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Sleep/wake problems in Parkinson's disease: pathophysiology and clinicopathologic correlations

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Abstract In his initial description of shaking palsy, James Parkinson first noted that sleep became disturbed with advancing paralysis agitans. More recent studies have confirmed that the majority of patients with Parkinson's disease (PD) suffer from some sleep disturbances. This can manifest as difficulty in falling or staying asleep, fractionated sleep, specific parasomnias, and daytime sleepiness. In this article, we will explore the pathophysiology of these varied sleep disorders. In most cases, however, the definitive etiology is debated, and phenotypes are often felt to be multifactorial. Some of these may be associated with dopaminergic dysfunction, some presumed to arise from varied non-dopaminergic PD pathology, and some from PD treatments.

Keywords Parkinson's disease · Sleep · REM behavioral disorder · Hypocretin · Restless legs syndrome

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder. Clinically defined by rigidity, bradykinesia and tremor, PD symptoms also include numerous sensory, autonomic, sleep/wake symptoms, and other non-motor symptoms. Some of these symptoms likely result from dopamine cell loss, while others do not. There is actually relatively little pathologic data that directly compare PD patients with any specific sleep/wake disorder versus PD patients without that problem. However, the pathophysiology of sleep/week disorders is increasing elucidated by epidemiologic data, physiological assessments, and a better understanding of the pathology sleep/wake disorders in the general population.

This article will first explore alterations in sleep/wake function and its two main consequences, insomnia and sleep fractionation, then at excessive daytime sleepiness, including alterations in circadian control, and then review the pathophysiology of specific common sleep issues including REM behavioral disorder (RBD), sleep apnea (OSA), restless legs syndrome (RLS), and periodic limb movements of sleep (PLMS).

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Alteration of sleep architecture and sleep fragmentation

Sleep is divided into different stages, the composite of which is termed architecture. We usually enter light sleep (manifest by slow eye movements and loss of occipital alpha activity). Stage 2 sleep is defined by the presence of sleep spindles and usually constitutes the majority of the sleep epoch. Slow-wave sleep (formal stage 3 or 4) is the "deepest" sleep manifest by delta activity on EEG. Patients often then cycle into rapid eye movement (REM) sleep. This peculiar state includes EEG activity similar to the wake state, loss of muscle activity (atonia), and rapid jerky eye movements. They may then cycle back to light sleep and imperfectly cycle through these states. REM sleep is relatively more prevalent in the second half of the sleep event.

Some studies do not show any marked or consistent abnormalities in sleep architecture in PD, other than reduced REM atonia (Happe et al. 2003; Diederich et al. 2013). The most consistently observed abnormalities are

reduced sleep efficacy, sleep fragmentation and frequent arousals (Tandberg et al. 1998; Porter et al. 2008). In other studies, PD patients had less total sleep time, lower sleep efficiency, increased sleep latency, longer stage 2 of sleep and shorter or longer REM sleep stage compared to healthy controls (Young et al. 2002; Yong et al. 2011; Antczak et al. 2013). There are some reports showing increased alpha activity during REM sleep (Brunner et al. 2002) and less sleep spindles during non-REM sleep (Friedman 1980). That said it is somewhat surprising that basic sleep architecture is not more consistently abnormal, and overall sleep efficiency is independent of motor functions in many studies (Young et al. 2002; Diederich et al. 2005).

The specific causes of these documented abnormalities are multifactorial and direct pathological assessments are limited. Sleep fragmentation has been associated with longer disease duration, female gender and depression (Gjerstad et al. 2007). They occur more frequently in light sleep (stage 1 and 2), but can happen during any sleep stage (Porter et al. 2008). Sleep fragmentation in PD can be primary, i.e. the consequence of a disruption of sleep architecture, or secondary to nocturnal recurrence of PD symptoms (tremor, dystonia, rigidity), effect of medications, OSA, PLMS, or nocturia.

The effect of dopaminergic treatments on sleep in PD is a complex subjects and will not be discussed in detail. In general, dopaminergic drugs and STN DBS usually improve sleep (Amara et al. 2012); however, higher doses of dopaminergics, especially L-dopa, have been associated with sleep fragmentation and insomnia (Chahine et al. 2013).

Only one autopsy study has primarily compared PD and PD/dementia patients with, versus without, "sleep problems" (Kalaitzakis et al. 2013). There was a significant association between disturbed sleep in PD and α-synuclein pathology in the locus coeruleus (most robust) and raphe nuclei; hypothalamic areas including the paramammillary nuclei and posterior nucleus; subcortical/limbic system including the amygdala, thalamus, and entorhinal cortex regions. A statistically significant increase of tau pathology was observed in the amygdala, CA2 sector of the hippocampus and entorhinal cortex. In general, there was more widespread pathology in PD cases that reported more sleep problems.

The pedunculopontine tegmental nucleus (PPN) has specifically been proposed to be involved in PD-associated sleep disruption, as it is involved in the control of sleep cycling and REM sleep via cholinergic ascending thalamic pathways (Monderer and Thorpy 2009). DBS stimulation of this area, used for severe gait disorders, has improved subjective sleep and increased observed REM sleep (Amara et al. 2011; Peppe et al. 2012), but specific pathologic confirmation is lacking.

Table 1 Summary of sleep latency testing in patients with PD

	Epworth scale	Sleep latency minute (SD)	Sleep onset REM
Arnulf et al. (2002) ($N = 54$)	14.3 (4.1)	6.3 (0.6)	39 % of pt. had ≥2 episode
Ondo et al. (2005) ($N = 40$)	15.1	5.1 (4.9)	9/148 episodes
Razmy et al. (2004) ($N = 80$, DA)	6.6 (4.9)	12.1 (5.1)	NR
Rye et al. (2000) ($N = 27$)	NR	11.0 (6.1) 40/134 < 5	6/27 subjects 13/108 episodes
Monaca et al. (2006) ($N = 36$)	13.0 (5.8)	10.0 (5.5)	10/36 had ≥2 ep.
Poryazova et al. (2010) ($N = 30$)	>10 in 57 %	11/30 had <5	0

Excessive daytime sleepiness and circadian function

In 1999, an article first reported "sleep attacks" while driving in patients taking either pramipexole or ropinirole (Frucht et al. 1999), drawing attention to this subject. Sleep attacks correlate well with general excessive daytime sleepiness (EDS) and people are usually amnesic of sleepiness leading to short sleep episodes, so the term "sleep attack" has given way to EDS. A large number of studies subsequently confirmed "sleep attacks" and associated EDS. Overall, EDS frequency, usually defined by elevated Epworth Sleep Scale scores (>7 or >10 depending on the study), ranges from 15 to 50 % of PD patients (Ondo et al. 2001; Gjerstad et al. 2002; Hobson et al. 2002; Razmy et al. 2004; Ferreira et al. 2006; Suzuki et al. 2011). Major and consistent risk factors for EDS include older age, more advanced PD, dopaminergic use and male sex (Ondo et al. 2001; Hobson et al. 2002; Roth et al. 2003). Male sex is also a risk factor in the general population. Less consistent risk factors include cognitive decline, hallucinations, rapid progression of PD, onset of PD on the left body (right brain), anxiety, depression, and postural instability (Ondo et al. 2001; Gjerstad et al. 2002; Razmy et al. 2004; Ferreira et al. 2006; Boddy et al. 2007; Ghorayeb et al. 2007; Stavitsky et al. 2008; Suzuki et al. 2011).

The main physiologic controversy is whether these sleep episodes truly represent early onset REM sleep, which is a characteristic of narcolepsy. Although data are mixed, a minority of PD patients do seem to have early onset REM (Rye et al. 2000; Ulivelli et al. 2002; Razmy et al. 2004; Ondo et al. 2005; Monaca et al. 2006; Arnulf et al. 2008; Poryazova et al. 2010) (Table 1). It should be noted that determining REM state is difficult in the PD population due to the lack of REM atonia, which may account for some of the variance among studies.

The mechanisms by which PD is associated with EDS are likely multifactorial. Potential explanations may include exogenous medications, loss of dopamine, loss of norepinephrine and serotonin (alerting monoamines), loss of hypocretin pathways, loss of autonomic function, and loss of circadian control, which has been demonstrated physiologically, and at the molecular level.

Initial investigations into EDS assumed that this resulted from poor nocturnal sleep. Counter-intuitively, this did not seem to be culpable. Several studies using polysomnography and MSLT suggest that patients with more total sleep at night actually have similar or more EDS compared to patients who slept less well (Rye et al. 2000; Arnulf et al. 2002; Roth et al. 2003). Other specific sleep abnormalities such as RBD, RLS, PLMS, and OSA generally fail to correlate with EDS. (Ondo et al. 2001; Cochen De Cock et al. 2010; da Silva-Junior et al. 2014; Plomhause et al. 2013).

The loss of monoamines neurotransmitters through neurodegeneration may contribute to EDS. Endogenous dopamine is generally considered a wake-promoting neurotransmitter, especially when it interacts with D1 receptors. Various lesioning studies of nigral and ventral tegmental areas of non-human primates usually result in sedation and in some cases alter circadian function (Barcia et al. 2004; Barraud et al. 2009). Dopamine receptor type 2 knockout mice are also sleepy (Qu et al. 2010). Exogenous dopamine studies in animals, however, have yielded a spectrum of often contradictory results, seemingly very dependent on dose and animal species and dose. No specific pathologic study has attempted to correlate dopamine cell loss specifically with EDS.

Both serotonin and norepinephrine, which potentiate wakefulness, are also markedly reduced in PD, although no pathologic assessment has specifically tested this.

Hypocretin controls sleep/wake cycling and is markedly reduced in narcolepsy and cataplexy. EDS may result from degeneration of hypocretin cells in the hypothalamus, which are lost in parallel to symptomatic PD progression (Fronczek et al. 2007; Thannickal et al. 2007). However, CSF hypocretin levels, which are markedly reduced in cataplexy/narcolepsy, are usually not very reduced in PD when obtained via lumbar puncture (Yasui et al. 2006; Baumann et al. 2008; Compta et al. 2009). A single ventricular CSF measure done during DBS surgery did show marked CSF hypocretin reduction, and one would speculate that neuron count would correlate to the physiology better than CSF levels (Maeda et al. 2006). Loss of hypocretin function is an attractive model, as it results in sleep/wake instability and could thus explain both sleep fragmentation and frequent daytime sleep episodes.

There are no robust findings from genetic studies that have looked for sleep/wake disorder associations. "Sleep attacks" in PD have been weakly associated with the dopamine D2 receptor gene polymorphism Taq1A (Rissling et al. 2004) and a polymorphism of prehypocretin (Rissling et al. 2005).

Others attribute EDS, and to some extent nocturnal sleep problems, to perturbations in the circadian cycle (Videnovic et al. 2013). Many normal circadian patterns are blunted or desynchronized in PD, including circadian motor activity, increased day and decreased at night (Niwa et al. 2011), R–R variability measured by Holter monitor (Pursiainen et al. 2002), and 24-h cortisol levels (Videnovic and Golombek 2013). There is mixed data on circadian melatonin levels in PD (Fertl et al. 1991; Bordet et al. 2003), but a recent very carefully controlled trial showed reduced melatonin in general and a marked attenuation of the nighttime melatonin spike, suggesting a blunting of normal circadian wake/sleep cycling (Videnovic and Golombek 2013).

There is no human pathological study that specifically correlates alterations circadian control center pathology to sleep/wake phenotype. Cellular loss in PD is seen in almost all circadian control areas including the suprachiasmatic nucleus (SCN). Peripheral autonomic dysfunction, commonly found in PD, may also mitigate circadian physiology responses (perspiration and skin temperature changes).

There is increasing understanding of the molecular basis of circadian function, alterations in which may also contribute to sleep/wake problems in PD. At the most superficial level, cellular endogenous circadian control transcriptional–translational feedback loops are centered in the SCN. The protein products of Bmal1 and CLOCK heterodimerize, forming complexes that stimulate transcription of the "negative feedback" genes Period (Per 1, 2, and 3) and Cryptochrome (Cry 1 and 2) (Lowrey and Takahashi 2011). These proteins then heterodimerize and translate back into the nucleus where they inhibit transcription of Bmal1 and CLOCK genes. Eventually, the Per and Cry proteins breakdown and Bmal1 and CLOCK translation begins again, starting the cycle over again. The process takes on average a little longer than 24 h, although individual SCN cells have periods that vary from 23 to 28 h. They are synchronized by a number of proteins including vasoactive intestinal polypeptide (VIP). The system is also modulated and entrained by physical activity, other environmental factors, and most robustly, by light. Interestingly, retinal dopaminergic cells control light input into the SCN and seem to have their own independent circadian clocks (Wirz-Justice et al. 1984). Perturbation of these has been speculated to blunt downstream circadian function, although no study has attempted to correlate this to empiric sleep/wake disorders in PD (Willis 2008).

Dopamine and CLOCK genes have a complex reciprocal interaction. Dopamine production, especially tyrosine

hydroxylase gene activation, the rate-limiting step in dopamine production, is controlled by CLOCK genes (Yujnovsky et al. 2006). Conversely D2/D3 agonists inhibit mCLOCK and mPer1 gene expression, whereas a D1 agonist stimulates these genes (Imbesi et al. 2009). Most importantly, studies have demonstrated that PD patients have a decrease in the expression of the Bmal1 gene during night, suggesting a blunted CLOCK system (Cai et al. 2010). Further research is clearly needed to determine if this underlies many sleep/wake issues in PD.

REM sleep behavior disorder

REM sleep behavioral disorder (RBD) has been extensively studied as a precursor to Lewy body disease and is discussed in general terms elsewhere. In short, RBD is defined by the absence of the normal muscle atonia during the REM phases of sleep. This can lead to dream enacting with potential injury to the patient or the bed partner (Schenck and Mahowald 2002). REM sleep without atonia (RWA) lacks the manifest behavior but demonstrates abnormal muscle activation during REM sleep (Gagnon et al. 2002).

It is now widely accepted that RBD is robustly associated with the development of Lewy body pathology (synucleinopathies, including PD, multiple systems atrophy and Lewy body dementia). Pathological examinations of subjects with RBD show that more than 90 % have Lewy body pathology (Boeve et al. 2013). A number of PD biomarker studies that have evaluated primary RBD in subjects without clinical motor signs of PD have shown abnormalities in between those of PD and normal controls, suggesting RBD heralds impending synucleinopathy diseases (Iranzo et al. 2010; Miyamoto et al. 2011; Shin et al. 2013a). Primary RBD is associated with other pre-motor features of PD including visual changes and olfactory deficits (Postuma et al. 2006; Iwanami et al. 2010; Iranzo et al. 2013). Most clinically important, longitudinal studies of RBD subjects show that a large number eventually develop clinical parkinsonism (Schenck et al. 1996; Iranzo et al. 2006; Kumru et al. 2007; Britton and Chaudhuri 2009; Postuma et al. 2009). In the longest followed series, 81 % of the original cohort, not lost to follow-up, developed parkinsonism, a mean of 14 years after the onset of RBD (Schenck et al. 2013). Within the PD population, active RBD is seen in about half, more commonly males, and the presence of current RBD symptoms has been associated with a worse prognosis, increased dementia, increased hallucination, increased falls, and increased autonomic dysfunction, suggesting a more widespread disease process (Vendette et al. 2007; Sixel-Doring et al. 2011; Postuma et al. 2012; Sorensen et al. 2013; Videnovic et al. 2013). Higher doses of dopaminergic drugs, especially L-dopa, are also associated with RBD, although the direction of causality, if any, is not known (Ozekmekci et al. 2005; Gjerstad et al. 2008; Nihei et al. 2012).

The general anatomy involved in RBD has been long known, but understanding of the specific culpable nuclei is recent and still in flux. The most accepted model of primary pathology of RBD involves the pontine sublateral-dorsal (SLD) nucleus, aka "subcoeruleus", which sends excitatory glutamate projections caudally to the ventrolateral medulla (including the nucleus raphe magnus and ventral and α-gigantocellular reticular nuclei) (Luppi et al. 2013). These send inhibitory GABA and probably glycine projections to the α-motor neurons in the spinal cord, resulting in atonia. Ascending projections from the SLD, thought to be responsible for cortical activation during REM, seem less effective. Other areas are also proposed to be involved with RBD but a primary dopaminergic pathology is unlikely (Luppi et al. 2013).

Pathologic studies of RBD both prior to and after the onset of parkinsonism show Lewy bodies and cell loss in these areas; however, this is not specific, as these areas are thought to be involved in PD in general, and studies to date have not quantified these areas to see if they specifically correlate with RBD within the PD population. This pathology correlates nicely with the concept that RBD is a form fruste of PD. Braak pathology suggests that Lewy body pathology within the CNS starts in the lower brainstem, affecting REM modulating centers before the substantia nigra, thereby potentially explaining the onset of RBD preceding motor features of PD (Braak et al. 2003).

Sleep apnea

When assessed with polysomnography, 20–50 % of PD patients are diagnosed with sleep apnea, usually obstructive (OSA). While some research shows that PD patients have a greater frequency of sleep apnea than healthy age-matched controls, the majority actually show similar or less OSA (Trotti and Bliwise 2010; Yong et al. 2011; Peeraully et al. 2012; Cochen De Cock 2013; Zeng et al. 2013), and when PD/OSA patients are compared to control OSA patients, they have less oxygen desaturations (Nomura et al. 2013). This likely relates to lower body mass index seen in PD (Nomura et al. 2013; Zeng et al. 2013). Moreover, no association has been found between the Apnea–Hypopnea index and multiple sleep latency tests, further suggesting that sleep apnea is not a major contributing factor to the severity of sleepiness in PD patients (Zeng et al. 2013). There may also be less medical consequences because the usual sympathetic discharge associated with apnea is blunted in PD (Valko et al. 2012).

Given the frequent absence of OSA risk factors in PD patients with documented OSA, the pathophysiology in PD is not well understood. It does not correlate with PD duration, motor severity, or PD medications (Wetter et al. 2000). It has been postulated to result from pharyngeal narrowing secondary to degeneration of brainstem neurons that innervate the pharyngeal dilator muscles, which play an important role of maintaining tracheal patency during sleep (Veasey et al. 1996; Friedman and Millman 2008). However, there is no pathologic data to associate this, and brainstem PET imaging of dopaminergic and serotonergic ligands failed to correlate with OSA in PD subjects (Lelieveld et al. 2012).

Restless legs syndrome in PD

Restless legs syndrome is defined by the simultaneous presence of (1) desire to move the extremities, often associated with paresthesia/dysesthesia; (2) worsening of symptoms at rest; (3) transient improvement with movement; and (4) worsening of symptoms in the evening or night (Allen et al. 2003). No widely available biomarker or test corroborates the diagnosis, which is made exclusively via interview. RLS most closely resembles akathisia, also reported in PD, but differs in that (1) the urge to move is isolated in the limbs, rather than the entire body, (2) there is more dramatic relief with ambulation, and (3) there is a more robust worsening at night, with near complete cessation of symptoms in the early morning. RLS is very common, affecting about 10 % of Caucasian populations, although it appears less common in Asian and African populations (Ondo 2002). There is a strong genetic component (Winkelmann et al. 2007).

RLS and PD both respond to dopaminergic treatments and are both variably associated with PLMS. Therefore, a relationship between the two conditions has long been sought.

The pathology of idiopathic RLS involves CNS iron homeostatic dysregulation. CSF ferritin and other measures of iron are lower in RLS cases (Earley et al. 2001), MRI imaging and transcranial ultrasound show reduced iron stores in the striatum and substantia nigra (Allen et al. 2001), and pathologic data show reduced ferritin staining, reduced iron staining, increased transferrin stains, and reduced iron regulatory protein-1 activity (Connor 2008). In contrast, PD is associated with increased iron in dopaminergic areas.

Dopaminergic medications, especially dopamine agonists, robustly improve RLS, even at low doses. However, dopamine imaging studies of the striatum have been inconsistent and difficult to interpret, but do not show any clear dopamine deficiency. Most importantly, pathologic data does not suggest reduced dopamine in RLS. CSF studies and human brain studies of the nigro-striatal system generally suggest normal or even increased dopaminergic turnover (Earley et al. 2013). Specifically, substantia nigra dopaminergic cells are not reduced in number, nor are there markers associated with neurodegenerative diseases, such as tau or alpha-synuclein abnormalities (Pittock et al. 2004). PD, of course, exhibits reduced dopamine cells and multiple neurodegenerative markers. In summary, there are no clear pathologic similarities between PD and idiopathic RLS.

Nevertheless, most surveys that have queried the prevalence of RLS symptoms in PD populations show a twofold increase, compared to control populations (Table 2). Although the absolute number of people with both PD/RLS and idiopathic RLS is lower in Asian surveys, almost all still show relative increases compared to controls.

There is almost no evidence to support that RLS becomes PD, as the vast majority of PD/RLS cases report onset of PD motor symptoms prior to RLS. In fact, the few studies that have looked specifically at RLS populations or idiopathic RLS subjects found no clear increased risk of parkinsonism, and in fact showed a later onset PD in subjects with longstanding RLS (Dragan and Ondo 2010). In short, RLS in this population seems to be a consequence of the PD.

Aside from epidemiologic data, there is relatively little data exploring the pathophysiology of RLS in PD. Two Korean studies have evaluated CNS iron, as measured by sonography, in subjects with both PD and RLS, compared to PD without RLS and idiopathic RLS (Kwon et al. 2010; Ryu et al. 2011). Both found that the PD/RLS group had increased CNS iron similar to PD without RLS. Idiopathic RLS showed reduced CNS iron similar to other studies. It should be noted that patient with PD/RLS generally had PD first and later developed RLS. Similar studies on subjects with young onset RLS, who later developed PD, have not been done.

Genes associated with RLS generally do not seem to be risk factors for PD (Vilarino-Guell et al. 2008). One large family with PD caused by Parkin mutations included a large number of members with RLS, both with and without concurrent PD (Adel et al. 2006). The RLS inheritance pattern was consistent with an autosomal dominant pattern; however, the authors did not find an association between RLS and Parkin mutations within the family. In a South Tyrolean population, Parkin status did not independently predict onset or severity of RLS but did synergistically interact with RLS to predict a younger age at RLS onset (Pichler et al. 2010).

Iatrogenic RLS is a possible consequence of PD treatment. One recent German study specifically evaluated for RLS in untreated PD subjects, and then followed them

Table 2 Summary of RLS in PD Studies

Study	Population	RLS in PD	Risk Factors	Onset of RLS and PD	Comment
Ondo et al. (2002)	U.S.	63/303 (20.8 %)	Reduced serum ferritin	PD first in 85 %	Older age of onset and less family history than idiopathic RLS
Driver-Dunckley et al. (2006)	U.S.	6/25 STN DBS (24 %)	NR	NR	Improved with STN DBS
Peralta et al. (2009)	Austria	28/113 (24 %)	Younger age Lower "on" Hoehn and Yahr	PD first in 83 %	RLS symptoms during "wearing off" episodes
Simuni et al. (2000)	U.S.	42/200 (21 %)	Tendency for "fluctuators" ($P = 0.14$)	PD first in 93 %	RLS undiagnosed in 59 %
Braga-Neto et al. (2004)	Brazil	45/86 (49.9 %)	Longer duration of PD, but not age	NR	RLS not associated with daytime sleepiness
Chaudhuri et al. (2006)	U.S. and Europe	46/123[a] (37.4) Control (28.1)		NR	Part of a non-motor survey
Verbaan et al. (2010)	Holland	269 (11 %)	Female	NR	RLS severity correlated with PD severity
Loo and Tan (2008)	Singapore	400 (3.0 % vs. 0.5 %)	RLS correlated with H&Y and poor sleep	RLS onset 61.7	
Kumar et al. (2002)	India	21/149 (14.1 %) Control (0.9 %)	NR	NR	RLS diagnosis based on a single question
Krishnan et al. (2003)	India	10/126 (7.9 %) Control (1.3 %)	Older age Depression	NR	
Nomura et al. (2006)	Japan	20/165 (12 %) Control (2.3 %)	Younger age	PD first in 95 %	RLS worsened PSQI
Tan et al. (2002)	Singapore	1/135 (0.6 %) Control (0.1 %)	–	–	"Motor restlessness in 15.2 %"
Angelini et al. (2011)	Italy	5.5 % of 109 denovo PD 4.3 % of 116 controls		NR	
Jagota et al. (2012)	Thailand	3/183 (1.6 %)	none	NR	
Bhalsing et al. (2013)	India	11.9 % of 134 2.9 % 172 controls		NR	Less RLS in PSP and MSA
Shin et al. (2013b)	Korea	16.5 % of 151 denovo PD	Increased H&Y		
Rana et al. (2013)	Canada	21.3 % of 127 4.7 % of 127 controls			Associated with pain

PSQI Pittsburg Sleep Quality Index

[a] A single written question, not full RLS criteria

prospectively after initiation of dopaminergic treatments (Calzetti et al. 2014). After starting therapy, they found an incidence of new RLS of 4.7 and 3.7 %, if they excluded possible secondary causes of RLS. This is much higher than would be expected and suggested that the dopaminergic medications, which are also used to treat idiopathic RLS, may actually initiate the RLS symptoms. This is not entirely counter-intuitive as the use of these medications in idiopathic RLS often results in augmentation. Augmentation is defined by the gradual presentation of an earlier onset of symptoms and a general intensification of RLS symptoms (Garcia-Borreguero et al. 2007). In idiopathic RLS, this often eventually requires the discontinuation of dopaminergics, which results in an acute worsening of symptoms, but subsequent improvement in most cases. This is a compelling argument that RLS in PD is iatrogenic, but cannot control for progression of disease (perhaps RLS most commonly occurs around the same time that dopaminergic therapy is clinically indicated), and is not supported by retrospective trials that show no correlation to dose (Ondo et al. 2002), and a recent prospective trial that did show increased RLS prevalence in untreated PD patients (Shin et al. 2013b).

Interestingly, several reports also suggest that CNS surgeries for PD may also result in RLS symptoms. Kedia et al. (2004) reported the emergence of RLS after subthalamic nucleus (STN) deep brain stimulation (DBS) postoperatively in 11 of 195 patients. The mean reduction

in antiparkinsonian medication was 74 %. Parra et al. (2006) also reported a case of RLS emergence after DBS. Both postulated that RLS may have resulted from reduction in PD medications. In contrast, several studies report improvement in RLS after both ablative and DBS procedures to both the globus pallidus internus, and STN (Chahine et al. 2011).

Finally, non-dopaminergic medications used to treat PD including anticholinergics/anti-histaminergics, serotonin re-uptake inhibitors, and anti-psychotics are recognized to exacerbate idiopathic RLS.

Periodic limb movements of sleep in PD

Periodic limb movements of sleep are defined by the American Academy of Sleep Medicine as "at least four periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep". The incidence in the general population increases with age and is strongly associated with RLS (Ancoli-Israel et al. 1991). The physiology of PLM is only partially understood but thought to result from disinhibition of the spinal cord (Bara-Jimenez et al. 2000). PLMS are associated with autonomic lability with transient hypertension and tachycardia accompany and K-complexes (Shneyder et al. 2013).

PD is associated with higher rates of PLMS in some (Trenkwalder 1998; Wetter et al. 2000), but not all reports (Yong et al. 2011; Peeraully et al. 2012). When present, PLMS correlate with the severity of PD, both clinically and on dopamine imaging studies (Happe et al. 2003; Covassin et al. 2012; Sixel-Doring et al. 2012) but have only modest subjective clinical correlates (Covassin et al. 2012). There are mixed data on whether PLMS in PD patients are associated with RLS (Loo and Tan 2008; Covassin et al. 2012).

Conclusion

With the possible exception of sleep apnea, nearly the entire cannon of sleep/wake disorders are more prevalent in PD compared to controls. This probably reflects the widespread pathology in PD. This broad pathologic scope, the confounders of treatment, and associated features, such as aging, all make isolating the exact pathophysiology for specific problems more challenging. Nevertheless, the past few years have afforded tremendous advances in our understanding of sleep/wake issues in PD. Future physiologic, pathologic, molecular, and genetic research will increase our understanding of sleep/wake disorders in PD, some of which will no doubt be extrapolated into a better understanding of sleep/wake physiology in general.

References

Adel S, Djarmati A, Kabakci K, Pichler I, Eskelson C, Lohnau T, Kock N, Hagenah J, Hedrich K, Schwinger E, Kramer PL, Pramstaller PP, Klein C (2006) Co-occurrence of restless legs syndrome and Parkin mutations in two families. Mov Disord 21:258–263

Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ (2001) MRI measurement of brain iron in patients with restless legs syndrome. Neurology 56:263–265

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J (2003) Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 4:101–119

Amara AW, Watts RL, Walker HC (2011) The effects of deep brain stimulation on sleep in Parkinson's disease. Ther Adv Neurol Disord 4:15–24

Amara AW, Standaert DG, Guthrie S, Cutter G, Watts RL, Walker HC (2012) Unilateral subthalamic nucleus deep brain stimulation improves sleep quality in Parkinson's disease. Parkinsonism Relat Disord 18:63–68

Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O (1991) Periodic limb movements in sleep in community-dwelling elderly. Sleep 14:496–500

Angelini M, Negrotti A, Marchesi E, Bonavina G, Calzetti S (2011) A study of the prevalence of restless legs syndrome in previously untreated Parkinson's disease patients: absence of co-morbid association. J Neurol Sci 310:286–288

Antczak JM, Rakowicz MJ, Banach M, Derejko M, Sienkiewicz J, Zalewska U, Wieclawska M, Jakubczyk T, Jernajczyk W (2013) Negative influence of L-dopa on subjectively assessed sleep but not on nocturnal polysomnography in Parkinson's disease. Pharmacol Rep 65:614–623

Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, Lacomblez L, Golmard JL, Derenne JP, Agid Y (2002) Parkinson's disease and sleepiness: an integral part of PD. Neurology 58:1019–1024

Arnulf I, Leu S, Oudiette D (2008) Abnormal sleep and sleepiness in Parkinson's disease. Curr Opin Neurol 21:472–477

Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett M (2000) Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. Neurology 54:1609–1616

Barcia C, De Pablos V, Bautista-Hernandez V, Sanchez-Bahillo A, Fernandez-Barreiro A, Poza M, Herrero MT (2004) Measurement of motor disability in MPTP-treated macaques using a telemetry system for estimating circadian motor activity. J Neurosci Methods 134:59–64

Barraud Q, Lambrecq V, Forni C, McGuire S, Hill M, Bioulac B, Balzamo E, Bezard E, Tison F, Ghorayeb I (2009) Sleep disorders in Parkinson's disease: the contribution of the MPTP non-human primate model. Exp Neurol 219:574–582

Baumann CR, Scammell TE, Bassetti CL (2008) Parkinson's disease, sleepiness and hypocretin/orexin. Brain 131:e91

Bhalsing K, Suresh K, Muthane UB, Pal PK (2013) Prevalence and profile of Restless Legs Syndrome in Parkinson's disease and other neurodegenerative disorders: a case–control study. Parkinsonism Relat Disord 19:426–430

Boddy F, Rowan EN, Lett D, O'Brien JT, McKeith IG, Burn DJ (2007) Subjectively reported sleep quality and excessive daytime somnolence in Parkinson's disease with and without dementia, dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry 22:529–535

Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, Ahlskog JE, Caselli RJ, Jacobson S, Sabbagh M, Adler

C, Woodruff B, Beach TG, Iranzo A, Gelpi E, Santamaria J, Tolosa E, Singer C, Mash DC, Luca C, Arnulf I, Duyckaerts C, Schenck CH, Mahowald MW, Dauvilliers Y, Graff-Radford NR, Wszolek ZK, Parisi JE, Dugger B, Murray ME, Dickson DW (2013) Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 14:754–762

Bordet R, Devos D, Brique S, Touitou Y, Guieu JD, Libersa C, Destee A (2003) Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. Clin Neuropharmacol 26:65–72

Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211

Braga-Neto P, da Silva FP, Jr., Sueli Monte F, de Bruin PF, de Bruin VM (2004) Snoring and excessive daytime sleepiness in Parkinson's disease.[erratum appears in J Neurol Sci. 2004 Apr 15;219(1–2):171]. Journal of the Neurological Sciences 217:41–45

Britton TC, Chaudhuri KR (2009) REM sleep behavior disorder and the risk of developing Parkinson disease or dementia. Neurology 72:1294–1295

Brunner H, Wetter TC, Hogl B, Yassouridis A, Trenkwalder C, Friess E (2002) Microstructure of the non-rapid eye movement sleep electroencephalogram in patients with newly diagnosed Parkinson's disease: effects of dopaminergic treatment. Mov Disord 17:928–933

Cai Y, Liu S, Sothern RB, Xu S, Chan P (2010) Expression of clock genes Per1 and Bmal1 in total leukocytes in health and Parkinson's disease. Eur J Neurol 17:550–554

Calzetti S, Angelini M, Negrotti A, Marchesi E, Goldoni M (2014) A long-term prospective follow-up study of incident RLS in the course of chronic DAergic therapy in newly diagnosed untreated patients with Parkinson's disease. J Neural Transm 121:499–506

Chahine LM, Ahmed A, Sun Z (2011) Effects of STN DBS for Parkinson's disease on restless legs syndrome and other sleep-related measures. Parkinsonism Relat Disord 17:208–211

Chahine LM, Daley J, Horn S, Duda JE, Colcher A, Hurtig H, Cantor C, Dahodwala N (2013) Association between dopaminergic medications and nocturnal sleep in early-stage Parkinson's disease. Parkinsonism Relat Disord 19:859–863

Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, Brown RG, Koller W, Barone P, MacPhee G, Kelly L, Rabey M, MacMahon D, Thomas S, Ondo W, Rye D, Forbes A, Tluk S, Dhawan V, Bowron A, Williams AJ, Olanow CW (2006) International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 21:916–923

Cochen De Cock V (2013) Recent data on rapid eye movement sleep behavior disorder in patients with Parkinson disease: analysis of behaviors, movements, and periodic limb movements. Sleep Med 14:749–753

Cochen De Cock V, Abouda M, Leu S, Oudiette D, Roze E, Vidailhet M, Similowski T, Arnulf I (2010) Is obstructive sleep apnea a problem in Parkinson's disease? Sleep Med 11:247–252

Compta Y, Santamaria J, Ratti L, Tolosa E, Iranzo A, Munoz E, Valldeoriola F, Casamitjana R, Rios J, Marti MJ (2009) Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia. Brain 132:3308–3317

Connor JR (2008) Pathophysiology of restless legs syndrome: evidence for iron involvement. Curr Neurol Neurosci Rep 8:162–166

Covassin N, Neikrug AB, Liu L, Corey-Bloom J, Loredo JS, Palmer BW, Maglione J, Ancoli-Israel S (2012) Clinical correlates of periodic limb movements in sleep in Parkinson's disease. J Neurol Sci 316:131–136

da Silva-Junior FP, do Prado GF, Barbosa ER, Tufik S, Togeiro SM (2014) Sleep disordered breathing in Parkinson's disease: A critical appraisal. Sleep Med Rev 18:173–178

Diederich NJ, Vaillant M, Mancuso G, Lyen P, Tiete J (2005) Progressive sleep 'destructuring' in Parkinson's disease. A polysomnographic study in 46 patients. Sleep Med 6:313–318

Diederich NJ, Rufra O, Pieri V, Hipp G, Vaillant M (2013) Lack of polysomnographic Non-REM sleep changes in early Parkinson's disease. Mov Disord 28:1443–1446

Dragan E, Ondo W (2010) Does idiopathic restless legs syndrome protect against Parkinson's disease? Neurology 74(supple 2):A352

Driver-Dunckley E, Evidente VG, Adler CH, Hillman R, Hernandez J, Fletcher G, Lyons MK (2006) Restless legs syndrome in Parkinson's disease patients may improve with subthalamic stimulation. Mov Disord 21:1287–1289

Earley CJ, Hyland K, Allen RP (2001) CSF dopamine, serotonin, and biopterin metabolites in patients with restless legs syndrome. Mov Disord 16:144–149

Earley CJ, Kuwabara H, Wong DF, Gamaldo C, Salas RE, Brasic JR, Ravert HT, Dannals RF, Allen RP (2013) Increased synaptic dopamine in the putamen in restless legs syndrome. Sleep 36:51–57

Ferreira JJ, Desboeuf K, Galitzky M, Thalamas C, Brefel-Courbon C, Fabre N, Senard JM, Montastruc JL, Sampaio C, Rascol O (2006) Sleep disruption, daytime somnolence and 'sleep attacks' in Parkinson's disease: a clinical survey in PD patients and age-matched healthy volunteers. Eur J Neurol 13:209–214

Fertl E, Auff E, Doppelbauer A, Waldhauser F (1991) Circadian secretion pattern of melatonin in Parkinson's disease. J Neural Transm Park Dis Dement Sect 3:41–47

Friedman A (1980) Sleep pattern in Parkinson's disease. Acta Med Pol 21:193–199

Friedman JH, Millman RP (2008) Sleep disturbances and Parkinson's disease. CNS Spectr 13:12–17

Fronczek R, Overeem S, Lee SY, Hegeman IM, van Pelt J, van Duinen SG, Lammers GJ, Swaab DF (2007) Hypocretin (orexin) loss in Parkinson's disease. Brain 130:1577–1585

Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S (1999) Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 52:1908–1910

Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, Carrier J, Montplaisir J (2002) REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 59:585–589

Garcia-Borreguero D, Allen RP, Kohnen R, Hogl B, Trenkwalder C, Oertel W, Hening WA, Paulus W, Rye D, Walters A, Winkelmann J, Earley CJ (2007) Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. Sleep Med 8:520–530

Ghorayeb I, Loundou A, Auquier P, Dauvilliers Y, Bioulac B, Tison F (2007) A nationwide survey of excessive daytime sleepiness in Parkinson's disease in France. Mov Disord 22:1567–1572

Gjerstad MD, Aarsland D, Larsen JP (2002) Development of daytime somnolence over time in Parkinson's disease. Neurology 58:1544–1546

Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP (2007) Insomnia in Parkinson's disease: frequency and progression over time. J Neurol Neurosurg Psychiatry 78:476–479

Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP (2008) Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. J Neurol Neurosurg Psychiatry 79:387–391

Happe S, Pirker W, Klosch G, Sauter C, Zeitlhofer J (2003) Periodic leg movements in patients with Parkinson's disease are

associated with reduced striatal dopamine transporter binding. J Neurol 250:83–86
Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J (2002) Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. JAMA 287:455–463
Imbesi M, Yildiz S, Dirim Arslan A, Sharma R, Manev H, Uz T (2009) Dopamine receptor-mediated regulation of neuronal "clock" gene expression. Neuroscience 158:537–544
Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, Tolosa E (2006) Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 5:572–577
Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, Molinuevo JL, Serradell M, Duch J, Pavia J, Gallego J, Seppi K, Hogl B, Tolosa E, Poewe W, Santamaria J (2010) Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol 9:1070–1077
Iranzo A, Serradell M, Vilaseca I, Valldeoriola F, Salamero M, Molina C et al (2013) Longitudinal assessment of olfactory function in idiopathic REM sleep behavior disorder. Park Rel Disord 19:600–604
Iwanami M, Miyamoto T, Miyamoto M, Hirata K, Takada E (2010) Relevance of substantia nigra hyperechogenicity and reduced odor identification in idiopathic REM sleep behavior disorder. Sleep Med 11:361–365
Jagota P, Asawavichienjinda T, Bhidayasiri R (2012) The low prevalence of primary restless legs syndrome in Thai Parkinson's disease patients at Chulalongkorn University Hospital. J Med Assoc Thai 95:175–180
Kalaitzakis ME, Gentleman SM, Pearce RK (2013) Disturbed sleep in Parkinson's disease: anatomical and pathological correlates. Neuropathol Appl Neurobiol 39:644–653
Kedia S, Moro E, Tagliati M, Lang AE, Kumar R (2004) Emergence of restless legs syndrome during subthalamic stimulation for Parkinson disease. Neurology 63:2410–2412
Krishnan PR, Bhatia M, Behari M (2003) Restless legs syndrome in Parkinson's disease: a case-controlled study. Mov Disord 18:181–185
Kumar S, Bhatia M, Behari M (2002) Sleep disorders in Parkinson's disease. Mov Disord 17:775–781
Kumru H, Santamaria J, Tolosa E, Iranzo A (2007) Relation between subtype of Parkinson's disease and REM sleep behavior disorder. Sleep Med 8:779–783
Kwon DY, Seo WK, Yoon HK, Park MH, Koh SB, Park KW (2010) Transcranial brain sonography in Parkinson's disease with restless legs syndrome. Mov Disord 25:1373–1378
Lelieveld IM, Muller ML, Bohnen NI, Koeppe RA, Chervin RD, Frey KA, Albin RL (2012) The role of serotonin in sleep disordered breathing associated with Parkinson disease: a correlative [11C]DASB PET imaging study. PLoS ONE 7:e40166
Loo HV, Tan EK (2008) Case–control study of restless legs syndrome and quality of sleep in Parkinson's disease. J Neurol Sci 266:145–149
Lowrey PL, Takahashi JS (2011) Genetics of circadian rhythms in Mammalian model organisms. Adv Genet 74:175–230
Luppi PH, Clement O, Valencia Garcia S, Brischoux F, Fort P (2013) New aspects in the pathophysiology of rapid eye movement sleep behavior disorder: the potential role of glutamate, gamma-aminobutyric acid, and glycine. Sleep Med 14:714–718
Maeda T, Nagata K, Kondo H, Kanbayashi T (2006) Parkinson's disease comorbid with narcolepsy presenting low CSF hypocretin/orexin level. Sleep Med 7:662
Miyamoto T, Miyamoto M, Iwanami M, Hirata K (2011) Follow-up study of cardiac (1)(2)(3)I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. Eur J Neurol 18:1275–1278
Monaca C, Duhamel A, Jacquesson JM, Ozsancak C, Destee A, Guieu JD, Defebvre L, Derambure P (2006) Vigilance troubles in Parkinson's disease: a subjective and objective polysomnographic study. Sleep Med 7:448–453
Monderer R, Thorpy M (2009) Sleep disorders and daytime sleepiness in Parkinson's disease. Curr Neurol Neurosci Rep 9:173–180
Nihei Y, Takahashi K, Koto A, Mihara B, Morita Y, Isozumi K, Ohta K, Muramatsu K, Gotoh J, Yamaguchi K, Tomita Y, Sato H, Seki M, Iwasawa S, Suzuki N (2012) REM sleep behavior disorder in Japanese patients with Parkinson's disease: a multicenter study using the REM sleep behavior disorder screening questionnaire. J Neurol 259:1606–1612
Niwa F, Kuriyama N, Nakagawa M, Imanishi J (2011) Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease. Auton Neurosci 165:195–200
Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K (2006) Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. Mov Disord 21:380–384
Nomura T, Inoue Y, Kobayashi M, Namba K, Nakashima K (2013) Characteristics of obstructive sleep apnea in patients with Parkinson's disease. J Neurol Sci 327:22–24
Ondo W (2002) Epidemiology of restless legs syndrome. Sleep Med 3(Suppl):S13–S15
Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J (2001) Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 57:1392–1396
Ondo WG, Vuong KD, Jankovic J (2002) Exploring the relationship between Parkinson disease and restless legs syndrome. Arch Neurol 59:421–424
Ondo WG, Fayle R, Atassi F, Jankovic J (2005) Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry 76:1636–1639
Ozekmekci S, Apaydin H, Kilic E (2005) Clinical features of 35 patients with Parkinson's disease displaying REM behavior disorder. Clin Neurol Neurosurg 107:306–309
Parra J, Brocalero-Camacho A, Sancho J, Gallego-Sanchez JM, Ortiz-Sanchez P, Barcia-Albacar JA (2006) Severe restless legs syndrome following bilateral subthalamic stimulation to treat a patient with Parkinson's disease. Rev Neurol 42:766–767
Peeraully T, Yong MH, Chokroverty S, Tan EK (2012) Sleep and Parkinson's disease: a review of case-control polysomnography studies. Mov Disord 27:1729–1737
Peppe A, Pierantozzi M, Baiamonte V, Moschella V, Caltagirone C, Stanzione P, Stefani A (2012) Deep brain stimulation of pedunculopontine tegmental nucleus: role in sleep modulation in advanced Parkinson disease patients: 1-year follow-up. Sleep 35:1637–1642
Peralta CM, Frauscher B, Seppi K, Wolf E, Wenning GK, Hogl B, Poewe W (2009) Restless legs syndrome in Parkinson's disease. Mov Disord 24:2076–2080
Pichler I, Marroni F, Pattaro C, Lohmann K, de Grandi A, Klein C, Hicks AA, Pramstaller PP (2010) Parkin gene modifies the effect of RLS4 on the age at onset of restless legs syndrome (RLS). Am J Med Genet B Neuropsychiatr Genet 153B:350–355
Pittock SJ, Parrett T, Adler CH, Parisi JE, Dickson DW, Ahlskog JE (2004) Neuropathology of primary restless leg syndrome: absence of specific tau- and alpha-synuclein pathology. Mov Disord 19:695–699
Plomhause L, Dujardin K, Duhamel A, Delliaux M, Derambure P, Defebvre L, Monaca Charley C (2013) Rapid eye movement

sleep behavior disorder in treatment-naive Parkinson disease patients. Sleep Med 14:1035–1037
Porter B, Macfarlane R, Walker R (2008) The frequency and nature of sleep disorders in a community-based population of patients with Parkinson's disease. Eur J Neurol 15:50–54
Poryazova R, Benninger D, Waldvogel D, Bassetti CL (2010) Excessive daytime sleepiness in Parkinson's disease: characteristics and determinants. Eur Neurol 63:129–135
Postuma RB, Lang AE, Massicotte-Marquez J, Montplaisir J (2006) Potential early markers of Parkinson disease in idiopathic REM sleep behavior disorder. Neurology 66:845–851
Postuma RB, Gagnon JF, Vendette M, Montplaisir JY (2009) Idiopathic REM sleep behavior disorder in the transition to degenerative disease. Mov Disord 24:2225–2232
Postuma RB, Bertrand JA, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, Panisset M, Gagnon JF (2012) Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. Mov Disord 27:720–726
Pursiainen V, Haapaniemi TH, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllyla VV (2002) Circadian heart rate variability in Parkinson's disease. J Neurol 249:1535–1540
Qu WM, Xu XH, Yan MM, Wang YQ, Urade Y, Huang ZL (2010) Essential role of dopamine D2 receptor in the maintenance of wakefulness, but not in homeostatic regulation of sleep, in mice. J Neurosci 30:4382–4389
Rana AQ, Siddiqui I, Mosabbir A, Athar A, Syed O, Jesudasan M, Hafez K (2013) Association of pain, Parkinson's disease, and restless legs syndrome. J Neurol Sci 327:32–34
Razmy A, Lang AE, Shapiro CM (2004) Predictors of impaired daytime sleep and wakefulness in patients with Parkinson disease treated with older (ergot) vs newer (nonergot) dopamine agonists. Arch Neurol 61:97–102
Rissling I, Geller F, Bandmann O, Stiasny-Kolster K, Korner Y, Meindorfner C, Kruger HP, Oertel WH, Moller JC (2004) Dopamine receptor gene polymorphisms in Parkinson's disease patients reporting "sleep attacks". Mov Disord 19:1279–1284
Rissling I, Korner Y, Geller F, Stiasny-Kolster K, Oertel WH, Moller JC (2005) Preprohypocretin polymorphisms in Parkinson disease patients reporting "sleep attacks". Sleep 28:871–875
Roth T, Rye DB, Borchert LD, Bartlett C, Bliwise DL, Cantor C, Gorell JM, Hubble JP, Musch B, Olanow CW, Pollak C, Stern MB, Watts RL (2003) Assessment of sleepiness and unintended sleep in Parkinson's disease patients taking dopamine agonists. Sleep Med 4:275–280
Rye DB, Bliwise DL, Dihenia B, Gurecki P (2000) FAST TRACK: daytime sleepiness in Parkinson's disease. J Sleep Res 9:63–69
Ryu JH, Lee MS, Baik JS (2011) Sonographic abnormalities in idiopathic restless legs syndrome (RLS) and RLS in Parkinson's disease. Parkinsonism Relat Disord 17:201–203
Schenck CH, Mahowald MW (2002) REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 25:120–138
Schenck CH, Bundlie SR, Mahowald MW (1996) Delayed emergence of a parkinsonian disorder in 38 % of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 46:388–393
Schenck CH, Boeve BF, Mahowald MW (2013) Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 14:744–748
Shin HY, Joo EY, Kim ST, Dhong HJ, Cho JW (2013a) Comparison study of olfactory function and substantia nigra hyperechogenicity in idiopathic REM sleep behavior disorder, Parkinson's disease and normal control. Neurol Sci 34:935–940
Shin HY, Youn J, Yoon WT, Kim JS, Cho JW (2013b) Restless legs syndrome in Korean patients with drug-naive Parkinson's disease: a nation-wide study. Parkinsonism Relat Disord 19:355–358
Shneyder N, Adler CH, Hentz JG, Shill H, Caviness JN, Sabbagh MN, Beach TG, Driver-Dunckley E (2013) Autonomic complaints in patients with restless legs syndrome. Sleep Med 14:1413–1416
Simuni T, Wilson R, Stern MB (2000) Prevalence of restless legs syndrome in Parkinson's disease. Mov Disord 15:1043
Sixel-Doring F, Trautmann E, Mollenhauer B, Trenkwalder C (2011) Associated factors for REM sleep behavior disorder in Parkinson disease. Neurology 77:1048–1054
Sixel-Doring F, Trautmann E, Mollenhauer B, Trenkwalder C (2012) Age, drugs, or disease: what alters the macrostructure of sleep in Parkinson's disease? Sleep Med 13:1178–1183
Sorensen GL, Mehlsen J, Jennum P (2013) Reduced sympathetic activity in idiopathic rapid-eye-movement sleep behavior disorder and Parkinson's disease. Auton Neurosci 179:138–141
Stavitsky K, McNamara P, Durso R, Harris E, Auerbach S, Cronin-Golomb A (2008) Hallucinations, dreaming, and frequent dozing in Parkinson disease: impact of right-hemisphere neural networks. Cogn Behav Neurol 21:143–149
Suzuki K, Miyamoto M, Miyamoto T, Iwanami M, Hirata K (2011) Sleep disturbances associated with Parkinson's disease. Parkinsons Dis 2011:219056
Tan EK, Lum SY, Wong MC (2002) Restless legs syndrome in Parkinson's disease. J Neurol Sci 196:33–36
Tandberg E, Larsen JP, Karlsen K (1998) A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 13:895–899
Thannickal TC, Lai YY, Siegel JM (2007) Hypocretin (orexin) cell loss in Parkinson's disease. Brain 130:1586–1595
Trenkwalder C (1998) Sleep dysfunction in Parkinson's disease. Clin Neurosci 5:107–114
Trotti LM, Bliwise DL (2010) No increased risk of obstructive sleep apnea in Parkinson's disease. Mov Disord 25:2246–2249
Ulivelli M, Rossi S, Lombardi C, Bartalini S, Rocchi R, Giannini F, Passero S, Battistini N, Lugaresi E (2002) Polysomnographic characterization of pergolide-induced sleep attacks in idiopathic PD. Neurology 58:462–465
Valko PO, Hauser S, Werth E, Waldvogel D, Baumann CR (2012) Heart rate variability in patients with idiopathic Parkinson's disease with and without obstructive sleep apnea syndrome. Parkinsonism Relat Disord 18:525–531
Veasey SC, Panckeri KA, Hoffman EA, Pack AI, Hendricks JC (1996) The effects of serotonin antagonists in an animal model of sleep-disordered breathing. Am J Respir Crit Care Med 153:776–786
Vendette M, Gagnon JF, Decary A, Massicotte-Marquez J, Postuma RB, Doyon J, Panisset M, Montplaisir J (2007) REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. Neurology 69:1843–1849
Verbaan D, van Rooden SM, van Hilten JJ, Rijsman RM (2010) Prevalence and clinical profile of restless legs syndrome in Parkinson's disease. Mov Disord 25:2142–2147
Videnovic A, Golombek D (2013) Circadian and sleep disorders in Parkinson's disease. Exp Neurol 243:45–56
Videnovic A, Marlin C, Alibiglou L, Planetta PJ, Vaillancourt DE, Mackinnon CD (2013) Increased REM sleep without atonia in Parkinson disease with freezing of gait. Neurology 81:1030–1035
Vilarino-Guell C, Soto AI, Young JE, Lin SC, Uitti RJ, Wszolek ZK, Farrer MJ (2008) Susceptibility genes for restless legs syndrome are not associated with Parkinson disease. Neurology 71:222–223

Wetter TC, Collado-Seidel V, Pollmacher T, Yassouridis A, Trenkwalder C (2000) Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 23:361–367

Willis GL (2008) Parkinson's disease as a neuroendocrine disorder of circadian function: dopamine-melatonin imbalance and the visual system in the genesis and progression of the degenerative process. Rev Neurosci 19:245–316

Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, Fulda S, Putz B, Eckstein G, Hauk S, Trenkwalder C, Zimprich A, Stiasny-Kolster K, Oertel W, Bachmann CG, Paulus W, Peglau I, Eisensehr I, Montplaisir J, Turecki G, Rouleau G, Gieger C, Illig T, Wichmann HE, Holsboer F, Muller-Myhsok B, Meitinger T (2007) Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 39:1000–1006

Wirz-Justice A, Da Prada M, Reme C (1984) Circadian rhythm in rat retinal dopamine. Neurosci Lett 45:21–25

Yasui K, Inoue Y, Kanbayashi T, Nomura T, Kusumi M, Nakashima K (2006) CSF orexin levels of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy and corticobasal degeneration. J Neurol Sci 250:120–123

Yong MH, Fook-Chong S, Pavanni R, Lim LL, Tan EK (2011) Case control polysomnographic studies of sleep disorders in Parkinson's disease. PLoS ONE 6:e22511

Young A, Home M, Churchward T, Freezer N, Holmes P, Ho M (2002) Comparison of sleep disturbance in mild versus severe Parkinson's disease. Sleep 25:573–577

Yujnovsky I, Hirayama J, Doi M, Borrelli E, Sassone-Corsi P (2006) Signaling mediated by the dopamine D2 receptor potentiates circadian regulation by CLOCK:BMAL1. Proc Natl Acad Sci USA 103:6386–6391

Zeng J, Wei M, Li T, Chen W, Feng Y, Shi R, Song Y, Zheng W, Ma W (2013) Risk of obstructive sleep apnea in Parkinson's disease: a meta-analysis. PLoS ONE 8:e82091