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CLINICAL REVIEW

# A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015☆

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SUMMARY

Sleep disorders are among the most common non-motor manifestations in Parkinson's disease (PD) and have a significant negative impact on quality of life. While sleep disorders in PD share most characteristics with those that occur in the general population, there are several considerations specific to this patient population regarding diagnosis, management, and implications. The available research on these disorders is expanding rapidly, but many questions remain unanswered. We thus conducted a systematic review of the literature published from 2005 to 2015 on the following disorders of sleep and wakefulness in PD: REM sleep behavior disorder, insomnia, nocturia, restless legs syndrome and periodic limb movements, sleep disordered breathing, excessive daytime sleepiness, and circadian rhythm disorders. We discuss the epidemiology, etiology, clinical implications, associated features, evaluation measures, and management of these disorders. The influence on sleep of medications used in the treatment of motor and non-motor symptoms of PD is detailed. Additionally, we suggest areas in need of further research.



## Introduction

While the non-motor manifestations of Parkinson's disease (PD) were noted when it was first described in 1817, early research focused on motor symptoms. Decades of research have improved management of motor manifestations in PD, while also shedding light on the protean non-motor manifestations. Among these, sleep disorders stand out given their high prevalence and their severe impact on quality of life (QOL) [1–3]. Additionally, sleep dysfunction can be associated with and influence other motor and non-motor symptoms in this patient population. While the past decade has seen major advances in our understanding of sleep disorders in PD, much remains to be learned. Applying rigorous and comprehensive literature search/identification criteria, we review the state of our knowledge from the past decade on some of the most common disorders of sleep and wakefulness in PD, namely, rapid eye movement (REM) sleep behavior disorder (RBD), insomnia, nocturia, restless legs syndrome (RLS)/periodic limb movement disorder (PLMD), sleep disordered breathing (SDB), excessive daytime sleepiness (EDS), and circadian rhythm disorders. We provide an overview of findings from the past decade of research, and propose key priorities for research in this area for the coming decade.

## Methods

This was a qualitative systematic review conducted according to PRISMA guidelines [4]. This methodology was chosen as it allows for systematic vetting of all references on a given topic that meet pre-specified inclusion and exclusion criteria, and provides a comprehensive account of all references meeting those criteria (in contrast to narrative reviews) [4]. Two electronic databases, PubMed and Embase, were searched for articles published between January 1, 2005 and January 1, 2015. The supplement to this manuscript details the search terms and methodology used for queries pertaining to each sleep disorder, including article inclusion and exclusion criteria.

☆ Refs [101] – [355] were present in the Supplementary material.

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**Abbreviation**

| | |
|---|---|
| AHI | apnea hypopnea index |
| BP | blood pressure |
| CPAP | continuous positive airway pressure |
| CSF | cerebrospinal fluid |
| DBS | deep brain stimulation |
| DLB | dementia with lewy bodies |
| EDS | excessive daytime sleepiness |
| ESS | Epworth sleepiness scale |
| HRQoL | health related quality of life |
| HR | heart rate |
| LED | levodopa equivalent dose |
| LED-DA | levodopa equivalent dose contributed by dopamine agonists |
| MSA | multiple system atrophy |
| OSA | obstructive sleep apnea |
| PD | Parkinson's disease |
| PDD | parkinsons disease dementia |
| PLMD | periodic limb movement disorder |
| PLMS | periodic limb movements of sleep |
| pRBD | probable REM sleep behavior disorder (not polysomnographically confirmed) |
| PSP | progressive supranuclear palsy |
| QOL | quality of life |
| RBD | REM sleep behavior disorder |
| RLS | restless legs syndrome |
| RSWA | REM sleep without atonia |
| SIT | suggested immobility test |
| SOS | suddent onset sleep |
| SPECT | single-photon emission computed tomography |
| STN | subthalamic nucleus |
| SWEDD | scans without evidence of dopamine deficiency |
| TST | total sleep time |
| WASO | wake time after sleep onset |

## REM sleep behavior disorder

RBD is a parasomnia characterized by loss of the atonia that normally occurs during REM sleep, associated with dream enactment behavior. RBD has been an intensive area of investigation over the past decade, both as a characteristic of the "premotor" PD state [5], and as a potential marker of more severe disease manifestations in PD.

### *Epidemiology*

The prevalence of RBD among individuals without PD or other neurodegenerative parkinsonian syndromes has not been well studied. Studies on the prevalence of RBD among community-dwelling older adults have not been conducted in over a decade.

Among patients with established PD seen at tertiary care centers, the prevalence of polysomnographically-defined RBD is 39–46% [6,7]. In early and de novo PD, the prevalence may be lower, at 30% [8]. There are no apparent sex differences in prevalence in this population [7,8]. REM sleep behavioral events, i.e., purposeful motor behaviors and/or vocalizations in REM sleep (irrespective of REM sleep without atonia (RSWA)), were identified in half of early PD patients [9].

RBD accounts for the majority of complex motor behaviors during sleep in PD, though apnea-related arousals are on the differential diagnosis [10], as are periodic limb movements of sleep (PLMS). In studies of probable RBD (pRBD) in PD, violent dream content is often reported, especially in males [11], and there is a significantly increased risk of injury [12]. Normal language and non-violent, culturally-specific movements also occur [13]. Of note, seemingly normal motor function and vocalizations occur during dream enactment in PD patients with RBD [14], often in stark contrast to the bradykinesia and hypophonia seen during wakefulness.

As mentioned, RBD may precede PD motor manifestations or develop after PD onset [15]. In studies of pRBD in PD, RBD preceding PD was associated with younger age of PD onset and more severe disease manifestations [16]. Shorter duration between RBD symptom onset and development of motor manifestations has also been associated with greater risk of cognitive impairment [17], possibly indicating greater neurodegeneration in these cases [17]. RBD persists in some patients throughout the course of their disease but resolves in others; in one study, approximately 30% of PD patients had resolution of pRBD within 4 y [18].

### *Etiology*

Progress to determine the etiology of RBD has been slow, but several theories have been put forth, based largely on animal data and supported by imaging and pathological data in humans. It has been proposed that RBD results from dysfunction in brainstem nuclei including the glutamatergic peri-locus coeruleus, combined with abnormalities in brainstem locomotor centers [19–21].

### *Evaluation*

RBD diagnosis requires polysomnographic demonstration of RSWA combined with either a history of dream enactment or demonstration of dream enactment during polysomnography [22]. The definition of what constitutes RSWA is an area of active ongoing research [23–26]. Several screening questionnaires have been applied for the diagnosis of RBD in PD [27–31] (Table 1), but demonstrate low specificity [27,32]. Questionnaires also poorly predict RSWA [32]. On the other hand, actigraphy may have high specificity but low sensitivity for the diagnosis of RBD in PD [67]. Four main conclusions that may be drawn from the literature over the past decade on diagnosis of RBD in PD include i) both patient and bed-partner input is essential in optimizing sensitivity of any questionnaire used to diagnose RBD ii) questionnaire-based diagnosis has low specificity iii) RSWA is necessary for definitive diagnosis vi) polysomnography is required to detect RSWA.

### *Clinical implications*

There are three broad implications of RBD. First, it is one of the strongest clinical predictors of future PD risk, and is thus seen as a prodromal state to PD [68] (as discussed further below, excessive daytime sleepiness [69] may be a manifestation prodromal to PD as well). As will be discussed, significant advancements have been made in identifying characteristics in RBD that are strongly associated with this risk of conversion to PD [70]. The second important implication is that among PD patients, several reports in recent years have suggested that RBD is associated with more severe motor and non-motor manifestations (Table 2). Finally, dream enactment behavior imposes significant risk of injury to the patient and bed-partner.

**Table 1**
Methods of evaluation of disorders of sleep and wakefulness in Parkinson's disease (ESS: epworth sleepiness scale; ICSD II: International classification of sleep disorders II; OSA: obstructive sleep apnea; PD: Parkinson's disease; PLMD: Periodic limb movement disorder; RBD1Q: REM sleep behavior disorder single-question screen; RBD: REM sleep behavior disorder; REM: rapid eye movement; RLS: Restless legs syndrome; PLMD: Periodic limb movement disorder; STOP: Snoring, Tiredness/sleepiness, Observed cessation of breathing, blood Pressure; STOP-BANG: Snoring, Tiredness/sleepiness, Observed cessation of breathing, blood Pressure, BMI, Age, Neck circumference, Gender.).

| | Objective measures | Questionnaires |
|---|---|---|
| **REM sleep behavior disorder** | – Polysomnography with assessment of atonia during REM sleep | – REM behavior disorder screening questionnaire (RBDSQ) [27]: 10-item questionnaire with scores ranging from 0 to 13. Sensitivity of English version in PD for ≥6 cutoff 68–90%, specificity 63–82.8% [30,33]<br>– REM sleep behavior disorder questionnaire Hong Kong (RBDQ-HK) [34]: 13 item questionnaire. Sensitivity 82.2%, specificity 86.9% mixed (idiopathic and secondary) RBD population<br>– Mayo sleep questionnaire (MSQ) [35] item 1: Single question. Sensitivity in PD 90.3%, specificity 87.9% among PD patients meeting ICSDII criteria [30]<br>– RBD1Q [36]: Single question. Sensitivity 93.8%, specificity 87.2% in idiopathic RBD population (not validated in PD).<br>– Innsbruck REM sleep behavior disorder inventory [37]: five item questionnaire. In mixed (idiopathic and secondary) RBD population, sensitivity 91.4%, specificity 85.7%. For single RBD summary question, sensitivity 74.3%. specificity 92.9%. |
| **Insomnia** [38] | – Polysomnography (in sleep maintenance insomnia, to exclude OSA or PLMD as a cause)<br>– Actigraphy [40,41] | – Parkinson's disease sleep scale version-2 [39]: Developed specifically for PD, version 1 recommended [38]. 15 item questionnaire<br>– Scales for Outcomes in Parkinson's disease sleep [42]: developed specifically for PD and recommended [38]. six item night-time questionnaire [42]. Includes nocturia item, which is an important component of any PD sleep questionnaire [43]<br>– Pittsburgh sleep quality index [44] (not developed specifically for PD but among recommended scales [38]) |
| **Nocturia** | – New-onset nocturia and/or acute worsening warrants a urinanalysis [45].<br>– Post-void residual volume should also be checked [45].<br>– Assessment for benign prostatic hypertrophy, bladder calculi, and/or other urologic disorders that may be contributing to nocturia is essential.<br>– In select cases, and in consultation with urology, urodynamic and cystoscopy may be appropriate for some patients [45]. | – Parkinson's disease sleep scale version-2 [39] and Scales for Outcomes in Parkinson's disease sleep (SCOPA) [42] both include a nocturia item.<br>– Other possible tools not yet validated in PD include bladder diaries and symptom questionnaires such as the nocturia, nocturnal enuresis and sleep-interruptions questionnaire (NNES-Q) [46,47] and the overactive bladder symptom score [48]. |
| **Restless legs syndrome** | – Suggested immobilization test (SIT). Mean leg discomfort cutoff of 11, yields a sensitivity of 91% and specificity of 72% for RLS diagnosis in PD [49]. | |
| **Periodic limb movement disorder** | – Polysomnography (>5/hr in children and >15/hr in adults consistent with PLMD in appropriate clinical context) | |
| **Sleep disordered breathing** | – Diagnostic polysomnography (with additional in-lab monitoring as needed for positive airway pressure titration [50])<br>– Out of center sleep testing (OCST): effective in diagnosis, but may underestimate respiratory events per hour if EEG is not recorded [22] | – Berlin questionnaire: 10 items; three categories: snoring behavior, daytime sleepiness, hypertension/BMI; High risk if positive in at least two categories. Predicts respiratory disturbance index >5 with 86% sensitivity and 77% specificity in general population [51]<br>– STOP questionnaire: four questions snoring, tiredness/sleepiness, observed cessation of breathing, blood Pressure. Considered high risk if answer positively for at least two questions. Predicts AHI >5 with sensitivity of 65.6% in general population [52]<br>– STOP-BANG: STOP questionnaire plus BMI, age, neck circumference, gender. Predicts AHI >5 with sensitivity of 83.6% and AHI >30 with sensitivity of 100% in general population [52] |
| **Circadian rhythm disorders** | – Actigraphy<br>– Dim light melatonin onset: onset of melatonin secretion under dim light conditions | |
| **Excessive daytime sleepiness** | – Multiple sleep latency test (MSLT) (measures tendency to fall asleep over five nap opportunities [22])<br>– Maintenance of wakefulness test (MWT) (measures ability to stay awake over four trials [55])<br>– Actigraphy | – Epworth sleepiness scale (ESS): subject rates tendency to doze off in eight different situations over the past month; validated in PD [53,54]<br>– Stanford sleepiness scale (SSS): 1 question item, subject rates level of alertness at time of assessment [56]<br>– Scales for outcomes in Parkinson's disease-SLEEP-daytime sleepiness (SCOPA-SLEEP-DS): 6-question evaluation of daytime sleepiness designed for use in PD [42]. Also validated in Thai [57]<br>– Parkinson's disease sleep scale (PDSS): items 14: “Do you feel tired and sleepy after waking in the morning?” and 15: “Have you unexpectedly fallen asleep during the day?” [58]. Item 15 is an independent predictor of sleepiness in one study [59] but not another [60]. Also validated in Italian, Chinese, Japanese, and Portugese [61–64]<br>– Movement disorders society-unified parkinson's disease rating scale (MDS-UPDRS): item 1.8: “daytime sleepiness” [65]. Shown to be effective screening tool for EDS, having good correlation with ESS [66] |

**Table 2**
Clinical implications (including associated motor and non-motor manifestations) identified in PD patients with specified sleep disorders compared to those without (DBS: deep brain stimulation; EDS: Excessive daytime sleepiness; ICDs: Impulse control disorders; LED: levodopa equivalent dose; MIBG: iodine-123-meta-iodobenzylguanidine; pRBD: Probable REM sleep behavior disorder; PLMS: Periodic limb movements of sleep; pRBD: Probable REM sleep behavior disorder; RBD: REM sleep behavior disorder; RLS: restless legs syndrome; SCOPA-AUT: Scales for outcomes in Parkinson's—Autonomic; UPDRS: Unified Parkinson's disease rating scale).

| Motor manifestations | Neuropsychiatric manifestations | Co-morbid sleep problems | Autonomic manifestations |
|---|---|---|---|
| **RBD** | | | |
| – Longer disease duration [7,17] and more advanced Hoehn and Yahr stage [7]<br>– More axial as compared to limb involvement [17]<br>– More prevalent non-tremor dominant PD subtype [15,71,72]<br>– Greater propensity to fall [7,72] and freeze [17,73]<br>– Greater requirements for dopaminergic medications [7,17,95] (not supported in other studies [96–98])<br>– Less response to dopaminergic medications [71]<br>– More dyskinesias [17]<br>– Worse outcomes after DBS (in pRBD) [99]<br>– More symmetry of motor manifestations [73]<br>– More prevalent motor fluctuations [7]<br>– Greater increases (deterioration) in total UPDRS scores [108] and bradykinesia subscores [109] | – Increased risk of multi-domain cognitive impairment cross-sectionallly [74–81]<br>– Increased risk of cognitive decline (longitudinally) [82–84]<br>– Greater prevalence of depression [6,73]<br>– Greater prevalence of fatigue [6]<br>– Greater prevalence of psychotic symptoms [7,83,100], [101]<br>– Greater prevalence of delusions [100] and nocturnal hallucinations [102] (in pRBD)<br>– Increased risk of ICDs [19], [103] (not confirmed in another study [104]) | – Sudden onset sleep leading to car accidents [85]<br>– Greater rates of sleep onset and maintenance insomnia and early morning awakenings [86–88] (data conflicting; one large study [7] showed better objective sleep in PD patients with RBD compared to those without)<br>– Abnormalities of circadian rhythm [89]<br>– Sleep related injury (sustained by patients and bed-partners) [90]<br>– Higher prevalence of nightmares, sleep talking, RLS [105–107]<br>– More excessive daytime sleepiness [97], hypersomnolence [110] (in pRBD) and shortened sleep latency [8] | – Greater risk of orthostatic hypotension [72,73,91]<br>– Reduced heart rate variability [92,93],<br>– Reduced MIBG uptake in pRBD [94]<br>– Constipation [16,73,91]<br>– Erectile dysfunction [91] |
| **Insomnia** | | | |
| – Higher UPDRS scores (associated with sleep questionnaire scores [111] and with less total sleep time and sleep efficiency on polysomnography [112])<br>– Longer disease duration [119,120] (associated with self-reported sleep problems)<br>– Higher Hoehn and Yahr stage [124] (associated with reduced sleep efficiency)<br>– Higher LED [124] (associated with reduced total sleep time) | – Greater prevalence of cognitive impairment and dementia [113,114] (self-reported and objectively-measured)<br>– Lower scores on measures of attention/executive function [115] and working memory [81] (associated with actigraphically-measured sleep measures)<br>– Association with depression prevalence [117,121–125] (Depression predicts poor sleep in PD, and insomnia is a predictor of depression [126])<br>– Increased prevalence of fatigue [116,117], psychosis, anxiety, and pain<br>– Psychosis [128] | – Greater prevalence of RBD (mainly in studies of pRBD [87,88] but also in studies with polysomnographic confirmation) [6]<br>– Associated with restless legs syndrome (RLS) [125] and leg motor restlessness (leg restlessness not meeting criteria for RLS) [127] | – More autonomic symptoms [116–118] (gastrointestinal and urinary domains of SCOPA-AUT) |
| **RLS/PLMD** | | | |
| – Severity of RLS correlated with presence of motor fluctuations [129] | – Severity of RLS correlated with cognitive problems [129], depressive symptoms, and psychotic symptoms | – PLMS in PD are associated with worse subjective sleep [130]<br>– Reduced sleep efficiency on polysomnogram [131] though other studies have not found differences in polysomnographic findings [130]<br>– Severity of RLS correlated with excessive daytime sleepiness [129] | – Autonomic symptoms [116–118] (gastrointestinal and urinary domains of SCOPA-AUT) |
| **Excessive daytime sleepiness** | | | |
| – Greater PD severity [132]<br>– Wearing off of PD medications [133]<br>– Increased fall risk in some studies [142] (not confirmed by others [143]) | – EDS experienced by more PD patients with dementia than PD without dementia or controls [134–136], and PD patients with EDS had lower scores on cognitive tests [137]<br>– EDS is a significant predictor of cognitive dysfunction [138] and incident development of cognitive dysfunction over 5 y [139], although another longitudinal study found no association [84]<br>– Depression (EDS is associated with depression [63] and is a significant predictor of depression [126,144] though not confirmed in other studies [145,146])<br>– Greater prevalence of fatigue [147,148] (not confirmed in other studies [149–151]), anxiety [152], and impulsive behavior [153], and hyposmia [154] | – Worse subjective sleep [63] | – Autonomic dysfunction, including: cardiovascular, urinary, and pupillomotor [116,140,141] |

**Table 2** (*continued*)

| Motor manifestations | Neuropsychiatric manifestations | Co-morbid sleep problems | Autonomic manifestations |
|---|---|---|---|
| | – Psychosis [155,156] (psychosis more common in PD patients with EDS, and PD patients with hallucinations more likely to have unexpected EDS) [157]<br>– Greater risk of incident hallucinations over 5 y [158] (relationship may be driven by other factors) [100,155,159] | | |

In a subset of patients with RBD, an identifiable non-neurodegenerative cause is present at the time of presentation (including focal brainstem lesions or narcolepsy [20,68]). However, as mentioned, in the vast majority of so-called idiopathic RBD cases, a neurodegenerative disorder emerges years after onset of the dream enactment. Use of the term "idiopathic" RBD is thus likely a misnomer in most cases, and other terminology may be more appropriate (such as "cryptogenic" and "symptomatic" RBD in those with versus without an identifiable underlying etiology, respectively).

Several reports over the past decade have provided ample evidence that the majority of patients with RBD will go on to develop a neurodegenerative disorder [68], [160], with synucleinopathies (PD, dementia with Lewy bodies (DLB), or multiple system atrophy (MSA)) being the most common [161]. Clinical progression from idiopathic RBD to a clinically-diagnosable synucleinopathy, often with associated cognitive impairment, is largely consistent with Braak's proposed PD neuropathological staging system [162], though not all patients follow this progression. In the largest prospective series (174 RBD patients) published at the time of our literature query, the 5-y and 14-y cumulative risk of developing a diagnosable neurodegenerative syndrome was 33.1% and 90.4%, respectively [68]. As discussed further below, like RBD, excessive daytime sleepiness [69] may be a manifestation prodromal to PD as well.

Polysomnographically-confirmed RBD has only rarely been reported in neurodegenerative tauopathies (including progressive supranuclear palsy (PSP) [163] and Guadeloupian parkinsonism [164]). In fact, a history suggesting RBD in a patient otherwise presumed to have a tauopathy (based on clinical grounds) should prompt evaluation for RBD mimickers such as obstructive sleep apnea [165,166].

An exciting area of development has been delineation, in longitudinal studies, of clinical, imaging, and biochemical biomarkers that may help predict if and when so-called idiopathic RBD will progress to a diagnosable neurodegenerative disorder (Table 3). All potential biomarkers require validation in prospective cohorts and inclusion into multimodal models that minimize lead time, e.g., models that reliably predict future risk of neurodegeneration before disease onset (and long enough before disease onset to allow for preventative interventions (if/where available) to take effect).

In regards to RBD in already-manifest PD, QOL is reduced in PD patients with RBD compared to those without [17,97]. Whether this results from the RBD itself and/or the co-morbid signs and symptoms (Table 2) requires further study. Individuals with RBD are at a significantly increased risk of sleep-related injury, ranging from superficial wounds to serious injuries that require intensive care and can be fatal [90]. Importantly, bed-partners of individuals with RBD are at a significantly increased risk of injury as well.

In line with the hypothesis that RBD in PD reflects more advanced neurodegeneration, smaller thalamic volumes on MRI [179] have been found in PD patients with pRBD compared to those without (but without significant structural cortical or white matter differences [180]). Furthermore, PD patients with RBD have greater EEG slowing during wakefulness [181], also possibly suggesting more severe neurodegeneration.

### *Management*

Adequately powered, randomized studies for treatment of RBD in PD have not been conducted. Clonazepam and melatonin are commonly used based on guidelines established for idiopathic RBD [90], but there are limited data on the efficacy of these drugs in individuals with RBD and a diagnosed neurodegenerative disorder. While data are limited, it is probable that this group of patients are more susceptible to side effects of benzodiazepines. In regards to other drug classes examined in studies including more than 30 patients, open-label data suggest that memantine may reduce the frequency of dream enactment [182].

An integral part of the management of RBD is intervention aimed at reducing injury to both the patient and the bed-partner [90]. This includes not only pharmacologic management but also institution of environmental modifications, such as removing sharp objects on which the patient can injure themselves, placing the mattress on the floor, and securing windows [90].

Nocturnal hallucinations are common in PD, particularly advanced PD, and are more common in PD patients with pRBD

**Table 3**
Clinical, imaging, and biochemical biomarkers that may predict emergence of a neurodegenerative disorder in patients with "idiopathic" RBD (EEG: electroencephalography; EMG: electromyography; MCI: mild cognitive impairment; MIBG: iodine-123-meta-iodobenzylguanidine; PD: Parkinson's disease; PET: positron emission tomography; RBD: REM sleep behavior disorder; SPECT: single-photon emission computed tomography).

| |
|---|
| **Sensory and motor clinical assessments** |
| Greater olfactory loss [167] |
| Impaired color vision [70] |
| Abnormalities on objective motor testing [168] |
| **Autonomic** |
| Orthostatic hypotension [91] |
| Urinary dysfunction [91] |
| Constipation [91] |
| Reduced cardiac MIBG uptake [169] (only reported cross-sectionally) |
| **Imaging markers** |
| Striatal dopaminergic deficit [170] |
| PD-related covariance pattern on PET and SPECT [171] |
| Substantia nigra hyperechogenicity on transcranial doppler sonography [172], (though not in isolation [173]) |
| Increased hippocampal mean regional cerebral blood flow [174] |
| **Electrophysiologic markers** |
| Tonic surface EMG activity on submental EMG [175] |
| EEG slowing [176,177] (which predicts MCI but not parkinsonism). |
| **Biochemical biomarkers** |
| Uric acid levels (associated with duration of RBD prior to manifestation of PD) [178] |

compared to those without [102]. Anecdotally, individuals with PD, particularly those with vivid dreams as occurs in RBD, often have difficulty distinguishing nocturnal hallucinations from dreams. In such individuals, particularly when hallucinations are frightening and contribute to insomnia, consideration for treatment with antipsychotics such quetiapine is warranted. Of course, the risks of worsening parkinsonism and other side effects need to be weighed against potential benefits in such cases.

## Insomnia

### *Epidemiology*

While both sleep onset and sleep maintenance insomnia are common in PD, sleep fragmentation, a key indicator of sleep maintenance insomnia, has been the most commonly reported sleep complaint [111]. Poor nighttime sleep (questionnaire-assessed) is more common in PD than the general population [123].

There is a 20–80% prevalence of poor sleep reported in PD based on cross-sectional subjective assessments [59], [121,122]. The prevalence based on physician interview is 30–59% [59], [183] while it is 32% based on International classification of sleep disorders (ICSD)-II criteria [105,184]. Risk factors for poor sleep include more advanced disease [119,185], female sex [121–123], and sporadic (as opposed to familial) PD [186]. In a longitudinal study of 89 PD patients over 8 y, 83% experienced insomnia at one or more study visits while 33% reported insomnia at all three visits and 20% who were free from insomnia at baseline developed it in follow-up [122].

Regarding objective measures of poor sleep in PD, polysomnography is useful in identifying potential causes of insomnia, such as obstructive sleep apnea (OSA). One study found that PD patients have significantly lower total sleep time (TST), sleep efficiency (SE), and increased REM sleep latency compared to age-matched healthy controls. They spent more time in stage 1 and less in REM, but without difference in number of arousals [124]. Sleep efficiency and total sleep time were reduced in those with

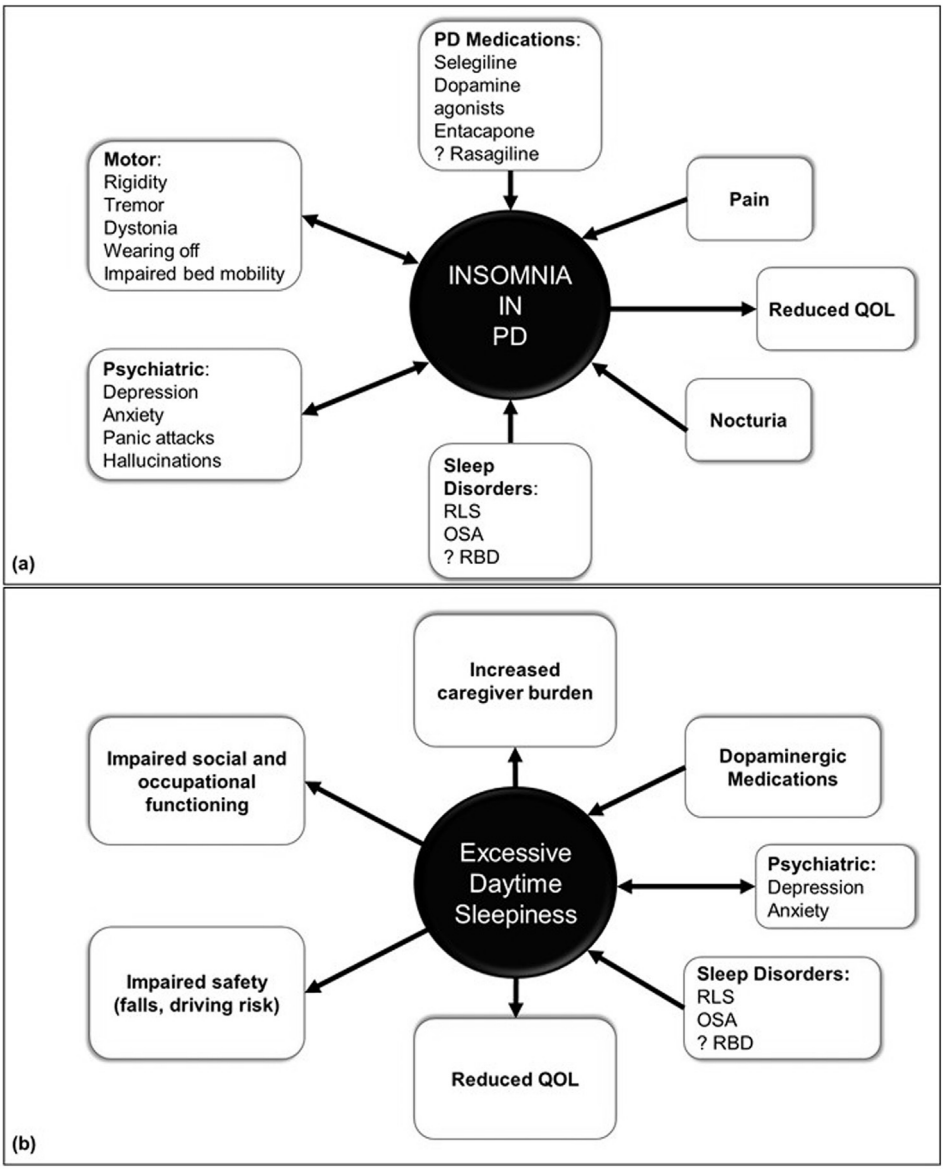


**Fig. 1.** Schematic of factors related to (a) insomnia and (b) excessive daytime sleepiness in Parkinson's disease (OSA: obstructive sleep apnea; PD: Parkinson's disease; QOL: quality of life; RBD: REM sleep behavior disorder; RLS: restless legs syndrome).

subjective insomnia but this was not statistically significant ($p = 0.07$) [124].

### *Etiology*

There are several potential causes of and/or contributors to insomnia in PD (Fig. 1a). Primary sleep disorders such as psychophysiologic insomnia (independent of the disease), RLS/PLMD, vivid dreams/nightmares, and OSA all may occur in the PD population, as discussed in this review. PD-related motor symptoms such as tremor [187], rigidity, leg cramps [187], and dystonia [111] are common. All of the latter may contribute to sleep-onset insomnia, and wearing off of dopaminergic medications overnight [111] may lead to or exacerbate sleep maintenance insomnia as well. Rigidity, bradykinesia, and other less well-defined causes also manifest with impaired bed mobility, which commonly presents subjectively with sleep-maintenance insomnia [188,189], and is associated with reduced sleep efficiency as assessed by polysomnography [188]. Given the significant contribution motor symptoms have on insomnia in PD, bedtime and overnight dopaminergic medication therapy may be required by some patients. Unfortunately while these medications can be helpful for motor-related sleep issues in some patients, they can have detrimental effects on sleep in others (Table 4).

Several PD-related non-motor symptoms may also play a prominent role, including psychiatric symptoms (anxiety, depression, panic attacks, nocturnal hallucinations and other psychotic symptoms) [126,128], pain (including nocturnal leg cramps) [111], and nocturia (see below).

The multifactorial nature of insomnia in PD is exemplified by the findings of one study that female gender, total levodopa equivalent dose (LED), levodopa equivalent dose from dopamine agonists (LED-DA), more depressive symptoms, better cognition, and more motor fluctuations accounted for 30% of variance in reported nighttime sleep problems, with depressive symptoms accounting for 21% [123]. Delving into any and all potential contributors to insomnia in PD is key to formulating a treatment plan (Table 4).

Studies examining objective correlates of poor subjective sleep have reported conflicting results. Some studies have reported greater amounts of polysomnographic evidence of sleep fragmentation in patients with worse subjective sleep [112], but others have not found associations between subjective and objective sleep in PD. The explanation for this discrepancy may be due to differences in methods used: polysomnography techniques, length of polysomnographic recording (1–3 nights of recording) and questionnaires used.

*Evaluation*: see Table 1

### *Clinical implications*

Several reports in recent years have suggested that insomnia is associated with more severe PD motor and non-motor manifestations (Table 2). Insomnia has a significant negative impact on QOL

**Table 4**
Considerations in the treatment of insomnia in Parkinson's disease (DA: dopamine agonist; LED: levodopa equivalent dose; LED-DA: levodopa equivalent dose—dopamine agonist amount; PD: Parkinson's disease; RCT: randomized controlled trial; UPDRS: Unified Parkinson's disease rating scale).

| Potential etiologic factors | Treatment considerations |
|---|---|
| **Motor symptoms and complications** [187,190]<br>Rigidity [187]<br>Tremor [187,190]<br>Motor fluctuations/nocturnal wearing off<br>Dystonia<br>Poor bed mobility [188,189] | – Limited evidence suggests long-acting dopamine agonists may be of benefit for subjective sleep disturbance and objective early morning motor symptoms [191–194]. Benefits on motor symptoms have to be weighed against risks of worsening insomnia due to dopaminergic therapy (see below)<br>– Limited evidence support referral to physical and occupational therapy for interventions to improve bed mobility [195].<br>– During an open-label, one-night, in-lab polysomnogram study, the group treated with a dose of controlled-release carbidopa/levodopa 50/200 mg had 15 min less mean wake time after sleep onset compared to those who remained off dopaminergic medications that night, a significant difference [120]. |
| **Medications** (increased risk of insomnia compared to placebo in RCTs):<br>Selegiline [196]<br>Dopamine agonists [197,198] and dopamine agonist withdrawal [199]<br>Rasagiline [200] (though some data suggest otherwise [201])<br>Entacapone [198] | – Limited data guides timing of dopaminergic medication intake in relation to sleep. Anecdotally, dosing of PD medications earlier in the day may be necessary for patients whose sleep is disrupted from dopaminergic meds. Higher total LED [202] and LED-DA [116] have been associated with worse measures of subjective and objective sleep in PD.<br>In more advanced PD, treatment of motor symptoms disruptive to sleep may outweigh any negative effects on sleep physiology of nocturnal dopaminergic stimulation [191] |
| **Psychiatric disorders** [123,126,128]:<br>Depression<br>Anxiety<br>Panic attacks | – Treatment of underlying psychiatric symptoms such as depression may improve insomnia in PD [203–205]. Low-level evidence and anecdotal experience suggest consideration for use of medications that treat psychiatric symptoms while capitalizing on sedating properties (such as trazodone and mirtazapine). Caution in worsening RBD and RLS is an important consideration [90] |
| **Nocturia** [111] | – Limited evidence is available to guide treatment of nocturia in PD.<br>In the non-PD population, behavioral interventions (bladder training, bladder control strategies, pelvic floor muscle training) are recommended as first-line therapy [45].<br>– Anti-muscarinics can be effective but in the PD population are associated with increased risk of cognitive dysfunction. Intradetrusor onabotulinumtoxin A may be of benefit in select cases [45].<br>Preliminary evidence suggests that posterior tibial nerve stimulation may be of benefit for nocturia in PD [206] and deserves further study.<br>– When possible, avoiding evening/nighttime administration of diuretics and other medications that may increase urine output may help.<br>– Potential benefit of dopamine agonists [111,207] and subthalamic nucleus deep brain stimulation [208,209] on nocturia warrant further study. |

in PD [3,210–214]; at least 10% of patients with advanced PD rank sleep problems as their most bothersome symptom [185].

*Management*

The majority of RCTs investigating treatment of insomnia in PD in the past decade have included <30 patients and were excluded from this review. The available evidence to support treatment of insomnia in PD was considered insufficient in the Movement Disorders Society Taskforce Guidelines of 2011 [215]. Controlled release carbidopa-levodopa, eszopiclone, and melatonin 3–5 mg were considered to have an acceptable risk without need for specialized monitoring. Since that time, some additional randomized trial data has become available for eszopicilone [216] and melatonin [217], though the quality of evidence for these and other agents continues to be suboptimal. Sodium oxybate [218] and rotigotine [192] show promise in open-label trials.

While insomnia can be a side effect of anti-depressants, placebo-controlled studies of nortriptyline, paroxetine, and venlafaxine provide evidence that treating depression in PD improves symptoms of insomnia [203–205]. Though evidence supporting treatment of other psychiatric disorders that may be contributing to insomnia are limited, targeting specific psychiatric symptoms such as anxiety, nocturnal panic attacks, and nocturnal hallucinations in the management of insomnia is worthy of consideration and investigation in clinical trials (Table 4). This applies also to treatment of other co-morbid signs/symptoms that may be contributing to insomnia in PD, such as nocturia and nocturnal PD motor symptoms, as detailed in Table 4.

## Nocturia

*Epidemiology*

Definitions of what constitutes clinically significant nocturia, or nighttime urination, vary but two or more episodes of nighttime urination lead to significant subjective sleep disruption and have detrimental effects on sleep in PD [219]. PD is a risk factor for nocturia among older adult men [220], and excessive nighttime urination is more common in PD than in age-matched controls [141], even early in the disease course [187,221]. It is one of the most commonly reported non-motor symptoms in PD, occurring in over two-thirds patients [47,121,208,210,222–225], and is among the most common urologic symptoms in PD patients presenting to movement disorders [226,227] and urology clinics [228]. Additionally, It is among the most common sleep complaints in this patient population [102,111,229], and is a key factor in sleep maintenance insomnia. In some studies, nocturia is more common in men [222,224,230,231], in older patients [231,232], in those with older age of PD onset [191,233] and increases with disease duration and severity [231].

*Etiology*

Nocturia in PD is likely multifactorial. Detrusor hyperactivity is present in most, but not all patients, with lower urinary tract symptoms such as nocturia [234,235]. Polyuria (production of greater-than-normal amounts of urine overnight) is present in some but not all patients. Other contributing factors may include factors unrelated to PD such as nocturnal diuresis and sleep apnea. Dopaminergic therapy [230] and higher LED [236] have been associated with greater report of nocturia, but whether this is a consequence of dopaminergic medications or a reflection of greater disease severity is not clear. In other studies, dopamine agonist use was associated with lower prevalence of nocturia [111].

*Evaluation*: see Table 1

*Clinical implications*

Nocturia in PD has a significant negative impact on quality of life [227]. As mentioned, it is cited as one of the most frequent nocturnal symptoms and contributes to sleep maintenance insomnia. The consequences of nocturia on daytime symptoms and function in PD are not well studied, but likely include excessive daytime sleepiness and possibly other non-motor and even motor problems associated with insomnia as detailed above. Objectively, nocturia in PD is associated with increased nocturnal activity as measured by actigraphy [133] and lower total sleep time and sleep efficiency on polysomnography [219].

*Management*

Little evidence guides management of nocturia in the PD population. Until such evidence becomes available, principles of nocturia management developed for the general older population may be of utility, though there are factors unique to the PD population that must be considered (Table 4).

## Restless legs syndrome and periodic limb movement disorder

Restless legs syndrome (RLS) or Willis Ekbom disease belongs to the group of sleep-related movement disorders. According to ICSD III criteria [22], RLS diagnosis requires “an urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs”. These symptoms must begin or worsen during periods of relative inactivity and must be partially or totally relieved by movement. The symptoms must cause significant distress or impairment in function. The interface of RLS and PD has been of increasing interest over the past decade.

Compared to RLS, PLMD has drawn less attention in PD research. PLMD is a sleep-related movement disorder characterized by periodic limb movements during sleep (PLMS) (>5/hr in children and >15/hr in adults) that result in clinically significant sleep disturbance or impairment of functioning [22].

*Epidemiology*

The temporal relationship between RLS and PD requires further study, but data to date suggest that RLS is not a risk factor for PD per se but rather that PD is a risk factor for a diagnosis of RLS [237] and RLS may be an early manifestation of PD [238].

Several recent reports focused on the prevalence of RLS in PD and its associations with PD symptoms. In a cohort of several parkinsonian disorders (PD = 134, PSP = 27, MSA = 21, DLB = 5), RLS was the most common in PD (11.9%) [239]. The prevalence of RLS in recent PD cohorts ranges from 3% [131] (compared to 0.5% of healthy controls) to 21.3% [129,240,241]. Late-onset patients develop RLS sooner after PD diagnosis compared to those with young-onset [242].

Primary RLS is frequently associated with PLMS. The relationship between PLMS and RLS in PD is less well understood, with research yielding conflicting results. Some studies report an association between presence of PLMS and RLS in these patients [131] whereas others do not [243].

*Etiology*

The question of possible pathophysiological overlap between PD and RLS has been a subject of debate. Brain imaging and genetic clinical research approaches may be useful in examining the biological links between these disorders. A recent imaging study demonstrates evidence for different pathophysiological pathways between RLS and PD at the level of nigrostriatal presynaptic function, finding that striatal dopamine transporter binding measured by Single-photon emission computed tomography (SPECT) is reduced in PD but not in primary RLS [244].

In regards to the genetics of RLS in PD, alpha-synuclein promoter Rep1 allele 2 is known to confer a PD risk. In a genotyping study of 258 patients with RLS the Rep1 allele 2 showed significantly decreased frequency compared with 235 healthy controls. These data suggest that low alpha-synuclein function may contribute to RLS pathogenesis [245].

Transcranial sonography has been applied to both PD and RLS populations and can be used to improve understanding of pathophysiological mechanisms of these disorders. While it is clear that PD is associated with substantia nigra (SN) hyperechogenicity, and RLS is associated with SN hypoechogenicity, studies that employed this technique in PD with co-existent RLS revealed contradictory findings [246,247].

*Evaluation*

There exists a clear need for more accurate assessment and diagnosis of RLS in PD. The suggested immobilization test may be useful for this (Table 1). Diagnosis of co-existent RLS in PD may be challenging due to several potential clinical confounders. For example, nocturnal leg restlessness is an important mimicker of RLS in PD, making the accurate diagnosis of RLS in PD difficult. Several studies have addressed nocturnal restlessness in the PD population [248–250]. In a cohort of 100 unmedicated PD patients, 40% had leg restlessness compared with 18% of age- and gender-matched controls [250]. However, only 15% of these PD patients met criteria for the diagnosis of RLS. Among PD patients with RLS, the urge to move legs and unpleasant sensations in the legs can be associated with wearing off [251]. These results emphasize the importance of differentiating between true RLS and RLS mimics. This has significant implications for patient care and clinical research.

*Clinical implications*

RLS in PD negatively impacts quality of life [130]. While one study found associations between RLS and younger age of PD onset, male gender, higher mini-mental state examination score and less advanced Hoehn and Yahr stage [240], another did not [239]. RLS has also been associated with non-motor PD symptoms (Table 2), which suggests the role of a non-dopaminergic system in the link between RLS and PD. However, domperidone treatment has been linked with higher rates of RLS in PD, suggesting a role for dopaminergic neurons outside of the blood-brain barrier in the pathophysiology of RLS [252]. The main obstacle in interpreting these studies is that most enrolled PD patients are already treated with dopaminergic agents, which may mask co-existent RLS. Associations between RLS and neuropathy have been well recognized, but not systematically studied. In one study, no correlations were found between RLS and neuropathy, levodopa exposure, and vitamin B12 levels in patients with PD [248]. Although not systematically studied in the PD population, it is likely that RLS contributes not only to sleep onset insomnia but also sleep maintenance insomnia in PD. This aspect is even more significant considering that RLS frequently mimics many symptoms intrinsic to PD, making timely diagnosis challenging.

*Management*

While many of the dopaminergic agents used to treat PD (levodopa, ropinirole, pramipexole, and rotigotine) also have been independently demonstrated in randomized trials to be effective in treating RLS, there are no randomized trials examining the treatment of RLS specifically in the PD population. In addition, the occurrence and management of augmentation of RLS symptoms in PD patients being treated with dopaminergic medications for their motor symptoms is poorly described. Two mainstays of evidence-based treatment of RLS in the non-PD literature are applicable to PD as well: i) assessment for and correction of any iron deficiency, and ii) consideration of reduction and/or discontinuation of contributing agents such as anti-depressants (Table 4).

Deep brain stimulation (DBS) is an important treatment modality for patients with PD. Several groups reported positive post-operative effects of subthalamic nucleus DBS on RLS [253,254]. However, emergence of RLS subsequent to subthalamic nucleus (STN) DBS may occur as well [255], emphasizing the need to screen for RLS postoperatively as the reduction in anti-parkinsonian medications may lead to unmasking of RLS.

## Sleep related breathing disorders

*Epidemiology*

In studies that prospectively evaluated PD participants without selection for sleep complaint, the prevalence of sleep disordered breathing (SDB) ranges from 15 to 76% [6,10,74], [112,117,124,163,243,256–262]. Because patients with PD have been reported to have both obstructive and restrictive pulmonary dysfunction [263,264] as well as abnormal response to hypercapnia [265], researchers have hypothesized that sleep apnea risk is increased in PD relative to the general population. However, controlled studies on sleep apnea in PD over the last 10 y consistently failed to demonstrate any increased risk for sleep apnea. Regardless, the negative health implications of sleep apnea in older adults have been extensively documented. For example, obstructive sleep apnea (OSA) has been associated with significant cardiovascular, psychiatric, and cognitive comorbidities as well as increased healthcare utilization [266,267]. Therefore, it is important to fully explore this sleep disorder in PD.

Regarding controlled studies of prevalence of SDB in PD, one study demonstrated no significant difference in apnea hypopnea index (AHI) among Asian PD patients and controls, with neither group having significant central sleep apnea. Surprisingly, OSA was present in 49.1% PD patients compared to 65.7% of controls [124]. Another study showed sleep apnea in 40% controls and 27% of PD subjects and patients with apnea had more severe motor disability than those without [256]. In early PD, there was no difference in AHI between PD and control groups [257]. Further, in a study designed to compare the frequency of SDB in PD and controls, Trotti and colleagues evaluated PD patients with polysomnography (PSG) and compared outcomes to an historical control [268,269] and found no difference in frequency or severity of OSA. Interestingly, neither subjective sleepiness nor snoring predicted sleep apnea in PD patients [262].

There are also uncontrolled studies reporting SDB prevalence in PD. One found a prevalence of 22.4% for moderate to severe sleep apnea (AHI >15) among unselected PD participants [260]. In another cohort of PD subjects, sleep apnea was present in 54.6% [112]. Among subjects with mild-moderate PD, SDB (AHI $\geq$10) was present in 55%

[6]. Other studies find at least mild apnea (AHI ≥5) in 74% of subjects [117] and severe apnea (AHI >30) in 17.9% [270]. In early PD, 33.7% of subjects had an AHI ≥5 [243]. Similarly, among treatment naïve PD, 43.3% had an AHI ≥5 and the mean AHI was 8.3 [271].

There have been a few studies of sleep disordered breathing in patients with other Parkinsonian syndromes such as PSP, DLB and MSA. One such polysomnographic study found that OSA was present in 30.7% of PD and 34.8% of DLB subjects [74]. In another study, 55% of PD and PSP patients had OSA, which increased with age in both groups, but PSP patients had worse sleep efficiency [163]. A questionnaire study comparing MSA, PD, and control subjects found sleep-related breathing complaints in 30% PD, 19.8% control, and 54.7% MSA subjects [272]. Among MSA, PSP, and PD patients, 38.5%, 14.3%, and 18.8%, respectively, screened high risk for sleep apnea [273].

*Etiology*

As discussed previously, pulmonary dysfunction has been proposed as a potential risk for SDB in PD patients [263,264]. In individual patients, SDB could be related to rigidity of muscles of the chest wall, restricted lung volumes secondary to changes in posture/kyphoscoliosis, or altered flow volume loop due to 4–8 Hz oscillations in upper airway muscles [274,275]. Interestingly, there was no increase in sleep apnea in PD patients with camptocormia [276]. Neurodegeneration was also proposed as a cause of SDB in PD, but studies show no correlation between SDB and caudal brainstem serotonergic innervation or striatal dopaminergic innervation [258]. For many PD patients, the etiology for sleep apnea is likely the same as for the general population.

*Clinical implications*

Extensive research has documented the negative health effects of untreated sleep apnea in the general population but this is less well explored in PD patients. Some studies show an association between subjective sleepiness and sleep apnea: PD patients with AHI ≥5 had more EDS than those with AHI <5 [112] and AHI correlates with subjective sleepiness in PD [152]. Other studies found no correlation between AHI and subjective sleepiness [6], [243,260,270]. PD patients with higher AHI have shorter mean sleep latency in several studies [117,124,261,270], but one study found no difference [259]. PD subjects with sleep apnea have worse scores on cognitive testing and sleep disordered breathing independently predicts cognitive dysfunction [6]. Arousal related paroxysmal nocturnal behaviors are more frequent in PD patients with sleep disordered breathing, though most complex paroxysmal nocturnal behaviors were related to RBD [10].

Due to differences in SDB characteristics between PD patients and controls, PD patients may have less severe SDB-associated health consequences [256]. For example, for the same AHI, PD patients maintain higher oxygen saturation than controls and control subjects have more of their AHI accounted for by apnea, whereas PD patients have more hypopneas [260,277] indicating less severe consequences despite similar AHI. One study also suggested more central sleep apnea among PD patients compared to controls [278], but other studies don't support this [124,256,277]. Central sleep apnea in PD patients has been associated with higher doses of dopamine agonists [278]. Interestingly, control subjects with OSA have higher levels of sympathetic activity during sleep than PD patients with OSA, suggesting that sympathetic dysfunction in PD leads to a blunted response to apneas [279]. These findings support the argument that sleep apnea in PD may have fewer cardiovascular consequences. In addressing cardiovascular health among PD patients with and without SDB, one study showed a trend toward more history of cardiovascular events in PD patients with sleep apnea, but this did not reach significance (33% versus 13%) [256]. Another study found no difference in presence of cardiovascular disease between PD participants with and without SDB or between controls and PD subjects with OSA [260].

*Evaluation methods*: See Table 1

*Management*

Treatment for SDB in Parkinson's disease is the same as for the general population. Only one study in the past ten years has addressed the impact of sleep apnea treatment in PD patients. This randomized, controlled study demonstrated that, compared to sham CPAP, therapeutic CPAP reduced AHI and improved the mean sleep latency [50].

## Excessive daytime sleepiness

*Epidemiology*

Excessive daytime somnolence is common among patients with Parkinson's disease, affecting 20–60% of patients [57,89], [102,123,124,137,144,145,151,182,183,243,259,261,270,272,273, 280–296]. Multiple factors influence the prevalence of EDS, including duration and severity of disease, age, gender, cognition, presence of nocturnal sleep disorders, and mood disorders. Some controversy exists as to whether excessive somnolence is a prodromal feature of PD or a symptom only in advanced disease. One study showed that EDS was significantly worse in drug-naïve PD patients compared to control subjects and even worse in advanced PD [187]. In contrast, another study showed no significant difference in EDS between newly diagnosed PD and controls, although PD subjects took more naps [243]. Two small studies found no difference in subjective or objective sleepiness between drug-naïve PD and controls [297,298]. Similarly de novo PD patients and SWEDD (scans without evidence of dopaminergic deficits) subjects had no significant difference in ESS and EDS was uncommon in both groups [299]. Interestingly, a large population-based study showed EDS to be a possible risk factor for future development of PD [69]. Larger, controlled studies in de novo PD patients are needed to further evaluate the true prevalence of daytime sleepiness in this population.

That subjective sleepiness is more common among PD patients than the general population is well established. Supportive controlled studies show subjective sleepiness in 33.5–54% of PD patients, compared to 16–19% controls [40], [151,284,291,296]. Similarly, a large study demonstrated EDS in 43% of PD patients compared to 10% of controls, with sleepiness being more common in PD patients with higher age, higher dopamine agonist dose, more severe disease, autonomic dysfunction, and psychiatric symptoms [123]. In longitudinal studies, the 8-y prevalence of EDS was 54.2% for all PD subjects evaluated and 46.5% in those never treated with dopamine agonists [137]. Similarly, a longitudinal evaluation at 3.5, 5, and 7-y time-points showed 49%, 53%, and 44%, respectively, had daytime somnolence [283].

Several studies have suggested that sleepiness is more likely to affect patients with advanced PD [102,144,146,282,298,300]. An objective study demonstrated that advanced PD patients had significantly shorter mean sleep latency (MSL) compared to early PD and controls. The MSL did not correlate with subjective sleepiness, but was related to disease duration and motor impairment [298]. Another study demonstrated that PD patients with Hoehn &Yahr stage 4 had significantly more daytime sleepiness than stages 1, 2, or 3, without group differences for dopaminergic therapy [301]. In a study of non-motor symptoms in

nursing home residents with PD, 68% reported daytime sleepiness [295], supporting the idea that EDS is related to disease duration and severity.

Sex also influences EDS prevalence in PD, with men being more likely to be sleepy [287]. In fact, EDS is best predicted by male sex, duration of PD, and presence of anxiety [282], and more men than women have subjective sleepiness, even after controlling for levodopa equivalent dose [41].

The prevalence of EDS has also been compared between PD and other movement disorders. One study found no difference in EDS between essential tremor (ET) and PD subjects [286], while another found EDS to be more common in PD than ET [280]. In a study comparing daytime sleepiness in MSA, PD, and controls, EDS was found in 28%, 29%, and 2% respectively [272]. EDS appears to be more common among subjects with Parkinson's disease dementia (PDD) or DLB compared to PD patients without dementia [182,281].

*Etiology*

The etiology of EDS in Parkinson's disease is multifactorial (Fig. 1b). Some studies report no significant correlation between nighttime sleep and subjective sleepiness [134]. However, nocturnal sleep disorders can certainly contribute to daytime somnolence. For example, two studies found more subjective sleepiness in PD patients with RBD compared to those without RBD, although in one of the studies, the difference became not significant after controlling for other predictors [86,97]. Interestingly, treatment-naïve PD patients without RBD had significantly shorter MSL than subjects with RBD, though neither group had abnormal MSL, and the epworth sleepiness scale (ESS) was not different between the groups [8]. Regarding restless legs syndrome (RLS), one study showed no difference in subjective sleepiness between PD patients with and without RLS [239]. However, other studies show that RLS severity correlates with

**Table 5**
Effects of medications on excessive daytime sleepiness in PD (EDS: excessive daytime sleepiness; ESS: Epworth sleepiness scale; MSL: mean sleep latency; MSLT: multiple sleep latency test).

| Dopamine agonists |
|---|
| **Pramipexole** |
| Somnolence is often reported by PD patients on immediate or extended release formulations in both placebo controlled and open label extension studies [134,243] |
| In early PD, patients randomized to pramipexole had slight worsening of subjective sleepiness compared to a slight improvement in those randomized to rasagiline [304] |
| Among patients randomized to initial therapy with pramipexole or levodopa, EDS was present at 6 y in 57% of those on initial pramipexole compared to 35% of those initially on levodopa [305] |
| EDS may be exacerbated in patients with kidney disease since pramipexole is renally excreted– One study showed correlation between EDS and renal function in patients on pramipexole but not ropinirole [306] |
| **Transdermal Rotigotine** |
| EDS affects 33% of PD patients on rotigotine compared to 20% on placebo [307,308] |
| EDS occurs at a rate of 23% per patient year on rotigotine [309] |
| In open label extension studies, ESS scores increased over time and EDS was reported as an adverse event in 13–24.9% of subjects on rotigotine [193,310,311] |
| **Ropinirole** |
| Studies of ropinirole do not show increased somnolence for immediate or extended release formulations in placebo-controlled or open label extension studies [194,312,313] |
| A within-subject study showed improvement in ESS following change from immediate to prolonged-release formulation of ropinirole [314] |
| **Apomorphine** |
| Somnolence was reported in 7.8–14.3% of PD patients on apomorphine in a placebo controlled trial [315] |
| EDS was reported as an adverse event by 21% PD patients on apomorphine in an open label extension study [316] |
| **Rasagiline** |
| No increased EDS compared to placebo [316] |
| **Entacapone** |
| Somnolence was reported by 6.5% of PD subjects who were switched from immediate release carbidopa/levodopa to carbidopa/levodopa/entacapone [317] |
| **Selegiline** |
| In an open label study, selegiline in combination with reduction or discontinuation of dopamine agonists led to reduction or resolution of somnolence in 94% subjects with EDS [196] |
| **Piribedil** |
| PD patients with EDS on pramipexole or ropinirole were randomized to either change to the non-ergot dopamine agonist piribedil or to remain on current therapy. Those changed to piribedil had improvement in sleepiness [318] |
| **Studies supporting relationship between dopaminergic therapy and EDS** |
| Levodopa equivalent dose independently predicts subjective sleepiness [117] |
| Sudden onset sleep (SOS) episodes are more likely among patients on dopamine agonists [319] |
| Subjective sleepiness correlates with use of dopamine agonists [261,293,320] |
| A longitudinal study showed that dopamine agonist use was an independent predictor of EDS at 7 y [283] |
| Micro-sleep episodes (by actigraphy) are more frequent in the 30 min following levodopa dose and PD patients report more somnolence within 1 h of taking dopamine agonists [259,321] |
| **Studies not supporting a relationship between dopaminergic therapy and EDS** [57], [285,290,322] |
| A longitudinal study showed no change in EDS one year after initiating dopaminergic therapy [322] |
| Dopamine agonist use correlated with EDS but was not an independent predictor of subjective sleepiness in regression analyses [282] |
| Objective evaluations of sleepiness (MSLT) show no effect of dopamine agonists on MSL [303] and no difference in MSL between those on levodopa alone versus dopamine agonists alone [124] |

**Table 6**
Priorities for research, areas of knowledge deficits, and potential future directions in PD Research. (CSF: cerebrospinal fluid; EDS: Excessive daytime sleepiness; ICSD: International Classification of Sleep Disorders; PLMS: periodic limb movements of sleep; RBD: REM sleep behavior disorder; RCT: randomized controlled trials; RLS: restless legs syndrome; RSWA: REM sleep without atonia; SDB: sleep disordered breathing.

| | RBD | Insomnia | Nocturia | RLS/PLMS | EDS | SDB | Circadian rhythm disruption |
|---|---|---|---|---|---|---|---|
| **Epidemiology** | (i) Validation of putative biomarkers predicting onset of a neurodegenerative parkinsonian syndrome<br>(ii) Investigation of multimodal prediction models including biochemical biomarkers (such as on CSF), genetics, and imaging<br>(iii) Improvement in nosology (consideration for renaming idiopathic RBD to cryptogenic RBD, and terming RBD associated with neurodegeneration as symptomatic) to facilitate research | (i) Delineation of insomnia types in PD based on ICSD criteria (eg sleep onset vs. sleep maintenance insomnia, psychophysiologic, environmental etc); essential for development of targeted treatment interventions | (i) Examining prevalence of nocturia among patients with PD at different disease stages | (i) Conducting longitudinal epidemiological studies to better understand the prevalence and incidence of RLS in the PD population | (i) Conducting large longitudinal studies to clarify if EDS a prodromal symptoms or simply a marker of disease progression and severity | (i) Examining prevalence of SDB among patients with PD at different disease stages<br>(ii) Studying the true prevalence of SDB subtypes (ie central vs. obstructive sleep apnea) | (i) Describing the prevalence of circadian rhythm disruption in PD<br>(ii) Understanding how the presence of these disorders varies based in relation to motor phenotype |
| **Etiology** | (i) Understanding why RBD occurs in synucleinopathies<br>(ii) Delineating the brainstem neurons that mediate REM sleep without atonia and if/why they have differential susceptible to abnormal synuclein phosphorylation and deposition<br>(iii) Better understanding of the restoration of normal motor control seen in PD patients with RBD during dream enactment [14] so that this knowledge could be utilized to improve movement during wakefulness<br>(iv) contribution of various neurotransmitter pathways to RBD pathophysiology and implications (such as association between cholinergic denervation [353,354] and cognitive function) | (i) Better understanding of etiology of insomnia in PD including contribution of primary sleep disorders, motor features/fluctuations, and effect of medications | (i) Characterization of nocturia in PD including prevalence of reversible/treatable causes | (i) Investigating the role of iron metabolism in the pathophysiology of RLS in PD<br>(ii) Examining genetic profile of RLS in PD | (i) Clarifying associations and contributions of both motor symptoms (including side of PD onset [355]), non-motor symptoms, medications, and level of physical activity to EDS | (i) Understanding if motor phenotype (tremor dominant vs. akinetic rigid/gait disorder) influences prevalence or severity of SDB Particularly relevant since motor symptoms may influence respiratory function. | (i) Conducting neuroimaging and pathologic changes to delineate the neuroanatomic underpinnings of circadian rhythm disruption in PD<br>(ii) Systematic study of molecular regulation of circadian timekeeping in PD. |
| **Evaluation** | (i) Improvement in questionnaires for diagnosis of RBD in PD is needed, for clinical screening and large-scale population studies that cannot feasibly incorporate polysomnography<br>(ii) Better definition of RSWA in PD and minimization of labor-intensivity of assessment, including delineation of optimal automated scoring methods | (i) Identifying and optimizing objective measures of insomnia in PD including actigraphy and mobile technologies | (i) Creating appropriate evaluation protocols specific to the PD population, including guidelines on instances in which urodynamic studies and cystoscopy are appropriate | (i) Developing RLS assessments tools to better account for the RLS mimics in the PD population | (i) Development of questionnaires aimed at resolving the discrepancy between subjective and objective outcomes of sleepiness in PD<br>(ii) Optimization of objective screening measures such as actigraphy | (i) Developing better screening methods for SDB in PD, since risk factors in PD differ from the general population [262] currently available questionnaire have not been sufficiently validated in the PD population [183,284]. | (i) Validation of available measures of circadian function in the PD population |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | (iii) Role of actigraphy and other mobile devices in diagnosis of RBD | | | | | | |
| **Clinical Implications** | (i) Better definition of implications of RBD in PD in regards to cognition and non-motor as well as motor features | (i) Further describing associations between poor sleep and both motor and non-motor manifestations.<br>(ii) Investigating of whether treating insomnia in PD improves the underlying PD motor and non-motor manifestations | (i) Better understanding of relation between autonomic function/ dysfunction and nocturia in PD | (i) Understanding the implications of PLMs in PD | What is the long-term impact of EDS on safety, motor outcomes, and healthcare utilization? | (i) Clarifying the cardiovascular and other health consequences of SDB in PD, including effects on motor symptoms and non-motor symptoms including mood and cognition | (i) Examining how circadian rhythm dysregulation influences motor and non-motor manifestations of PD |
| **Management** | (i) Conducting randomized trials to establish the most appropriate therapy, including therapies targeted at reducing injury to patient and bed-partner from dream-enactment<br>(ii) Understanding effects of treatments on dream enactment behavior, risk of injury to patient and bed-partner, and daytime side effects | (i) Conducting randomized trials to establish the most appropriate pharmacologic treatments<br>(ii) Developing an evidence base for treatment of PD manifestations that contribute to insomnia such as motor symptoms, psychiatric symptoms, and autonomic symptoms (with emphasis on nocturia)<br>(ii) Studies examining utility of non-pharmacologic methods of treatment sleep problems in PD, including deep bran stimulation and cognitive behavioral therapy | (i) Conducting randomized trials to establish the most appropriate non-pharmacologic treatments (including investigation of behavioral interventions and posterior nerve stimulation) and pharmacologic treatments (including newer agents that may have less likelihood of central side effects compared to anti-muscarinics, such as mirabegron) | (i) Conducting randomized controlled trials directed to the coexistent RLS and PD<br>(ii) Further defining the effect of surgical therapies such as deep brain stimulation and dopaminergic medication infusion therapies on RLS and augmentation | (i) How do available pharmacologic and surgical treatments of PD motor symptoms influence EDS and vigilance?<br>(ii) Additional placebo-controlled, blinded evaluations of promising therapeutic options.<br>(iii) What is the impact of non-pharmacologic interventions, such as exercise? | (i) Conducting RCTs to test if treating SDB in PD improves motor and non-motor outcomes | (i) Conducting RCTs to test light therapy, melatonin, and other treatments for circadian disruption in PD<br>(i) Conducting RCTs to test if treating circadian disruption in PD improves motor and non-motor symptoms, including other disorders of sleep and wakefulness |

sleepiness [129] and RLS is an independent predictor of EDS in PD patients [272].

The association between daytime sleepiness and sleep apnea has not been definitively established in PD. Among PD patients not selected for any sleep complaint, patients with objective sleepiness by MSLT had higher apnea hypopnea index (AHI), with no correlation between subjective sleepiness and AHI [258,270]. Similar findings of absence of correlation between ESS and AHI have been reported in other studies as well [256,260,262,293], and one study found no correlation between self-reported snoring and subjective sleepiness [302]. In contrast, other studies have demonstrated a relationship between subjective sleepiness and sleep apnea [112,303], including one showing significant correlation between both subjective and objective sleepiness and AHI [261]. Available data indicate that objective sleepiness is consistently influenced by the presence of sleep-disordered breathing, but its effect on subjective sleepiness is less well established. This suggests that some PD patients may underestimate their degree of sleepiness.

Dopaminergic medications may also affect levels of somnolence, and studies of dopamine agonists frequently note somnolence as an adverse effect. However, some investigations have shown no correlation between medications and subjective sleepiness [134,243]. Studies investigating the impact of medications on somnolence are outlined in Table 5. To summarize, dopaminergic medications, particularly dopamine agonists, influence subjective sleepiness in some patients, but do not appear to cause changes in objective measures of sleepiness. This is another example of the disconnect between patient perception and objective outcomes.

Imaging has been explored in an effort to identify neurodegenerative changes that could explain the etiology of somnolence in Parkinson's disease. In studies comparing PD patients with and without EDS, SPECT imaging showed that left parietal hypoperfusion and right thalamus hyperperfusion were significant predictors of EDS [323] and diffusion tensor imaging showed reduced fractional anisotrophy in the fornix in PD subjects with EDS [324]. Additionally, PD patients with EDS have regional brain atrophy in the frontal lobes, temporal lobes, occipital lobes, and in the area of the nucleus basalis of Meynert [325] as well as in the middle cerebellar peduncle compared to PD patients without sleepiness [273]. Neurodegeneration could also impact circadian rhythm regulation. In fact, PD patients with EDS have lower amplitude of the melatonin rhythm [89]. In a search for genetic causes of EDS in PD, no relationship was found between sleepiness and the catechol-O-methyltransferase $val^{158}met$ polymorphism [326]. Additional imaging and post mortem studies in larger groups of patients with and without EDS are needed to determine the true impact of neurodegenerative brain changes on somnolence in PD.

### *Clinical implications*

Excessive daytime sleepiness has been associated with many motor and non-motor symptoms, as outlined in Table 2. EDS negatively correlates with and is an independent predictor of QoL in PD [1], [289], although another study showed that nocturnal sleep quality was a better predictor of QoL [2]. EDS is also an independent predictor of health related quality of life (HRQoL) through its impact on activities of daily living [327]. In addition, EDS in PD negatively impacts caregiver burden [328].

Studies investigating the safety implications of EDS in PD have shown that subjective sleepiness predicts worse driving performance during distraction [329] and sleepiness predicts poorer processing speed/reaction time even after controlling for levodopa equivalent dose [330]. Among 5210 PD patients with a driver's license, 8% reported sudden onset sleep (SOS) while driving; 27% and 28% of those, respectively, had near or actual accidents associated with SOS [85]. In a French PD cohort, EDS and male sex were predictors of drowsy driving and SOS while driving [287]. SOS was more frequent and more likely to occur during active behaviors in PD compared to control subjects, but subjective sleepiness was not a good predictor of SOS [296]. PD subjects may be less likely to adjust their behavior based on sleepiness (don't adjust driving speed based on sleepiness) [331]. In addition to safety concerns among PD patients who continue to drive, there is also the potential for loss of independence, increased caregiver burden, and further impairment of quality of life in those who no longer drive due to sleepiness.

While some PD patients reported improved motor symptoms on awakening from nighttime or daytime sleep, there was no difference between EDS in PD patients with or without sleep benefit (improvement in motor symptoms following sleep) [332].

### *Evaluation methods*

Measures for evaluation of EDS in PD are listed in Table 5. Comparison between studies can be challenging due to use of different measures and different definitions of EDS, such as defining sleepiness as epworth sleepiness scale [117,135,333] and others demonstrating a significant relationship [259,261]. Similarly, actigraphy measures of napping correlate with subjective sleepiness in some studies but not others [321,334]. These findings again raise concern that PD patients may have poor insight about their degree of sleepiness.

Because the profound hypersomnolence in PD patients is reminiscent of narcolepsy, hypocretin levels in CSF have been examined in PD. In one study, levels were normal in PD but did correlate with mean sleep latency [298]. In another study, there was no correlation between hypocretin levels and subjective or objective measures of sleepiness in PD patients with or without dementia [135].

### *Management*

Several therapies have been evaluated for management of excessive sleepiness in PD. Treatments found to be no more effective than placebo for EDS include: modafinil up to 400 mg/d for 4 wk [335], memantine [182,336], and bright light therapy [337]. Additionally, following STN DBS, PD patients report improvement in sleep quality but not subjective sleepiness [338]. Melatonin at 5 mg improved subjective sleepiness on the general sleep disturbance scale, but not on the ESS [339]. Some potentially promising therapies for EDS include: sodium oxybate, which improved ESS, but was associated with a small but significant increase in apneic events [218]; atomoxetine [340]; and caffeine, which showed a trend toward improvement in sleepiness compared to placebo [341]. These studies indicate that some treatment options may improve somnolence in PD, but the promising studies need to be replicated in larger groups.

## Circadian rhythms disruption

Circadian rhythms are biological rhythms with a periodicity of approximately 24 h in humans. These rhythms influence many physiological and behavioral functions. The sleep–wake cycle is one of the most robust outputs of circadian timekeeping. Compared to other sleep disorders in PD, systematic clinical investigations of circadian rhythm disruption are just recently emerging.

Endogenous circadian rhythms can be characterized by analyzing circadian markers (Table 1). Prolongation of the phase angle of melatonin rhythm was recently reported in medicated compared to un-medicated PD patients and controls [342].

Although two other studies did not show alterations in the circadian phase of melatonin secretion, both reported decreased amplitudes of melatonin secretion, which was significantly lower in patients with EDS [343,344]. PD patients are also found to have elevated cortisol levels, and flattened expression rhythm of a major core clock gene, Bmal1 [344]. Additionally, the mesor and nocturnal fall in core-body temperature were lower in PD compared to controls [345]. Somatotrophic, thyrotrophic and lactotrophic axes appear to be intact in early-stage PD [346]. Overall, these investigations strongly suggest alterations of the endogenous circadian rhythmicity in PD. This will need to be better delineated in longitudinal studies employing larger cohorts of PD patients.

Blood pressure (BP) and heart rate (HR) have a distinct diurnal rhythm, and are important outcomes for investigations of the interface of circadian biology and autonomic function in PD. 24-hour ambulatory BP monitoring reveals significant differences in the rhythm of non-dipping, the percent of nocturnal BP decrease, nighttime BP levels, and nocturnal decrease of HR between PD patients and controls [347]. These changes do not appear related to disease severity and phenotype, supporting the hypothesis that these alterations may stem from intrinsic circadian dysregulation. Reversal of circadian BP rhythm, postprandial hypotension and nocturnal hypertension in PD has also been reported [348]. Circadian profile of BP and HR may be good metrics to differentiate between MSA and PD as patients with MSA have higher nocturnal HR and lower nocturnal decline in HR compared with PD [349]. Low frequency components of heart rate variability and the low/high frequency ratio tend to be more reduced in patients with MSA compared to PD patients [350,351]. Further studies will be needed to better delineate these findings.

Circadian disruption has been associated with neuropsychiatric disturbances in PD. PD patients with hallucinations have diminished inter-daily stability of rest–activity cycle, reduced amplitude of activity and increased nighttime activity compared to non-hallucinators [352]. Similarly, PD patients with depression have lower amplitudes of core body temperature and higher minimum rectal temperature relative to PD patients without depression [301].

Systematic study of circadian function in the PD population is in early stages. While clinical significance of circadian disruption may prove to be very relevant to both motor and non-motor aspects of the disease, published literature to date provides the rationale for exploring circadian based interventions in the management of disrupted sleep–wake cycle, especially excessive daytime somnolence.

## Influence of dopaminergic therapy on sleep in Parkinson's disease

The complexity of sleep dysfunction in Parkinson's disease is further compounded by the influence of dopaminergic and other PD medications on sleep. The majority of studies investigating sleep in PD have included patients already on therapy, with only a few exploring sleep in unmedicated patients [9], [199,250,342]. For each sleep disorder discussed in this review, anti-parkinsonian medications can have potential positive or negative effects. For example, in RBD, anecdotally, many patients report improvement in dream-enactment behavior with dopaminergic therapy. As discussed in the section on insomnia and in Table 4, insomnia can be worsened both by wearing off of medications [111,199] as well as by use of certain medications such as selegiline [196] and others. Excessive daytime sleepiness in the context of dopamine agonist use has been extensively evaluated, as outlined in Table 5. The influence of PD therapeutic medications on sleep disorders is further explored throughout this review within each specific section. The influence of these treatments on sleep dysfunction in combination with the heterogeneity of the PD phenotype further emphasizes the need for additional studies to address this complex non-motor symptom.

## Conclusions and future directions

This review of the literature of sleep-related disorders in PD research over the past decade demonstrates that sleep dysfunction is common in these patients and has a significant impact on quality of life, motor symptom severity, and other non-motor symptoms. As is evidenced from our findings, significant advancements have been made in our understanding of disorders of sleep and wakefulness in PD. Despite the growing body of knowledge, much remains to be understood in terms of diagnostic assessments, epidemiology, pathophysiology, clinical impact and implications on the underlying disease and its manifestations, and evidence-guided management. In Table 6, gaps in knowledge and priorities for future research are proposed.

### Practice points

- REM sleep behavior disorder is a clinical biomarker of increased risk of synuclein-related neurodegeneration in individuals without evidence of a neurologic disorder. It is associated with increased risk of injury to the patient and bed-partner, and institution of safety measures is a key component of its management.
- Insomnia in PD is multifactorial, resulting from a combination of nocturnal motor symptoms, nocturia, impaired bed mobility, medications, depression, and co-morbid primary sleep disorders. Etiologies contributing to insomnia may need to be treated separately. Reduced sleep time related to insomnia has the potential to worsen motor symptoms.
- RLS is common in patients with PD, and is sometimes challenging to diagnose and distinguish from motor restlessness of PD and other RLS mimics. A detailed history and evaluation is essential in a PD patient with possible RLS, as its presence may influence timing and nature of therapy.
- Circadian dysfunction is under-recognized in PD and likely influences not only sleep–wake cycles, but also may affect mood, cognition, autonomic and motor functions. Circadian based therapies, such as timed light exposure and melatonin, should be considered in PD patients with evidence of circadian dysregulation.
- EDS is common among PD patients and negatively impacts quality of life and impairs safety. This symptom can be severe enough to cause sudden onset sleep episodes and significantly impair driving safety. Further, the propensity for sleep during the daytime can interrupt work and social activities, increase caregiver burden, and has the potential to further disrupt nighttime sleep.
- While sleep disordered breathing is not more common among PD patients compared to the general population, patients may not present with the typical symptoms of snoring and daytime sleepiness, so a low threshold for polysomnography should be considered. Though some data suggest that PD patients may have fewer cardiovascular consequences of apnea than the general population, CPAP therapy is effective and should be recommended.

**Research agenda**

- Future research on REM sleep behavior disorder will be facilitated by the development of improved diagnostic criteria, specifying practical and yet sensitive and specific definitions of REM sleep without atonia, as well as questionnaires with improved specificity.
- In regards to knowledge gaps pertaining to insomnia in PD, treatment options are markedly under-studied and randomized clinical trials of pharmacologic and non-pharmacologic approaches to treatment of insomnia in PD are much needed.
- Further research is needed to understand a potential overlap in pathophysiological mechanisms that underlie PD and restless legs syndrome. Future investigations will need to define criteria specific to restless legs syndrome in the PD population and established guidance for the optimal treatment approaches for restless legs syndrome in co-existent PD.
- Future research on sleep disordered breathing in PD should include development of screening tools more sensitive to detection of sleep apnea in this population and execution of randomized controlled trials to determine the impact of treatment of sleep disordered breathing on motor and non-motor as well as cardiovascular outcomes in PD.
- Important areas of future research on daytime sleepiness in PD will include understanding the discrepancy between objective and subjective measures of sleepiness in PD and conducting placebo-controlled trials of both pharmacologic and non-pharmacologic treatments with the potential to improve sleepiness in these patients.
- One of the main questions in the field of circadian rhythms and PD is whether circadian disruption represents a consequence of PD-specific neurodegeneration, or whether it may lead to and/or promote the neurodegenerative process of PD. Longitudinal studies centered on circadian function in PD will be needed to answer this and similar questions that may position circadian system as a novel diagnostic and therapeutic target in PD

## Conflicts of interest

Dr. Chahine receives royalties from Wolters Kluwel (for book authorship). The other authors do not have any direct conflicts of interest with this work.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2016.08.001.

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* The most important references are denoted by an asterisk.

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