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SLEEP AND CIRCADIAN RHYTHM DISORDERS IN PARKINSON'S DISEASE

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Abstract

Purpose of review—Sleep disorders are among the most challenging non-motor features of Parkinson's disease (PD) and significantly affect quality of life. Research in this field has gained recent interest among clinicians and scientists and is rapidly evolving. This review is dedicated to sleep and circadian dysfunction associated with PD.

Recent findings—Most primary sleep disorders may co-exist with PD; majority of these disorders have unique features when expressed in the PD population.

Summary—We discuss the specific considerations related to the common sleep problems in Parkinson's disease including insomnia, rapid eye movement sleep behavior disorder, restless legs syndrome, sleep disordered breathing, excessive daytime sleepiness and circadian rhythm disorders. Within each of these sleep disorders, we present updated definitions, epidemiology, etiology, diagnosis, clinical implications and management. Furthermore, areas of potential interest for further research are outlined.

Keywords

Parkinson's disease; sleep disorders; sleepiness; circadian rhythm disorders; non-motor symptoms

INTRODUCTION

Sleep disruption was recognized in the initial description of Parkinson's disease (PD) two centuries ago (1). Disrupted sleep and excessive daytime sleepiness are among the most common non-motor manifestations of PD. These symptoms negatively affect the quality of life, and may have significant implications for morbidity and safety in the PD population. Despite its common presence, sleep disruption is frequently under-reported by patients and under-recognized by health care providers. Treatment may be quite challenging due to

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CONFLICT OF INTERESTS

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limited treatment options and its potential side effects. In this article, we present an overview of the most common sleep and circadian disorders associated with PD.

1) INSOMNIA

Definition—The International Classification of sleep disorders (ICSD-3) has defined insomnia as the difficulty of initiating sleep, maintaining sleep or waking earlier than desired (2). The symptoms should occur at least 3 nights per week for at least 3 months and cause significant personal distress, interference with personal functioning in daily living (2–4). In patients with dementia, insomnia can manifest as the resistance to go to bed on appropriate schedule or the difficulty sleeping without caregiver intervention (2).

Epidemiology—Insomnia is thought to be the most common sleep disorder in PD and its prevalence ranges from 27% to 80%, part of the variability being due to differences in diagnostic criteria (5, 6). Sleep maintenance insomnia, including frequent awakenings/sleep fragmentation, is the most prevalent sleep disturbance in PD patients (81%) (5, 7). Difficulty falling asleep (18%) and early awakenings (40%) are also encountered (5, 6).

Etiology—The factors associated with insomnia in PD are multiple (8). Motor symptoms that emerge overnight causing sleep fragmentation include tremor, dyskinesia, nighttime cramps, dystonia (9). Overnight non-motor symptoms that negatively affect sleep include nocturia, autonomic dysfunction and psychiatric symptoms (9, 10). Comorbid primary sleep disorders such as obstructive sleep apnea (OSA), rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS) or periodic limb movements of sleep (PLMS) contribute to sleep fragmentation as well (11). Circadian dysfunction is another potential factor that may contribute to insomnia, and will be discussed separately in this review. PD-associated neurodegenerative process itself negatively impacts regulation of sleep due to changes within sleep regulatory networks. Finally, dopaminergic medications also may have negative impact on sleep continuity. Its effects on sleep are influenced by the dose and activation of specific dopaminergic receptors. Low doses of dopaminergic medications act on pre-synaptic D2 receptors, facilitating sleep and reducing wakefulness (9, 12, 13). In contrast, higher doses of dopaminergic medication act at post-synaptic D1 and D2 receptors, inhibiting sleep and increasing insomnia (9, 10, 14). Overall, chronic insomnia appears to increase with the duration of PD (5, 15).

Diagnosis—A detailed sleep history is necessary as an initial step in diagnosing insomnia in PD. Several instruments have been developed to assess sleep quality. Some of these instruments are not PD specific such as the Pittsburgh Sleep Quality Index (PSQI) or the Insomnia Severity Index (ISI) (5, 16). Other instruments are validated in the PD population. The newest version of the PD Sleep Scale (PDSS-2) addresses sleep initiation, sleep maintenance and daytime sleepiness (17). PDSS correlates well with sleep fragmentation on PSG (18). The Scale for Outcomes in PD (SCOPA) is a two subscales questionnaire that include a nighttime scale addressing sleep initiation, sleep fragmentation, sleep efficiency, sleep duration and early wakening, and a daytime scale for alertness (19). Polysomnography (PSG) is not indicated for the diagnosis of primary insomnia, both in the general population and in PD, as the diagnosis is based on the clinical diagnostic criteria. PSG, however, is

indicated when co-existing sleep disorders associated with PD are suspected, such as sleep-disordered breathing, RLS, PLMS or RBD. Actigraphy is another objective tool that has gained interest due to its simplicity of use and ability to monitor rest-activity cycles over prolonged period of time. (20). It is however unable to differentiate activity due to wakefulness versus to other PD sleep disturbances such as RBD or OSA (20).

Clinical implications—Good sleep quality is of essence of PD patients. This has been long recognized as “sleep benefit in PD”, which emphasizes improved performance and responsiveness to dopaminergic medications after a good night of sleep. Poor motor function, mostly axial symptoms as well as OFF periods (i.e. time when medication is not working optimally (21)), have been associated with poor sleep in PD, including reduced total sleep time and sleep efficiency (18, 22, 23). Insomnia is also associated with autonomic dysfunction, such as gastrointestinal, urinary, pupilomotor and thermoregulatory dysfunction (5, 24, 25), as well as with depression and lower scores on cognitive tests in PD (26, 27). However, associations between insomnia dementia in PD are less clear (28), and this topic deserves more attention in future clinical investigations. Poor health-related quality of life and daytime sleepiness are other consequences of insomnia associated with PD (5, 29).

Management—The management of insomnia starts by correctly identifying its causes. Dopaminergic medications may have a role in improving sleep quality. In the context of nighttime motor dysfunction, controlled release formulation of levodopa/carbidopa may be considered, although its chronic effects on sleep architecture require further study (23, 30). Dopamine agonists have garnered recent interest in treating sleep disorders in PD. Ropinirole improved the PDSS score in a double blind study in PD patients with motor fluctuations (31). Trenkwalder et al. suggest that 24 hour transdermal rotigotine can improve sleep by improving nighttime PD symptoms such as limb restlessness, pain, cramps and early morning symptoms such as fatigue and mood (17). Another trial suggests rotigotine can increase sleep efficiency and reduce wakefulness after sleep onset and sleep latency (32). Treatment of underlying behavioral, psychiatric and sleep disorders is an important step in improving sleep duration and continuity in a well selected group of PD patients. Non-pharmacologic options such as cognitive behavioral therapy (CBT), utilized in general sleep medicine, have been explored in the PD population. Rios Romenets et al. compared 6 weeks of CBT with placebo, and reported an improvement in Insomnia Severity Index as well as examiner-reported clinical global impression of change, but not in the SCOPA score (33). Yang and Petrini studied 4 weeks of CBT found an improvement in PDSS score and sleep diary measures (onset latency, wake after sleep onset, total sleep time, time in bed and sleep efficiency) (34). Circadian based interventions, such as light therapy, are increasingly being proposed as a treatment intervention not only for sleep dysfunction but also for other non-motor manifestations of the disease.

2) EXCESSIVE DAYTIME SLEEPINESS

Definition—Excessive daytime sleepiness (EDS) is a symptom defined as the difficulty to stay alert and awake during the major waking periods of the day, culminating in unintended lapses into sleep (35). It differs from hypersomnia, being a diagnosis in the ICSD-3, for which EDS is the most important symptom (2). Sleep attacks are described as sudden

"irresistible, overwhelming sleepiness without awareness of falling asleep", with or without preceding signs (e.g. yawning, closing of the eyelids, rapid decrease of mental alertness etc.) (36). Sleep attacks are commonly associated with dopaminergic therapy, especially to exposure to dopamine agonists (37). While sudden onset sleep or sleep attacks represent a spectrum of EDS associated with PD, it is not required to establish the diagnosis of EDS.

Epidemiology—EDS is frequent in PD and its prevalence is thought to range from 20 to 60% (8, 38–41). Subjective complaint of EDS does not correlate well to objective measures of EDS (42). The variability in prevalence is attributable to multiple definitions and cut-off scores for EDS, differences in tools used to measure EDS, variability of medication regimens and comorbidities (42). The prevalence of sleep attacks ranges between 6.6% and 43% (36, 43, 44). Sleep attacks are associated with nonergoline dopamine agonists, male sex, increased Epworth Sleepiness Scale score (ESS), advanced PD severity (44). A higher dose of dopamine agonists, or higher levodopa equivalent doses rather than the specific type of dopaminergic medication was an effective predictor of EDS in PD (45, 46).

Etiology—The factors associated with EDS are multiple. SPECT based studies suggest that PD-related neurodegeneration plays a role in EDS (47). The hypocretin system, a key regulator of the sleep-wake cycle, is affected by PD specific neurodegeneration (48, 49). Fronczek et al. reported reduced levels of hypocretin-1 for 40% in prefrontal cortex and 25% in ventricular CSF (49). Concomitant sleep disorders commonly prevalent in PD, such as RLS (50, 51), OSA (46, 52) and RBD (53, 54), may contribute to EDS. EDS has been associated with a higher AHI in PD, and treatment of OSA with CPAP is associated with reduced objective EDS in PD (52). Studies also reported other predictors of EDS such as age (39), body mass index (BMI) (42), duration and severity of PD (45, 46) and non-motor symptoms such as pain (42). Several pivotal trials of levodopa and dopamine agonists revealed somnolence as a side effect in 15% –35% PD patients. EDS is most common in patients treated with a combination therapy of levodopa and dopamine agonist, followed by dopamine agonist monotherapy, and levodopa monotherapy (36, 55). Circadian dysfunction was recently reported as a potential culprit of EDS in PD (56).

Diagnosis—The gold standard for EDS diagnosis is the Multiple Sleep Latency Test (MSLT) (57, 58). Tirunahari et al. proposed the introduction of microsleep determination during an MSLT as a more sensitive (42.9%) and specific test (63.6%) for EDS compared to the standard MSLT. The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire often used in clinical practice to screen for EDS (59). It is thought to successfully distinguish normal subjects from OSA, narcolepsy and idiopathic hypersomnia patients (59). The correlation between ESS and the sleep latency on MSLT remains a topic of debate (59, 60). At present, both MSLT and ESS are been used to assess EDS in the PD population (24, 52, 61–63).

Clinical implications—EDS in PD is associated with decreased health related quality of life (64, 65), worse cognitive impairment (66), worse motor and non-motor symptoms as well as increased medication wearing off (67, 68). In PD, depressive symptoms correlate significantly with EDS (27, 63). In patients with idiopathic RBD, EDS may be a marker of

alpha-synuclein related neurodegeneration (69). EDS in PD, in the context of daytime sleep attacks, RBD, nocturnal insomnia, hallucinations and depression is reminiscent of narcolepsy. As described above, several studies have found a decrease in hypocretin levels in PD. However, the clinical significance and contribution of hypocretin to a PD related narcolepsy-like syndrome is still not fully elucidated (70).

Management—EDS is a multifactorial disorder, and therefore the first step is to identify its potential causes and develop treatment plan accordingly. Safety for driving is one of major topics that should also be systematically addressed during the clinical assessment of EDS. There has been recent interest in non-pharmacological options for EDS management. Light therapy, typically used for psychiatric and primary circadian sleep disorders, may be an effective non-pharmacological intervention for improving EDS in PD (71). A recent randomized placebo controlled trial showed significant improvement in ESS score, sleep fragmentation and sleep quality after 14 days of bright light therapy (72). A careful review of the current dopaminergic medication regimen is necessary with possible dose reduction or change of dopaminergic medications. Pharmacological treatment options can also be considered. The efficiency of modafinil for EDS in PD remains somewhat controversial. Although some studies have shown improvement in EDS with modafinil (100–200 milligrams per day), others have not (73–75). Stimulants may be beneficial for EDS but are not frequently prescribed in the PD population due to potential side effects. Finally, one open label trial of sodium oxybate (3–9 g in split doses), a drug used in treatment of narcolepsy, showed improvement of fatigue and daytime sleepiness in PD patients (76). Further research should focus on alternative pharmacological options to improve EDS in PD.

3) SLEEP-DISORDERED BREATHING

Definition—Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing (SDB). OSA is defined as the cessation of breathing caused by repetitive transient pharyngeal airway collapse (77). Central and mixed apneas are less prevalent forms of SDB in the PD population.

Epidemiology—The prevalence of OSA in PD varies from 20–60% (24, 78–80). This wide range is likely due to methodological differences across studies including differences in scoring respiratory events (15, 81). Several recent studies that employed well-selected controls revealed similar prevalence of OSA in PD and general population (82, 83). Interestingly, three studies have suggested an increased risk of PD among patients with OSA with hazard ratios (HR) of 1.37, 1.84 and 2.26, respectively (84–86). Although the risks are higher, the absolute numbers remain low, and thus OSA might overall provide a minor risk for subsequent development of PD (84).

Etiology—Upper airway obstruction (UAO), pulmonary dysfunction and autonomic dysfunction have been described as common causes of OSA in PD (87, 88). Increased upper airway resistance in PD may be related to bradykinesia and chest wall rigidity. Several studies reported UAO being responsive to levodopa (89–91).

Diagnosis—The gold-standard for OSA diagnosis is polysomnography (PSG) (92). It is however expensive and inconvenient, as it requires a complex and expensive technical setting. Recently, there has been growing interests in alternatives, such as the level III portable monitoring (PM) at home (93, 94). Gros et al. suggested that PM had an acceptable specificity for moderate or severe OSA in PD patients (81), although the failure rate for study completion was higher and the signal quality poorer. PD patients can have central apnea, hypopneas with EEG arousals without desaturations, but also other comorbidities such as RBD or silent REM sleep without atonia etc. In these context, PSG remains the best option and should be favored as the diagnostic test of choice when possible. Other available tools such as the STOP-BANG and Berlin questionnaires (95, 96) have been used for OSA screening. The STOP-BANG in the PD population has a sensitivity of up to 80% for severe OSA with apnea-hypopnea index (AHI) ≥30/h, but the specificity is as low as 20% (97). The Berlin questionnaire appears to have higher specificity, that diminishes with OSA severity (100% for AHI ≥5/h, 53% for AHI≥30/h)(97).

Clinical implications—SDB has similar implications for overall health in PD compared with the general population. OSA has been linked with cognitive dysfunction in PD. Two studies reported lower scores on the Mini-Mental Status Exam (MMSE) and the Montreal Cognitive Assessment (MoCA) among PD patients with co-existent OSA compared with non-OSA patients (98, 99). Underlying mechanisms remain unclear, with intermittent hypoxemia (IH), systemic inflammation and/or hormonal imbalance being speculated as potential culprits (100). IH is thought to lead to oxidative and neural injury (101, 102), possibly via disruption of the blood-brain barrier (103). Hoth et al. found that high hypoxemia subjects performed better on learning and immediate recall than low hypoxemia subjects, suggesting a possible protective effect (104).

Management—Continuous positive airway pressure (CPAP) remains the main treatment modality for OSA in PD, similarly to the general population. Neikrug et al. reported that CPAP is well tolerated by PD patients with mild to moderate disease (52). The effect of CPAP beyond the improvement of OSA has also been explored. CPAP appears to improve attention and vigilance in the general population with OSA (105), but the effect on executive function and memory remains debatable (105, 106). Harmell et al. did not find an improvement on cognition in PD patients after 3 and 6 weeks of CPAP therapy. In another study however, MoCA score improved by 1.6±1.9 points (p=0.043) after 6 months of CPAP (107). Further research should investigate which domains of cognition are likely to improve by CPAP in PD patients.

CPAP can be difficult to tolerate among PD patients. There has been growing interest in alternative treatment modalities for OSA. Gros et al. reported improvements of OSA in PD patients with Sinemet CR 25/100, one to two tablets administered at bedtime (108). This finding possibly suggests that UAO are responsive to levodopa and are involved both in OSA and in PD pathophysiology. The interaction between OSA and PD certainly needs to be further explored.

4) RESTLESS LEGS SYNDROME

Definition—RLS has been defined by the ICSD-3 as an “unpleasant sensation in the legs at night or difficulty in initiating sleep”, usually accompanied or caused by an “disagreeable sensations” inside the calves that are often associated with general aches and pains in the legs and “relieved by movement of the limbs” (2, 109–111).

Epidemiology—The prevalence of RLS in PD ranges between 0 to 52.3%. Some studies found a higher prevalence of RLS in PD (51, 112, 113), especially in drug naïve patients (114, 115) that increased during the course of PD (114), while other studies have not (50, 116). The observed variability is controversial, as the IRLSSG diagnostic criteria have not been formally validated in PD.

Etiology—The etiology of RLS and RLS associated with PD is not fully elucidated. One of the possible mechanisms underlying RLS is central dopaminergic dysfunction. RLS is clinically responsive to dopaminergic agents and previous studies in rats found a favorable response of 6-hydroxydopamine injections in dopaminergic diencephalic spinal neurons (117). A study by Rios Romenets et al. found an increased prevalence of RLS in PD patients using domperidone, suggesting a potential contribution of dopaminergic neurons outside the blood brain barrier (118). Whether RLS and PD have common pathophysiology is debatable. Several studies found differences on SPECT imaging between idiopathic RLS and PD associated RLS, suggesting different pathophysiologic mechanisms (119, 120).

Diagnosis—The diagnosis of RLS is based on the diagnostic criteria defined in the International Classification of Sleep Disorders, third edition (2). The International RLS Study Group (IRLSSG) Rating Scale (121), has been recently updated in 2014 (111). The scale has been primarily been used in research settings and can be useful for the assessment of RLS severity. Moving forward, it will be important to validate the IRLSSG criteria in PD patients and possibly investigate what are the predisposing factors of RLS in PD (122). De Cock et al. have suggested the use of the suggested immobilization test (SIT) to differentiate PD with RLS from PD without RLS (123).

Clinical implications—PD patients with RLS tend to have higher age at PD onset as well as more advanced PD, more prominent limb parkinsonism especially tremor, depression, anxiety, autonomic dysfunction and worse nutritional status (114, 115, 124). They also tend to have delayed sleep onset, daytime sleepiness and overall poor sleep quality (114, 125, 126). RLS diagnosis in PD can be challenging, and therefore a thorough clinical interview is necessary to help differentiate between RLS and PD-specific mimickers or RLS. These include akathisia, motor restlessness, nocturnal leg restlessness, and sensory complains frequently reported by PD patients (122, 127).

Management—Evidence-based recommendations for moderate to severe RLS treatment suggest dopamine agonists including pramipexole (128–130), rotigotine (131, 132), ropinirole (133, 134) as well as gabapentin enacarbil (135–138), pregabalin (134, 136, 139) and IV ferric carboxymaltose use. To our knowledge, none have been studied in a randomized clinical trial in PD. Although dopamine agonists are initially efficacious for

RLS, long term treatment can result in decreased tolerability and efficacy. It can also lead to augmentation, corresponding to increased symptoms severity after initial response to treatment (140). In the context of the latter, dopamine agonists may eventually need to be discontinued and replaced with other agents such as gabapentin, pregabalin or opiods. Allen et al. compared pregabalin versus pramipexole in a 12-week double blind clinical trial. Participants treated with pregabalin showed significantly less augmentation compared with pramipexole treated individuals (2.1% vs 7.1%, p=0.001) with long-term treatment (134). Opioids may be very effective in relieving both motor and sensory RLS symptoms (141). A double blind randomized placebo controlled trial by Trenkwalder et al. suggested that prolonged release oxycodone-naloxone is efficacious for treatment of severe RLS refractory to first-line treatment options (142). Several studies suggested that subthalamic nucleus DBS can possibly improve RLS in PD (143, 144).

5) CIRCADIAN RHYTHM DISORDERS

Circadian rhythm sleep disorders are disturbances of sleep-wake rhythm due to alterations of the circadian timing system or to a misalignment between the timing of the endogenous circadian rhythm and the sleep-wake times required by social schedules. Circadian rhythm disorders have not been systematically studied in the PD population. The prevalence of these disorders in PD is unknown. Emerging evidence suggests significant modifications of circadian system in PD (145). These include, for example, changes in firing neuronal pattern of SCN neurons in animal models of PD, as well as change in circadian amplitude (56, 146). Dopamine and circadian system have bidirectional modulatory relationships (147). Both motor and non-motor manifestations of PD exhibit strong diurnal oscillations that may be influenced by circadian function. Hormonal and molecular markers of the circadian system, such as melatonin and clock genes, have lower amplitude of their circadian rhythms in PD patients compared with healthy controls (145, 148, 149). This blunting of circadian amplitude may be reflective of weakened alerting circadian signaling that may contribute to EDS in PD (56). Circadian-based interventions, such as supplemental light exposure (light therapy), has favorable effects on sleep-wake cycles, mood, and motor manifestations of PD (72, 150, 151). Light therapy is easily administered, widely available and well-tolerated intervention that holds significant promise as a novel therapeutic approach not only for disturbed sleep-wake cycles in PD, but also for other disease manifestations. In summary, evidence available to date has positioned circadian system as a novel diagnostic and therapeutic target in PD.

6) REM SLEEP BEHAVIOR DISORDER

Definition—Rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by enactment of dreams associated with loss of physiologic muscle atonia during REM sleep (152).

Epidemiology—The prevalence of RBD in PD patients is variable and ranges from 4 to 70% (153–156), whereas it is estimated 0.5–2% in the general population (157). RBD is considered an early feature of synucleinopathies. Multiple studies have found a conversion to either PD, dementia with Lewy bodies (DLB) or multiple system atrophy (MSA) in more than 80% of idiopathic RBD patients (158–160). Moreover, Boeve et al. found α-synuclein

deposition in 94% patients with a neurodegenerative disorder and RBD (161). In longitudinal studies, idiopathic RBD precedes onset of parkinsonism by a median time of 13 years (162), up to 50 years (163), with an annual risk of developing a neurodegenerative disease of approximately 9% (164). RBD is a predictor of future cognitive decline in PD, and is more prevalent in PD patients with dementia compared with than PD patients without cognitive deficits (165–168).

Etiology—Unless triggered by pharmacological agents such as antidepressants, RBD is thought to be related to dysfunction within pontomedullary centers that regulate REM sleep including the locus coeruleus/subcoeruleus complex (169, 170). Development of RBD prior to the onset of cardinal motor symptoms of PD is reflective of synuclein-related neurodegenerative process that stems from low levels of neuroaxis and spreads through brainstem regions that are critical in regulation of REM sleep (1, 171).

Diagnosis—The gold-standard for RBD diagnosis is polysomnography (PSG) that demonstrates REM sleep without atonia (RSWA). Video analysis of events is also useful, but often unpredictable, as events are either subtle or infrequent (172). Polysomnographic EMG analysis of RSWA has good night-to-night stability, and usually a single night is sufficient to establish presence of RSWA (172–174). Several questionnaires have been developed as the screening tool for RBD (167, 175–181). Sensitivity of these instruments ranged from 74–96% and specificity from 56 to 92%. Although those questionnaires had excellent sensitivity, specificity of some was affected by the inability of the questionnaire to differentiate RBD from non-REM parasomnias, sleep disordered breathing, and seizures. When applied outside of the context of a strict validation protocol, these instruments may have less robust capacity for detecting RBD. Some of these instruments have been tested in the PD population, such as the REM behavior disorder screening questionnaire (RBDSQ), the REM Sleep Behavior Disorder Single-Question Screen (RBD1Q) and the Mayo Sleep Questionnaire which respectively showed a sensitivity of 74.2–85.4% and specificity of 43.2–96.3% for the RBDSQ (175, 182), a sensitivity of 93–100% and specificity of 48–68% for the RBD1Q (183), and finally a sensitivity of 90.3–100% and specificity of 36–85.2% for the Mayo Sleep Questionnaire (178, 182, 183). Moreover, the Hong-Kong RBD questionnaire and the Innsbruck RBD Inventory have been developed but not been validated for PD (176, 177).

Clinical implications—RBD phenotype is commonly described as “acting out dreams”. Symptoms encompass variable degree of involuntary vocal and motor behaviors on a background of action-packed and usually distressing dreams. This symptom constellation predisposes patients and their bed partners to significant injuries. Polysomnography-confirmed idiopathic RBD is considered one of the most specific and most predictive markers of prodromal PD, and is included in diagnostic criteria for prodromal PD according to the Movement Disorder Society criteria (184). This provides exciting platform for ongoing research on early biomarkers and impacts the development strategies for neuroprotective therapies. Moreover, RBD in PD is associated with differences in clinical phenotype, such as worse motor and non-motor symptoms, increased falls, more prominent dyskinesias, more hallucinations, worse cognition and overall quality of life (185–187).

These differences warrant for screening and timely diagnosis of these common motor and non-motor manifestations of PD in patients with co-existent RBD.

Management—The initial step in the management of RBD is education of patients and their bed partners. This will help maximize safety within a sleep environment, which is a critical step in the management of RBD (188). Multiple studies recommend the use of clonazepam and melatonin as level B recommendations (152, 188–191). A placebo-controlled cross-over trial of melatonin in 8 male patients with mild RBD revealed complete or partial resolution of dream enactment behaviors in 7/8 patients (190). Although these two agents have not been compared, melatonin appears to be better tolerated and has fewer side effects than clonazepam (191). A combination of clonazepam and melatonin are sometimes needed to provide sufficient symptomatic effect. Pramipexole has shown some benefit in improving clinical events in a small cohort of patients, but has not been routinely used in clinical practice (192). Monoamine oxidase inhibitors, tricyclic antidepressants, serotonergic synaptic reuptake inhibitors, and noradrenergic antagonists should be avoided, as are thought to induce or aggravate RBD (189). Moving forward, future studies should design randomized controlled studies to better assess the efficacy of clonazepam and melatonin.

CONCLUSION

Sleep disorders are common in PD, and available treatment options are limited. Many of these sleep disorders have specific differences when co-expressed with PD compared with the general population. Insomnia is frequent in PD, is associated with other multiple PD sleep comorbidities and leads to sleep fragmentation that is the most common sleep disturbance in PD. EDS associated with PD can present as sleep attacks in context of dopaminergic therapy, and in certain cases in a narcolepsy-like syndrome. Safety implications, such as driving, should be therefore addressed systematically. Sleep-disordered breathing presents in somewhat different phenotype in PD compared with the general population. Obesity is less prevalent and less associated with SDB in the PD population, and central and mixed apneas more common. Circadian dysfunction has been an under-appreciated problem in PD and has started to gain more attention. Both motor and non-motor features of PD have strong diurnal oscillations that may be influenced by the circadian function. RLS may pose diagnostic challenges in PD patients, as there are numerous RLS mimickers. Moreover, RLS can be masked by dopaminergic medications used for treatment of PD symptoms. Long-term dopamine agonist use for RLS can lead to augmentation that is quite challenging to treat. RBD is linked to the premotor phase of PD and is gaining interest for disease modifying clinical trials. As evidenced in this review, there is a great opportunity and need to develop novel treatment approaches for impaired sleep and alertness in PD. Improvements in sleep may translate into beneficial effects on many other manifestations of PD. Further advancements of sleep therapeutics in PD will depend on advancement of the current understanding of pathophysiology of sleep and circadian disruption in PD. This will require an organized effort of international scientific community dedicated to this research direction.

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