% at 5 years [8]. This is thought to be related to neuronal loss in the dopaminergic and nondopaminergic brain circuits in the midbrain that are involved in sleep regulation, which is a slowly progressive process that continues throughout the course of PD.

Antiparkinsonian medications can also be associated with EDS, with dopamine agonists more likely to be associated than levodopa [9]. Patients with PD developing dementia may be predisposed to more drowsiness following each dose of levodopa. Reducing the dose of levodopa or replacing with carbidopa-levodopa controlled-release (and therefore allowing a slower rise of levodopa levels) can help with this problem.

31.4 Obstructive Sleep Apnea

It is controversial if obstructive sleep apnea (OSA) is more prevalent in PD compared to the general population. In fact, while many patients with PD also have OSA, most trials suggest that the prevalence of OSA is the same in the PD and general population [10]. Some studies have suggested that the prevalence of OSA may be lower than in the general population, which has been attributed to a lower body mass index of the PD patients [11]. On the other hand, there are many factors in PD that can predispose these patients to OSA, including aging [12], upper airway obstruction and restrictive lung disease due to hypokinesia and rigidity [13, 14], and autonomic dysfunction [15].

31.5 REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is associated with the development of neurodegenerative diseases. RBD without atonia is primarily associated with the synucleinopathies including PD, multiple system atrophy, and Lewy body dementia [16, 17]. RBD can precede or follow the onset of motor symptoms of PD. RBD is characterized by the loss of atonia that normally occurs during REM sleep and therefore is defined as an REM sleep parasomnia, in which abnormal behaviors occur during REM sleep. Patients with RBD experience vivid, distressing, and often

violent dreams (including of being chased or attacked). Bed partners and caregivers may note that the patient appears to be acting out dreams, such as talking or shouting or having more aggressive behaviors such as kicking, punching, and sometimes falling out of bed. Patients often are unaware of these events. RBD can lead to injuries to both the bedpartner and the patient.

While the precise prevalence of idiopathic RBD is not known, it is estimated to be about 42% in patients with PD [18]. Increased age is significantly associated with primary RBD. A majority of these patients are male, although the reasons behind the significant difference in gender are not clear. In one study of 45 patients with PD, eight participants (or 17.8%) had RBD preceding the onset of parkinsonism [19]. Eighty-six percent of these 45 participants recalled having frightening dreams. Indeed, several reports suggest a high rate of conversion of RBD to a synucleinopathy (PD, multiple system atrophy, or dementia with Lewy bodies), with risk estimates ranging between 20–45% by 5 years and 40–65% by 10 years [20, 21]. Another longitudinal study conducted postmortem quantitative analyses for alpha-synuclein on 40 PD patients with RBD and 41 PD patients without RBD revealed that PD patients with RBD had greater density and range of alpha-synuclein pathology on autopsy [22].

Neurons that induce REM sleep paralysis are thought to be involved in the pathophysiology of RBD. These neurons play a role in inducing REM sleep paralysis by (1) sending inhibitory GABAergic and glycinergic inputs to spinal cord motor neurons, (2) sending excitatory glutamatergic projections to the spinal cord interneurons which then inhibit the motoneurons, and (3) decreasing activity in the red nucleus, resulting in atonia [23]. Animal studies of rodents and cats as well as postmortem studies in humans have suggested that RBD is caused by dysfunction of the subcoeruleus nucleus and nuclei in the ventral medial medulla [24–26]. The pathophysiology of RBD is thought to be due to impaired GABAergic and glycinergic neurotransmission from the ventral medial medulla and glutamatergic neurotransmission from the subcoeruleus nucleus and the ventral medial medulla. An alternate pathophysiology has also been described to be secondary to damage to pathways that connect the subcoeruleus nucleus and ventral medial medulla to the dorsolateral hypothalamus and the limbic system.

Treatment of RBD is dependent upon its severity and its impact on the patient and the patient's bedpartner. If the RBD symptoms are resulting in injury and/or are bothersome to the patient or family, it is important to first caution the patient and bedpartner about protective measures, including moving furniture away from the bed, and pillows or other protection for the bedpartner if they are in the same bed. There are no controlled studies of oral pharmacologic agents. Initial treatment is melatonin starting at 3 mg, to be taken 60 min prior to bedtime [27]. Melatonin can be slowly titrated upward to 12 mg every evening. Usually, the patient is advised to gradually increase the dose at 1- to 2-week intervals, and should be attempted for at least 4–6 weeks. If no improvement with melatonin, clonazepam is used starting at 0.25 mg at bedtime, with slow uptitration to 2 mg at bedtime under close guidance by the physician. It is reasonable to reach the highest tolerable dose of either drug that reduces symptoms while minimizing side effects. Importantly, the physician should

set reasonable expectations for the patient and family that neither drug is likely to completely resolve RBD. Other drugs that have been reported to be of some benefit include the cholinesterase inhibitors donepezil or rivastigmine, although data are limited and conflicting, and therefore, these medications should be considered a third line after melatonin and clonazepam [27].

31.6 Restless Legs Syndrome and Periodic Limb Movements

Restless legs syndrome (RLS) is characterized by an urge to move the lower limbs, which is commonly (but not always) accompanied by uncomfortable and unpleasant "crawling" sensations in the lower limbs. The urge to move the legs and/or the unpleasant sensations can begin or worsen during periods of rest or inactivity and are partially or completely relieved by movement. The sensations are worse in the evening or night in comparison to the day, thus disturbing sleep onset [28].

RLS occurs fairly commonly in patients with PD. In a cohort of 113 patients with PD, 24% had RLS [29]. However, the association between RLS and PD is controversial. Some studies have suggested that RLS is more common in PD patients, while others have suggested its frequency is similar to the general population [30]. Although dopaminergic treatment can help with both RLS and PD, data suggest different pathophysiologic mechanisms. Postmortem examination in a small study of four patients with idiopathic RLS did not reveal Lewy bodies or alpha-synuclein [31]. Iron levels in the substantia nigra are reduced in RLS but increased in PD [32]. Neuroimaging studies using sonography have detected increased echogenicity of the substantia nigra in PD patients but not in RLS patients [33].

Treatment of RLS depends on its severity and if symptoms impair quality of life, daytime functioning, or sleep. Iron levels can be low in RLS and should be evaluated. Low or low normal ferritin levels suggest iron deficiency and can initially be treated with iron supplementation. Iron levels below 45 ng/ml should be treated with iron supplementation orally. If the patient cannot tolerate the iron or if the iron levels do not improve after 3 months, intravenous iron supplementation should be considered. There are two formulations of intravenous iron, namely iron dextran and low-molecular weight iron dextran, the latter of which has a better safety profile and lower risk of anaphylaxis compared to iron dextran.

In the setting of low ferritin levels, the severity of RLS correlates with the degree of ferritin reduction and first-line therapy is the replacement of iron, which has been shown to improve symptoms of RLS if iron deficiency is present [34, 35]. The cause of iron deficiency should also be evaluated. Gabapentin is a reasonable first-line medication and has been shown to be efficacious for the treatment of RLS at a dose of 800 mg and at 200 mg for patients on hemodialysis. Pregabalin is also efficacious for RLS when given at doses between 150 and 450 mg/day, 1–3 h before bedtime. Dopaminergic medications including levodopa, ropinirole, rotigotine, pramipexole, and cabergoline can be used and are likely to be helpful for the patient's PD symptoms. Levodopa is very effective in treating RLS and of course patients with

PD are likely to be on dopaminergic medications. However, chronic use and taking higher doses of dopaminergic medications can lead to augmentation. Risk of augmentation is higher with pramipexole in comparison to the other dopaminergic medications, although augmentation can occur with any dopaminergic treatment including levodopa [36]. Augmentation is an iatrogenic worsening of RLS symptoms following treatment of dopaminergic medications. Augmentation is described by RLS symptoms beginning earlier in the day, having an increased overall intensity of symptoms, shorter latency of symptoms at rest, reduced duration of treatment benefit, or symptoms occurring in a previously unaffected body area. Rebound is another phenomenon that can occur during the night with dopaminergic medications on board. Oxycodone or naloxone can also be used for RLS and is efficacious in patients with severe treatment-resistant RLS; however, special monitoring is warranted in those with addictive tendencies and possible sleep-related respiratory problems should also be monitored.

Medications that can worsen RLS and should be avoided or minimized include serotonin reuptake inhibitors, venlafaxine, and antihistamines. Dopamine receptor antagonists such as antipsychotics and antiemetics (including metoclopramide) should be avoided.

Periodic limb movements (PLMs) are movements that occur during sleep and are characterized by a stereotyped and repetitive pattern. PLMs may or may not co-exist with RLS and might be indicative of genetic susceptibility to RLS. Indeed, up to 80% of RLS patients may also suffer from PLMs [37]. A polysomnogram may reveal PLMs that can occur in the absence of RLS. The prevalence of PLMs in PD patients is comparable to the general population [38]; however, PLMs have been reported to occur with increased severity of PD [39] and with degree of nigrostriatal degeneration [40]. Interestingly, one study has also suggested that patients with PD who undergo deep brain stimulation surgery may have worsening of their PLMs after surgery, which is thought to be secondary to reduction in dopaminergic therapy following surgery [41].

PLMs are difficult to treat. Patients with PLMs may respond to dopaminergic treatment similar to RLS. They can also respond to pregabalin, gabapentin, or duloxetine.

31.7 Nocturia

Nocturia is characterized by a higher than average need to urinate during the night. Nocturia significantly impacts the continuity and therefore the quality of sleep in patients with PD, as patients can have difficulty with falling back asleep after waking up (often multiple times) at night to urinate. In fact, nocturia is one of the most common non-motor symptoms in PD patients and can affect 60–80% of patients with PD [42–44]. The odds of developing nocturia in PD are higher with increasing disease stage [45], increasing age and with male gender [46]. One cross-sectional study of 70 patients with a diagnosis of PD found an association between taking dopaminergic agonists and a lower presence of nocturia in comparison to patients on

levodopa [47]. This finding was initially thought to be due to the patients with PD who are on dopamine agonists being younger in age and having shorter disease duration in comparison to those on levodopa; however, when patients were subdivided according to whether they were on dopamine agonists as a monotherapy or combined therapy, the patients who were on combined dopamine agonist therapy had a lower presence of nocturia compared to those on levodopa as monotherapy despite being of an older age and having a longer disease duration [47].

The initial approach to nocturia should begin with investigating for the cause of nocturia (in addition to PD). Neurogenic detrusor overactivity is the most common cystometric abnormality in PD patients [48]. However, nocturia can be due to other causes in patients with PD. For example, patients with OSA have greater risk to develop nocturia [49] and patients with OSA who used continuous positive airway pressure had a statistically significant decrease in the number of nocturia episodes, with good to complete elimination of nocturia in 75% of the 97 patients in one study [50].

Nonpharmacologic treatment should be the first line of therapy in PD patients with nocturia. Evening alcohol and caffeine should be avoided. Water intake should be limited for 2–3 h prior to bedtime. However, it is important to emphasize to keep well hydrated during the morning and afternoon hours as patients with PD tend to be more sensitive to postural changes and are more predisposed to orthostatic hypotension, but to limit fluid intake closer to bedtime. Anticholinergics, alpha blockers, and 5-alpha reductase inhibitors may be attempted although with great caution given patients with PD are more prone to side effects from these medications given the autonomic dysfunction (including orthostatic hypotension, erectile dysfunction, and dry mouth) that can occur with PD. Referral to a urologist would be advisable in those with persistent or refractory nocturia.

Neuromodulation, including sacral nerve modulation, has been used as a treatment for detrusor overactivity in patients with PD; however, long-term efficacy still needs to be determined for patients with PD [51]. In addition, one study reported improvement of detrusor overactivity with stimulation of the posterior tibial nerve [52]. Interestingly, deep brain stimulation of the subthalamic nucleus has been reported to improve urinary symptoms in PD [53], with stimulation of the subthalamic nucleus having effects of inhibiting micturition [54].

31.8 Genetic Association Between PD and Sleep Disorders

Few genome-wide association studies have been completed in sleep disorders. Thus far, there is no association for genetic predisposition to PD and OSA, EDS, and RLS or PLMS, although additional studies are needed. However, there is convincing data of at least a partial genetic association between PD and RBD. Given that a majority of patients who develop RBD also develop a neurodegenerative synucleinopathy, a genetic association between PD and RBD is unsurprising. The strongest genetic association reported thus far is associated with mutations in the *glucocerebrocidase* (*GBA*) gene [18, 55]. Both *GBA* and RBD are associated with autonomic

dysfunction [56], more severe motor disease [56, 57], and more aggressive cognitive decline [58]. *GBA* mutations have been reported to be specifically associated with the RBD subtype of PD more so than with idiopathic RBD. From a pathophysiological point of view, both RBD-associated PD and *GBA*-associated PD likely have a more diffuse spread of alpha-synuclein accumulation [22, 59]. The *GBA* mutation is indeed currently in the spotlight and studies thus far are strongly suggestive [60], but more studies are needed to confirm the association between *GBA* and RBD.

On the other hand, *LRRK2* mutations have not been found to be associated with RBD in PD patients [61]. Patients with PD due to LRRK2 mutations tend to have a less aggressive course with a less rapid cognitive decline, less autonomic dysfunction, and less RBD [62, 63].

31.9 Circadian Disruption in PD

Recent literature suggests that there may be a disruption in circadian rhythm in PD [64]. This disruption is not surprising given the role of dopamine on the circadian regulation and may be a result of differences in neuronal firing in the suprachiasmatic nucleus found in animal models of PD [64]. Compared to healthy controls, the circadian rhythm of hormonal markers including melatonin is blunted in PD patients [64], which can contribute to excessive daytime sleepiness in PD patients.

There exists a growing literature on treatments focused on circadian rhythm in PD, namely light therapy. Light therapy is a noninvasive and nonpharmacologic treatment that is becoming increasingly utilized for sleep dysfunction (and even motor symptoms and other non-motor symptoms such as mood) in PD [65, 66]. Light therapy (LT) is administered most commonly as a bright light, but green and blue light therapy are also used. LT should be given on a scheduled basis and timing is important to avoid phase advances or delays of the circadian rhythm. LT, therefore, should be administered right after usual wake time or around the time of usual sleep time.

31.10 Conclusion

Problems with sleep are a very common non-motor symptom of PD and can be caused by multiple different sleep disorders that are seen with PD, including sleep fragmentation, excessive daytime sleepiness, obstructive sleep apnea, REM sleep behavior disorder, restless legs syndrome, altered sleep-wake cycle, periodic limb movements, and nocturia. Circadian disruption also likely plays a major role in contributing to several of these sleep disorders. All of the sleep disorders seen in PD can cause significant disability in these patients as their disease progresses. Both pharmacologic and conservative, nonpharmacologic therapies are available for all of these sleep disorders, prompting early evaluation and diagnosis of sleep disorders in PD patients. A growing body of literature reveals several genetic associations

between sleep and PD. Knowledge about genetic mutations and their association with sleep in PD is likely to help with prognosis and set expectations for disease course including the development of sleep disorders and will hopefully lead to individualized therapeutic approaches such as gene therapy in the future.

Key Points

1. Sleep disorders in patients with PD have the propensity to become increasingly disabling with a significant impact on quality of life with greater severity and duration of disease.
2. Pharmacologic and nonpharmacologic treatments are available for all of the sleep disorders seen in patients with PD; hence, an early evaluation and diagnosis of sleep problems in PD patients is warranted.
3. Increasing our knowledge regarding genetic associations with sleep in PD is likely to help predict specific types of sleep disorders seen with specific genetic mutation carriers and allows an individualized therapeutic approach in the future.

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