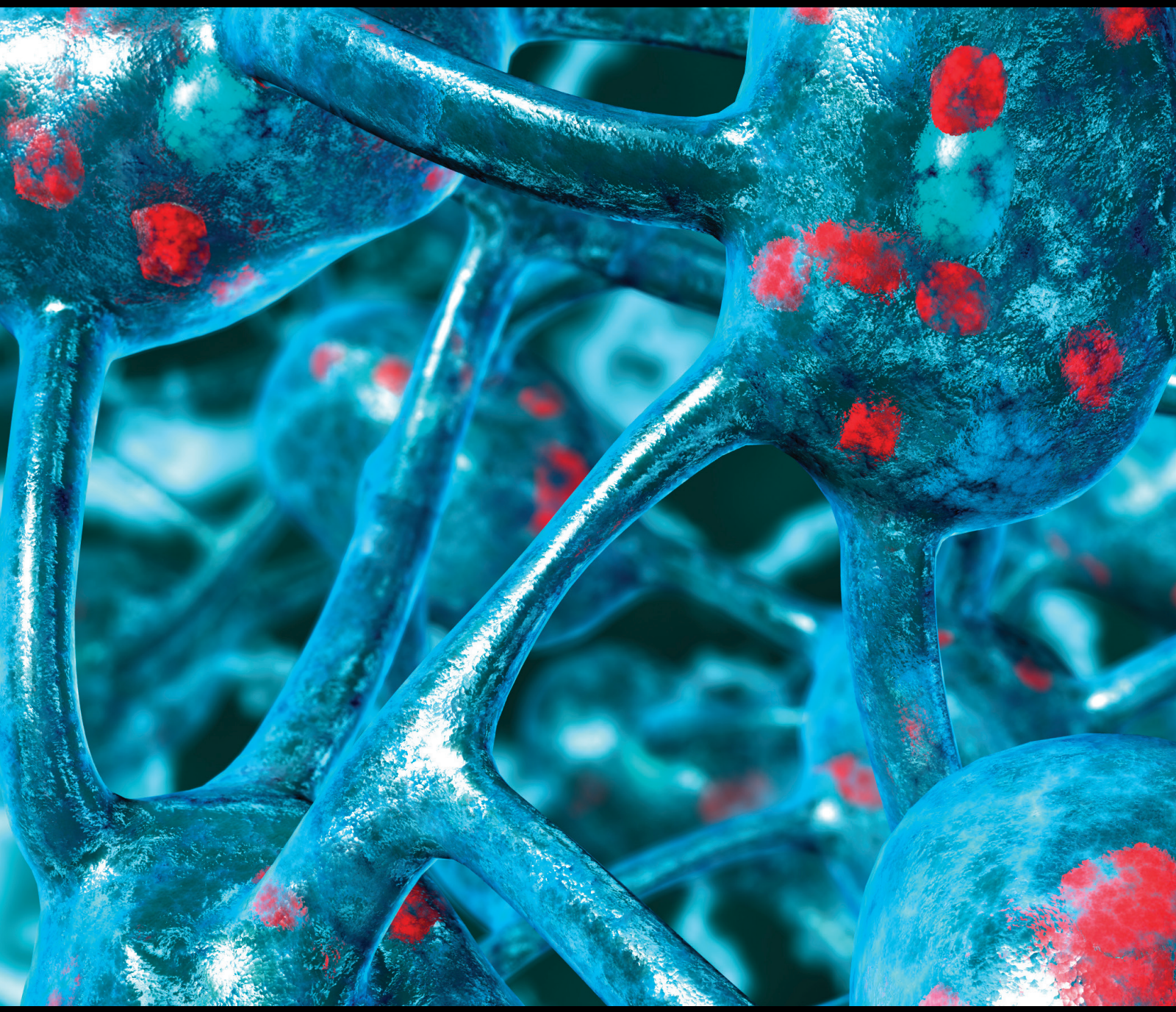
Parkinson's Disease

Sleep Problems in Parkinson's Disease

Guest Editors: Koichi Hirata, Birgit Högl, Eng King Tan, and Aleksandar Videnovic



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Editorial Board

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Editorial

Sleep Problems in Parkinson's Disease

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In his famous monograph "An Essay in Shaking Palsy," James Parkinson provided astute descriptions of impaired sleep in his case series of patients with Parkinson's disease (PD) two centuries ago. It is only three decades ago that sleep dysfunction started to attract attention of medical and scientific communities involved in the clinical care and research of PD. Tremendous advancements in our understanding of impaired sleep and alertness associated with PD have developed since then.

Sleep problems are one of the major, challenging issues in patients with PD, affecting a significant number of patients. The etiology of sleep problems is multifactorial, including disease-related nocturnal symptoms, medication adverse effects, and primary sleep disorders including restless legs syndrome, rapid eye movement sleep behavior disorder, and sleep apnea syndrome. These causes of impaired sleep-wake cycles in the PD population often coexist or even overlap, rendering the management of sleep problems in PD patients difficult. Also, excessive daytime sleepiness is observed in a significant number of patients. In PD patients, therefore, appropriate assessment of disease-related nocturnal disturbances and primary sleep disorders is imperative. This special issue addresses unmet need for understanding PD-related sleep problems.

PD sleep scale 2 (PDSS-2) is a recently developed tool for screening and managing sleep disturbance in PD patients, consisting of 15 items which are clinically relevant to nocturnal problems including nonmotor and motor problems in PD [1]. The original PDSS-2 (German and English) has been translated into several languages, including Japanese [2] and Italian [3]. The PDSS-2 has been used to observe treatment response. In a double-blind, placebo-controlled trial, including 287 PD patients, mean PDSS-2 total score decreased by −5.9 points with rotigotine and by −1.9 points with placebo [4]. In this special issue, K. Horváth et al. estimated the threshold representing minimal clinically important difference of the PDSS-2 total score: the study results showed −3.44 points for detecting improvement or the threshold of 2.07 points for observing worsening. This finding is important when planning studies using the PDSS-2 as outcome measures.

Full-night polysomnography (PSG) is a gold standard for diagnosing sleep apnea syndrome; however, applying PSG is often difficult in patients with PD, who have severe parkinsonism or psychiatric comorbidity. P. Gros et al. evaluated the usefulness of unattended portable monitoring (PM) for diagnosis of obstructive sleep apnea (OSA) in patients with PD. Although discrepancy between portable monitoring and PSG was greater in PD patients with more motor dysfunction, the authors confirmed the usefulness of portable monitoring in diagnosing moderate to severe OSA in PD patients. These results provide the rationale for the use of portable sleep monitoring in PD and are very relevant for circumstances where a complete PSG in a sleep laboratory is not available and/or feasible.

M. Kaminska et al. performed a review on the relationship between OSA and PD. Although the clinical significance of OSA in PD has been controversial [5, 6], the authors suggest the possibility that treatment of OSA could delay cognitive decline or motor dysfunction in patients with PD. This area

of research is of high significance as it is important to assess the prevalence of OSA and the impact of its treatment in the PD population.

D. Martinez-Ramirez et al. correlated PSG findings and sleep disorders with clinical characteristics in PD patients and found that sleep disorders and sleep architecture were poorly predictable by clinical characteristic of PD patients. This comprehensive study demonstrates the complexity of sleep dysfunction associated with PD and its complex associations with metrics of PD.

In a fine and thoughtful study K. Suzuki et al. provided an interesting insight into the complex relationship between PD and restless legs syndrome (RLS) and leg motor restlessness (LMR). A significant relationship between RLS and PD is suggested by observing a favorable response to dopaminergic treatment in both disorders. However, RLS prevalence in PD patients varies according to different studies. Recently, LMR, characterized by an urge to move the legs that does not fulfill the diagnostic criteria for RLS, has been reported more frequently in patients untreated with PD than healthy controls. This review article may provide a new insight into the relationship between RLS, LMR, and PD.

Finally, the complex and still only partially understood interaction of impulse control disorders in PD and sleep is discussed in a review from the clinic of one of the guest editors.

In summary, sleep problems are common but underreported by PD patients and underdiagnosed by health professionals. Further understanding of mechanisms that underlie impaired sleep and alertness in PD will allow for development of much needed treatment approaches for this nonmotor manifestation of PD.

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Review Article

Impact of Impulse Control Disorders on Sleep-Wake Regulation in Parkinson's Disease

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Sleep disturbances are common in patients with Parkinson's disease (PD) and are even more prevalent in patients with behavioural addictions, such as pathological gambling, compulsive sexual behaviour, compulsive buying, binge eating, punding, and the compulsive use of dopamine replacement therapy. An overview of the relationship between these impulse control disorders and sleep disturbances is given and potential underlying mechanisms and treatment strategies are covered.

1. Introduction

Impulsivity has been described as "a behaviour that is performed with little or inadequate forethought" [1] or as a failure to "resist an impulse." In Parkinson's disease (PD) impulse control disorders (ICDs), such as gambling disorder, compulsive shopping, binge eating, compulsive sexual disorder, and punding and dopamine dysregulation syndrome, are an increasingly well-recognised adverse-effect of dopaminergic medication, in particular dopamine agonists. Initial studies suggested that these problems arise in about 14% of treated patients [2], but more recent studies indicate that up to 40% of PD patients may be affected [3]. This discrepancy may be explained because ICD symptoms are underdiagnosed in clinical practise. Furthermore, much higher prevalence rates of ICDs are found when screening is performed with a caregiver or family member rather than with the PD patient alone [4] likely because patients often do not disclose aberrant behaviours due to shame or lack of insight [5].

It is unclear why only a subgroup of treated PD patients develops ICDs and others do not. This suggests that there are protective factors to prevent people from addiction, possibly of genetic origin [6]. Apart from dopamine replacement therapy other risk factors for developing ICDs in PD include younger onset of disease, higher novelty seeking personality traits, and a personal or family history of addictive behaviours [7]. Furthermore, several studies have suggested a relationship between sleep disturbances and ICDs in PD [8–10]. The purpose of this manuscript is to explore this relationship in more detail. A PubMed literature review searching for the terms "Impulse control disorders, Parkinson's disease, Impulsive compulsive behaviours, sleep disorders in Parkinson's disease, Sleep and Impulsivity" was carried out until May 2015; however, this is a narrative review with potential selection bias.

2. Impulse Control Disorders in PD

Behavioural addictions in PD include pathological gambling, compulsive sexual disorder, binge eating, compulsive shopping, the dopaminergic dysregulation syndrome (the overuse of dopaminergic medication), and punding, a stereotype, repetitive, purposeless behaviour driven by fascination. Although PD patients may exhibit only one addictive behaviour, at least a quarter has two or more addictions [2]. A brief summary of the most common behavioural addictions is given below.

2.1. Pathological Gambling. Pathological gambling has been now reclassified as gambling disorder and is defined as an inappropriate, persistent, and maladaptive behaviour. Typically PD patients prefer gambles that are repetitive, require little higher cortical processing, and have high reward

uncertainty [12] and brief loss periods. These include slot machines, lottery/scratch cards, and internet gambling, such as roulette which offers "near misses," and losses can be instantly chased. PD patients sometimes develop complex ritualistic behaviours such as lucky charms prior to gambling [13] and may develop loss chasing behavior. Diagnostic criteria of gambling disorder from DSM-V [11] are as follows:

(A) Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

(1) Needs to gamble with increasing amounts of money in order to achieve the desired excitement.

(2) Is restless or irritable when attempting to cut down or stop gambling.

(3) Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning next venture, and thinking of ways to get money with which to gamble).

(4) Often gambles when feeling distress (e.g., helpless, guilty, anxious, and depressed).

(5) Often returns another day to get even ("chasing" one's losses), After losing money gambling.

(6) Lies to conceal the extent of involvement with gambling.

(7) Has jeopardized or lost a significant relationship, job, or educational career opportunity because of gambling.

(8) Relies on others to provide money to relieve desperate financial situations caused by gambling.

(B) The gambling behavior is not better accounted for by a manic episode.

2.2. Compulsive Sexual Behaviour. The prevalence of compulsive sexual behaviour in PD has been found to be 3.5% [2] although these rates vary depending on cultural difference. Furthermore, standardized criteria are missing. It is, however, likely that this ICD is far more common as patients and their partners are often too embarrassed to declare the problem. Typically compulsive sexual behaviour is more problematic in males. Other phenomena such as zoophilia and paraphilia are much rarer but have also been described in PD [14, 15].

2.3. Punding. Punding is defined as a stereotype, repetitive, and nongoal orientated behaviour. It was first described in the 1970s in amphetamine and cocaine addicts [16] and much later in PD [17]. Typically, punding is idiosyncratic [18]. For example, men tend to tinker more often with technical equipment whereas women prefer sorting and cleaning. The prevalence rate for punding varies widely from 1.4% to 14%. Whether punding is more common in patients with cognitive decline is currently unknown.

Hobbyism, reckless generosity [19], hoarding [20], drug addiction [21], and compulsive smoking [22] are other albeit less reported phenomena.

2.4. Dopamine Dysregulation Syndrome (DDS). DDS is characterised by a compulsive overuse of typically fast acting dopaminergic medication, such as dispersible levodopa. Patients with DDS often take extra medication in order to avoid the unpleasant "off" periods despite the adverse consequences such as dyskinesia. Punding is frequently seen in this cohort of patients [23]. Estimates for DDS in PD range from 0.6% to 4% [24, 25]. Furthermore, new onset of DDS can occur in PD patients with dopamine agonist withdrawal syndrome in an attempt to improve their symptoms [26]. Diagnostic criteria for DDS [24] are as follows:

(i) Parkinson's disease with documented L-dopa responsiveness.

(ii) Need for increasing doses of dopamine replacement therapy (DRT) in excess of those normally required to relieve parkinsonian symptoms and signs.

(iii) Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being "on," drug hoarding, drug seeking behaviour, unwillingness to reduce DRT, and absence of painful dystonias.

(iv) Impairment in social or occupational functioning: fights, violent behaviour, loss of friends, absence of work, loss of job, legal difficulties, and arguments or difficulties with family.

(v) Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT.

(vi) Development of a withdrawal state characterized by dysphoria, depression, irritability, and anxiety on reducing the level of DRT.

(vii) Duration of disturbance for at least 6 months.

3. Mechanisms Underlying ICDs in PD

While the dopamine dysregulation syndrome, punding, and also walkabouts are commonly associated with levodopa, dopamine agonists are more likely to trigger the other addictive behaviours (e.g., compulsive shopping, gambling disorder, compulsive sexual disorder, and binge eating). The exact underlying pathophysiology of ICDs in PD remains elusive. It is, however, possible that differences in dopamine receptor stimulation play a key role in triggering these behaviours. Dopamine agonists mainly stimulate dopamine D2 and D3 receptors which are mainly located in the ventral striatum. Furthermore, dopamine agonists can cause neuroplastic changes in susceptible patients causing increased dopamine release in the ventral striatum to reward related cues [27, 28] and sensitization of the ventral striatum [27]. These elevated mesolimbic dopamine levels are thought to cause impaired decision making and risky choices and may play a major role in driving addictive behaviours [29]. Addiction can become habitual and compulsive [30, 31] which means

that behaviourally the outcome of an action is becoming less important. Instead, the patients' decision making shifts from a "goal directed" to a "stimulus-response" behaviour in which the stimulus (and not an outcome) drives an action [32]. Thus, habit formation requires little cortical activity as the behaviour is automatic and learning and reassessment of actions is not necessary.

Imaging studies have shown cortical thinning in the frontostriatal circuits in PD patients with ICDs which may lead to a reduction of "top-down control" and are likely responsible for poor inhibitory control in patients [33] as well as healthy volunteers [34]. Abnormalities in dopamine receptors with dysfunctional activation of autoreceptors in the midbrain and dysfunction of the cortical homeostasis have been shown in PD patients with ICDs [35] and may also contribute to poor decision making and impulsivity [36–38]. Only a few studies have assessed the relationship of ICDs in PD and genetic predisposing factors. A single study found a higher rate of polymorphism in the dopamine receptor 3 (DRD3) gene in PD patients with ICDs compared to those without [39], while other studies did not report any differences in the various candidate gene studies including DRD1, DRD 4, and the dopamine catechol-O-methyl transferase (COMT) [40–43]. Finally, it has been proposed that dyskinesias and ICDs are closely related [44] with similar pattern of oscillatory activity in the subthalamic nucleus [45] and support the notion of continuous dopaminergic stimulation as treatment strategies in these patients.

4. ICDs and Sleep

Sleep disturbances, such as sleep fragmentation and daytime sleepiness, have been often described by PD patients with ICDs [8–10]. For example, one study has shown that PD patients with ICDs had poorer sleep than PD controls and healthy volunteers assessed by self-reported PD sleep scales. Furthermore, in this study higher anxiety and depression scores correlated with poorer sleep [9]. Greater nocturnal awakenings, increased frequency of restless legs syndromes, and greater daytime sleepiness are also more common in PD patients with ICDs compared to PD controls [8]. It is, however, unclear whether sleep disturbances increase vulnerability to develop an ICD or are the result of addictive behaviours [8]. For example, it has been described that gamblers can play for days without proper sleep [46]. Furthermore, patients with behavioural addiction may lose track of time and the easy access to internet 24 hours per day is likely contributing to sleep deprivation [46]. Thus, a combination of psychosocial and biological factors plays a key role in sleep disturbances in PD patients with addictive behaviours.

However, the relationship between sleep disturbances and addiction is bidirectional [46–48]. Thus, addiction may also influence so-called clock genes, which are important for sleep-wake cycle regulation. The master clock is located in the suprachiasmatic nucleus of the anterior hypothalamus and clock genes coordinate other brain areas and peripheral organs [48]. Psychoactive drugs as well as behavioural addictions can cause alteration of the expression of these clock genes which in turn lead to sleep disturbances and increase the vulnerability for addictions [48–50]. For example, chronic alcohol intake can lead to a dysfunction of the sleep-wake cycle via disruption of the circadian gene expression [48]. Furthermore, it has been proposed that these clock genes may also be involved in mesolimbic dopaminergic regulation causing neuroplastic changes that may contribute to the development of addiction [48]. In addition, it has been shown that insufficient and mistimed sleep has a major impact on the human transcriptome and affects several distinct molecular pathways [51].

The pathophysiology of sleep deprivation and impulsivity is, however, still poorly understood. It is likely that sleep deprivation leads to a dysfunction of the prefrontal cortex and its connection to the limbic system [52], contributing to a further reduction in top-down inhibitory control in susceptible individuals. In line with this, sleep deprivation in healthy controls can cause impulsive choice possibly due to loss of inhibitory control [53, 54] and upregulation of brain reward networks [55]. Sleep disorders are also prevalent among psychiatric patients or patients with substance abuse as well as prisoners [56, 57] and correlate with increased self-rated aggression and impulsivity [57].

REM sleep behavioural disturbances (RBD) are common in PD and are characterized by loss of the normal REM sleep atonia, enabling patients to "act out" their dreams. Although the pathophysiology is still not completely understood, dysfunction of tonic areas in the lower brainstem is thought to be the key factors of RBD [58]. RBD occurs in approximately 35% to 50% of PD patients [59, 60] and has been associated with male gender, older age, longer disease duration, hyposmia, more advanced PD with motor handicaps, higher levodopa doses, and more psychiatric comorbidity [60, 61]. RBD symptoms either precede, cooccur, or follow parkinsonism. Several studies have shown that those patients who have RBD suffer from more motor and nonmotor symptoms, such as cognitive impairment and autonomic dysfunction, than those without RBD. Some [62, 63] but not all [64] studies have linked RBD with ICD. One study showed that RBD was associated with a more than twofold risk to develop ICD symptoms and a more than fourfold risk to develop pathological gambling [62]. In contrast to the study by Bayard et al. [64], Fantini et al. showed that RBD was associated with a more than twofold risk to develop ICD symptoms [62]. However, in the study by Fantini and colleagues the diagnosis of RBD was based entirely on questionnaires [62] while in the study by Bayard et al. polysomnography to confirm the diagnosis was performed in 30% of patients [64]. RLS is frequent in PD [65–67] although the differential diagnosis is challenging and other causes of restlessness must be excluded [68]. In RLS patients without PD, augmentation and ICDs are increasingly recognized as serious side effects of dopaminergic therapy [69–71].

5. Treatment of Sleep Disturbance in PD Patients with ICDs

It is of paramount importance to treat the underlying ICD by reducing the causative agent. In some cases hospital admission is required, due to side effects such as anxiety,

irritability, or worsening of motor symptoms [26]. A particular challenge in treating PD patients with ICDs is the dopamine agonist withdrawal syndrome. These withdrawal syndromes resemble those of other drug withdrawal syndromes. Insomnia, panic attacks, dysphoria, fatigue, and depression are commonly seen. Patients often insist to receive a higher amount of medication in order to treat these withdrawal symptoms and are at risk of developing dopamine dysregulation syndrome [26, 72].

As with any sleep disturbances clinicians should first assess whether a primary sleep disorder, such as insomnia, restless legs syndrome, REM sleep behaviour disturbance and periodic limb movements of sleep, sleep apnea, circadian rhythm disturbance, or other factors such as pain, depression, nocturia, dystonia, and difficulty turning in bed are the culprit of poor sleep [73]. In some cases further diagnostic steps, for example, a polysomnography or actigraphy to assess rest-activity cycles over a two-week period, are needed. If a specific sleep disorder is present, it should be treated accordingly. In some patients behavioural recommendations such as the recommendation to avoid long daytime napping can be helpful [74]. There are, however, no guidelines on how to treat sleep disturbances in PD patients with ICDs. Often poor patients' insight and low compliance are major therapeutic challenges.

5.1. Nonpharmacological Strategies. Access to credit cards, money, and particularly internet should be restricted [29] not only to improve the addiction but also night time sleep.

Behavioural interventions have been recommended by the American-Academy of Sleep Medicine for all patients who suffer from chronic insomnia [75]. One small randomised controlled study in PD patients without ICDs showed that cognitive behavioural therapy in combination with bright light improved insomnia [76], but these findings need to replicate in larger trials. Patients and their families are advised to consolidate day-night rhythms by timed light exposure and melatonin [77].

5.2. Specific Treatment Options. Often nonpharmacological therapies are insufficient in PD patients with ICDs to improve insomnia. The tricyclic antidepressant amitriptyline may be a useful off-label option in some patients, but side effects such as cognitive impairment, dry mouth, and regular heart monitoring are limiting factors. Trazodone, another sedating antidepressant, is sometimes used [78]. Similarly, the presynaptic alpha 2 adrenoreceptor antagonist mirtazapine can be useful to improve insomnia in PD [79].

One randomised controlled trial showed that in PD patients without ICDs melatonin significantly improved subjective sleep quality which, however, could not be demonstrated in polysomnography [80].

Quetiapine has been reported to improve punding, pathological gambling, and compulsive sexual disorder [81], and one preliminary study also showed improvement in insomnia severity [82]. Clozapine can also improve ICDs [83, 84] as well as sleep [85] but carries the potential risk of agranulocytosis.

Benzodiazepines, such as clonazepam, can be used with caution in ICD patients with RBD or in those who continue to suffer from insomnia, but confusion, risk of falling, and sleep apnea limit its use [78].

6. Conclusions

Sleep disturbances are very common in PD patients with ICDs but there are no specific guidelines on how to treat these problems. Reduction or complete cessation of dopamine agonists is often necessary to improve the underlying addictive behaviour. Behavioural intervention in combination with pharmacotherapy should be considered in all patients in order to improve night time sleep and ultimately quality of life of the patients and also their partners. Future studies assessing the causal relationship of sleep disturbances and impulsivity in PD as well as randomised controlled studies focussing on treatment strategies for sleep disturbances in PD patients with ICDs are an unmet need.

Practice Points

(i) Sleep fragmentation and changes in sleep-wake cycle are common in patients with Parkinson's disease and impulse control disorders.

(ii) Initial steps should focus on treating the underlying behavioural addiction and often include pharmacological and nonpharmacological strategies such as reduction of dopamine agonists, restricted access to computers, or credit cards.

(iii) Therapies with sedative antidepressants, neuroleptic drugs such as quetiapine or clozapine, or benzodiazepines should be considered.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Diagnosis of Obstructive Sleep Apnea in Parkinson's Disease Patients: Is Unattended Portable Monitoring a Suitable Tool?

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Purpose. Obstructive sleep apnea (OSA) is frequent in Parkinson's disease (PD) and may contribute to nonmotor symptoms. Polysomnography (PSG) is the gold standard for OSA diagnosis. Unattended portable monitoring (PM) may improve access to diagnosis but has not been studied in PD. We assessed feasibility and diagnostic accuracy in PD. *Methods.* Selected PD patients without known OSA underwent home PM and laboratory PSG. The quality of PM signals ($n = 28$) was compared with matched controls. PM accuracy was calculated compared with PSG for standard apnea hypopnea index (AHI) thresholds. *Results.* Technical failure rate was 27.0% and airflow signal quality was lower than in controls. Sensitivity of PM was 84.0%, 36.4%, and 50.0% for AHI cut-offs of 5/h, 15/h, and 30/h, respectively, using the same cut-offs on PM. Specificity was 66.7%, 83.3%, and 100%, respectively. PM underestimated the AHI with a mean bias of 12.4/h. Discrepancy between PM and PSG was greater in those with more motor dysfunction. *Conclusion.* PM was adequate to "rule in" moderate or severe OSA in PD patients, but the failure rate was relatively high and signal quality poorer than in controls. PM overall underestimated the severity of OSA in PD patients, especially those with greater motor dysfunction.

1. Introduction

In Parkinson's disease (PD), sleep-related problems are one of the most prevalent nonmotor symptoms (NMS), affecting 48 to 82% of patients and increasing with the disease severity [1]. Among them, obstructive sleep apnea (OSA) is common and is thought to occur in 20 to 60% of PD patients [2–5]. OSA is characterized by recurrent complete (apnea) or partial (hypopnea) upper airway obstruction resulting in intermittent hypoxemia and arousals from sleep. It is known to cause neurocognitive dysfunction, cardiovascular complications, and metabolic disorders in the general population [6]. Recent preliminary data suggest that, in PD patients, OSA appears to worsen other NMS, such as cognitive dysfunction and excessive daytime sleepiness [7]. Treatment of OSA could be a strategy to help improve important NMS, such as excessive daytime sleepiness [2]. Hence, early diagnosis and therapy for OSA could result in better outcomes for PD patients.

Polysomnography (PSG), or level 1 sleep testing, is currently the gold standard for OSA diagnosis [8, 9]. It includes at least 7 channels of data (typically ≥16) and requires an overnight stay in the sleep laboratory. It allows assessment of sleep-wake stages (EEG, EOG, and EMG), nasal airflow, snoring, respiratory efforts, oxygen saturation, body position and movements, cardiac electrical signals (EKG), and others when necessary. PSG is complex, expensive, and poorly accessible. In Canada, the waiting time to access PSG studies varies from 8 to 36 months [10]. In the United States, it varies from 2 to 10 months [10]. There is growing interest in novel diagnostic tools and methodologies, such

as American Academy of Sleep Medicine (AASM) level III testing which uses portable monitoring (PM) conducted in an unattended setting. A variety of different devices recording different signals are available [11]. The AASM recommends unattended PM use as a diagnostic tool for patients with a high pretest probability of moderate to severe OSA, with no major comorbidities and/or other sleep disorders [9]. In this context, a meta-analysis of 19 studies by Shayeb et al. found that sensitivity and specificity were generally both good, with increasing specificity and decreasing sensitivity as the disease severity increased [11]. The sensitivities and specificities were, respectively, 93% and 60% for AHI ≥ 5/h, 79% and 79% for AHI ≥ 15/h, and 79% and 90% for AHI ≥ 30/h [11]. Cost-effectiveness studies have suggested a decreased cost for PM of up to one-half compared to PSG [12].

In 2008, the US Centers for Medicare and Medicaid Services (CMS) committee released a landmark decision regarding the National Coverage Determination (NCD), approving "Home Sleep Testing (HST)" as a means to qualify patients with OSA for continuous positive airway pressure (CPAP) therapy [13]. This opens the way for more widespread use of PM. PM is an attractive alternative in patients with neurological disorders such as PD, who might otherwise decline in-laboratory PSG due to difficulties related to their disease such as impaired mobility, bladder dysfunction, anxiety, and cognitive impairment. However, PM is performed in an unattended setting, which can increase the rate of technically suboptimal studies, particularly in patients with motor or cognitive impairment. Furthermore, reduced sleep efficiency (i.e., greater proportion of wakefulness during recording) can lead to underestimation of the AHI on PM in that event indices are calculated based on recording rather than sleep time as no EEG is recorded [14]. Similarly, EEG arousals that are needed for scoring of some hypopneas cannot be detected on PM resulting in potential underestimation of OSA severity. Scoring so-called autonomic arousals (pulse accelerations) as a surrogate for EEG arousal can help improve sensitivity of PM for detection of OSA [15].

The feasibility and accuracy of PM have not been assessed in patients with PD. The objective of this prospective cohort study was therefore to assess the feasibility (quality of signals, study failure rates) and diagnostic accuracy of PM performed at home, compared with the gold standard of in-laboratory PSG, in PD patients with suspected OSA.

2. Materials and Methods

2.1. Study Subjects. PD patients with sleep complaints were recruited between November 2011 and July 2014 from the McGill Movement Disorder Clinic, an academic tertiary care centre. Inclusion criteria were a clear diagnosis of primary PD (as per established criteria [16, 17]), ability to undergo polysomnography (PSG), and adequate knowledge of English or French. Patients were excluded if they had another major neurological disorder (e.g., stroke), unstable cardiac disease, uncontrolled hypertension, an expected survival of <6 months, psychiatric or cognitive impairment precluding informed consent, or previously diagnosed OSA. Patients with other sleep disorders such as rapid eye movement sleep behavior disorder (RBD) or restless leg syndrome (RLS) were not excluded. Patients remained on their usual PD treatment regimen during the study. PM was offered to a selected group of patients based on their availabilities and their subjective capacity to use the device. Control PM studies performed on patients without major medical comorbidities referred to our general sleep-disorders clinic for suspected OSA were identified from our clinical sleep laboratory records. Records from the same period of time were reviewed sequentially until 2 control studies for each PD subject were identified, based on the same sex and age ±3 years.

2.2. Study Design. A prospective study protocol was used, in which patients completed both a PSG night and a PM night, separated by less than 30 days. The order in which these were done depended on subject availability. Prior to the PM night, patients were instructed by the research assistant on the correct use of the device, which was programmed to start recording automatically at the subjects' usual bedtime. The study visit consisted of a baseline questionnaire and a brief physical exam. Spirometry was performed according to American Thoracic Society guidelines; forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were measured [18].

Factors possibly affecting PM performance in PD were assessed. The Movement Disorder Society-sponsored revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS) was used to assess motor dysfunction [19]. A higher score is associated with a more severe PD. Cognitive impairment was assessed with the Montreal Cognitive Assessment [20]. A score of <26 is generally considered suggestive of cognitive impairment. We assessed dysautonomia using question 1.12 from the MDS-UPDRS, which evaluates lightheadedness on standing (scores 0–4). A score of 0 represents no dysautonomia, whereas a score of 1 to 4 represents dysautonomia.

2.3. Measurements

2.3.1. Polysomnography. Patients underwent standard overnight polysomnography, using a 6-channel recording system (C3, C4, F3, F4, O1, and O2), bilateral tibialis anterior and extensor digitorum electromyography (EMG), and digital video. Respiratory inductance plethysmography was used for thoracoabdominal motion, and nasal pressure cannula measured airflow. Oxygen saturation (SpO_2) was continuously monitored with a finger oximeter. Total sleep duration of minimum 3 hours during PSG was required. Data for PSG was scored manually by one certified registered polysomnographic technician using standard American Academy of Sleep Medicine (AASM) clinical criteria [21] for all measures except respiratory events, which were scored using AASM research criteria (Chicago criteria) [22]. The software Stellate Harmony (Natus, Mississauga, Canada) was used. The scoring was subsequently reviewed by an expert sleep physician. Outcomes of interest were apnea hypopnea index (AHI), respiratory arousal index (RAI), periodic limb movement arousal index (PLMAI), total arousal index (TAI), and oxygen desaturation index (≥4%, ODI_{PSG}).

2.3.2. Level III Home Portable Monitoring. Type III home portable monitoring (Embletta Gold Natus Medical Incorporated, San Carlos, CA, USA) was used. It included two respiratory inductance plethysmography belts, a nasal pressure cannula and a pulse oximeter. The machine was preset by the research assistant. Data from the PM was scored manually by the same certified technician who was blinded to the PSG results and subsequently reviewed by an expert sleep physician. Embla RemLogic software was used. Scoring was based on the "Chicago criteria" [22] used in our laboratory for PSG, modified for PM recordings. Apnea was defined as a cessation (≥90% decrease from baseline) of nasal airflow for at least 10 seconds. Hypopnea was defined as a clear decrease of nasal airflow from baseline (but <90%) lasting at least 10 seconds accompanied by either an oxygen desaturation ≥4% or a transient pulse acceleration ≥6 beats/min (bpm) as a surrogate marker for EEG arousal [15] ("autonomic hypopnea"), or a decrease in flow ≥50% with neither desaturation nor pulse increase. The respiratory disturbance index (RDI) was calculated as the number of apneas and hypopneas per hour of recording. An oxygen desaturation index (ODI_{PM}) was also calculated.

2.4. Data Analysis. Baseline demographic and polysomnographic data were described with means and standard deviations (SD). The Shapiro-Wilk test was used to test the normality of our data. Simple univariable comparisons between groups were performed with Student's t-test when the data were normally distributed, or the Mann-Whitney U test (MWU) if they were not. χ^2 or the Fisher exact tests were used as appropriate to compare nominal scale variables. Linear regressions adjusted for age and gender were performed as well.

The primary outcome of interest was the feasibility of PM studies in PD patients. The proportion of failures was estimated as well as its 95% confidence intervals (95% CI). A study was considered a failure when no signal at all was available on the recording for all channels. Quality of the PM recordings was assessed with the total recording time (minutes), the airflow signal quality (% of optimal signal), the oxygen saturation signal quality (% of optimal signal), and the pulse signal quality (% of optimal signal) as provided by the RemLogic software and was compared between cases and controls. We assessed correlations between signal quality and age as well as PD parameters: Hoehn and Yahr score, PD duration, motor part of the UPDRS, Montreal Cognitive Assessment (MOCA) score, and dysautonomia score, using the Pearson correlation coefficient. The secondary outcome of interest was the diagnostic performance of the PM device to rule in or rule out OSA in PD patients. Standard cut-offs for AHI as measured on PSG (gold standard) were evaluated: AHI ≥ 5/h (mild OSA), AHI ≥ 15/h (moderate OSA), AHI ≥ 30/h (severe OSA), and ODI ≥ 5/h. Receiver operator characteristic (ROC) curves and a Bland-Altman plot were built. To evaluate whether specific patient characteristics affected the accuracy of PM recordings, we assessed agreement between RDI and AHI, using the RDI/AHI ratio, comparing by t-test those with and without specific characteristics including age (dichotomized at the median), motor dysfunction (MDS-UPDRS dichotomized at the median), cognitive dysfunction (MOCA < 26 versus ≥26), the presence of dysautonomia, and negative chronotropic medications. Data were analyzed using SPSS statistics version 22.0 and SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina, 2010). Statistical significance was defined at the 5% level.

3. Results

3.1. Subjects' Characteristics. Of the 44 PD patients recruited, 7 declined because they were not confident about their ability to install the PM. From the 37 patients who used the device, 10 had a recording failure with no signal at all. Of those, 3 patients accepted a second attempt and one patient had a subsequent successful recording (Figure 1).

Patient characteristics are shown in Table 1. PD patients with a successful PM recording had a Parkinson's disease duration of 5.3 years (±5.2) on average, with a Hoehn and Yahr stage range from 1.0 to 4.0. The average Montreal Cognitive Assessment (MOCA) score of 25.4 (±3.7) and 39.3% had a MOCA score < 26, suggestive of cognitive impairment. None had frank dementia. Patients were on their usual PD medication during the study.

Subjects had OSA of moderate severity on average on PSG (AHI 28.2 ± 19.5/h). The obstructive apnea index was 2.5 ± 4.6 events/h; the central apnea index was 1.1 ± 2.8 events/h (Table 2). Most of the respiratory events were hypopneas with arousal, but there was little associated hypoxemia; the respiratory arousal index (RAI) was 24.3 ± 15.8/h and the oxygen desaturation index (≥4%, ODI_{PSG}) was only 7.3 ± 12.4/h. From PM recordings, the mean RDI was 15.0/h and the ODI_{PM} was 6.5/h (Table 3). "Autonomic hypopneas" represented 31.6% of the RDI.

3.2. Feasibility of PM in PD Patients. Feasibility of PM was assessed with the technical failure rate and the PM signal quality. Technical failure occurred in 27.0% of patients on their first attempt (Figure 1) and 2 of 3 (67%) on the second attempt. There were no significant differences in the demographic characteristics and in the polysomnographic data between the PD patients with a successful PM recording and those with a recording failure, except for the BMI, which was lower, and the percentage of sleep time in supine, which was higher for subjects with recording failure (Tables 1 and 2). There was a trend for lower PM signal quality in PD patients compared to controls. However, airflow signal quality recording was significantly lower in PD patients.

Correlation coefficients were calculated between the quality of the signals (proportion of adequate signal) and age (Table 4) as well as PD-specific variables (Table 7, in Supplementary Materials available online at http://dx.doi.org/10.1155/2015/258418). Trends were observed for negative correlations between age and quality of signals in PD patients. However, there was no significant correlation between quality of signals and the Hoehn and Yahr score, PD duration, MDS-UPDRS motor score, MOCA score, or dysautonomia.

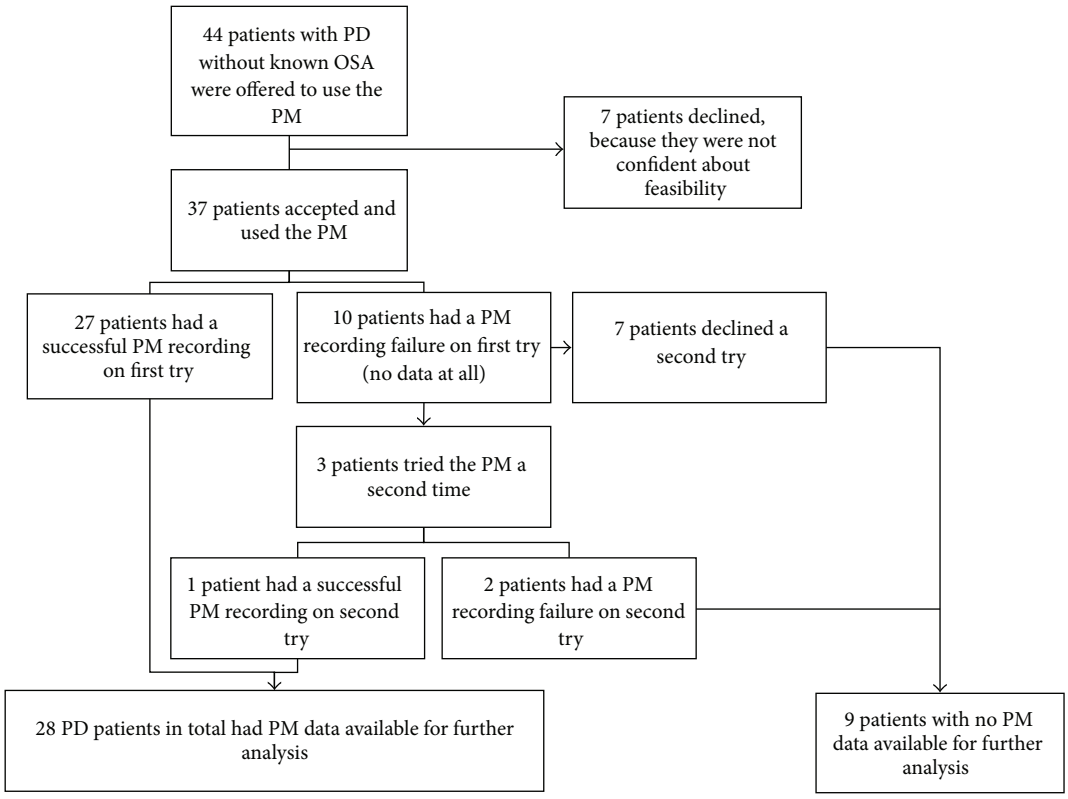


Figure 1: Patients' recruitment flow diagram.

3.3. Performance of PM in PD Patients. The diagnostic performance of the PM in categorizing mild, moderate, and severe OSA is presented in Table 5. The sensitivity of the PM was generally poor, except for AHI ≥ 5/h with a sensitivity of 84% (95% CI: 64%–95%). The specificity of PM was relatively high and reached 100% (95% CI: 82%–100%) for AHI ≥ 30/h. The positive predictive value was consistently high for all AHI cut-offs in our population. The negative predictive value (NPV) was poor except for AHI ≥ 30/h where it was 83% (95% CI: 61%–95%). The accuracy was above 80% for AHI ≥ 5/h and for AHI ≥ 30/h in our subject group.

For AHI ≥ 15/h, considered the most clinically relevant cut-off, several RDI cut-off values were evaluated to try to improve diagnostic accuracy: RDI ≥ 10/h, RDI ≥ 15/h, and RDI ≥ 20/h (Table 5). Sensitivity was doubled when RDI ≥ 10/h was used compared to the RDI ≥ 15/h cut-off, as there were less false negatives, with only mildly reduced specificity. On the other hand, specificity reached 100% when RDI ≥ 20/h was used compared to RDI ≥ 15/h, as there were less false positives, but sensitivity was poor.

The performance of ODI_{PM} ≥ 5/h as compared to ODI_{PSG} ≥ 5/h gave a different pattern than for AHI. It was more sensitive than specific and had a higher NPV than PPV. The overall accuracy was 78.6%. Receiver operating characteristics (ROC) curves for the different AHI cut-offs are shown in Figure 2. The best area under the curve (0.84; 95% CI: 0.68–1.00) corresponded to the AHI ≥ 5/h cut-off. The area under curve for ODI_{PM} ≥ 5/h was also high (0.85; 95% CI = 0.70–1.00).

3.4. Agreement between PM Studies and PSG. The Bland-Altman plot provides a visual representation of the agreement between PSG and PM (Figure 3). The mean difference (AHI from PSG, RDI from PM) was positive at 12.4 ± 20.1/h. In most cases, the PM underestimated the AHI, with only 14% of the data points below the line of no difference, suggesting a minority of overestimations by the PM. The difference between the two measures increased with increasing severity of OSA.

3.5. Effect of Patient Characteristics on Performance. We compared the mean RDI/AHI ratio in patients with and without certain characteristics that could affect PM performance, including older age, higher MOCA score, higher MDS-UPDRS motor score, dysautonomia, and negative chronotropic medication (Table 6). The two latter factors were chosen as they were thought to potentially affect the detection of autonomic arousals used in the scoring of hypopneas (cf. Materials and Methods). Increased motor dysfunction was associated with a significantly lower RDI/AHI ratio. Presence of dysautonomia and negative chronotropic medication was also associated with lower RDI/AHI ratio (not statistically significant).

4. Discussion

We found that PM was feasible in a selected PD population, although the rate of complete technical failures was relatively high, and airflow signal quality was lower than in the

Table 1: Patient baseline characteristics.

	PD patients with successful PM recording ($n = 28$)	PD patients with PM recording failure ($n = 9$)	PD patients who declined PM ($n = 7$)	Controls ($n = 56$)
Clinical data				
Sex (% male)	71.4	55.6	57.1	71.4
Age (years)	64.6 (11.0)	65.8 (11.2)	66.4 (8.2)	64.9 (10.4)
Body Mass Index (kg/m^2)	27.9 (3.7)	24.1 (3.2)	28.3 (4.0)	—
Hoehn and Yahr	2.0 (0.9) *(Range: 1.0 to 4.0)*	1.9 (1.0) *(Range: 1.0 to 4.0)*	2.4 (0.4) *(Range: 2.0 to 3.0)*	—
Total UPDRS	52.5 (25.2)	46.2 (24.0)	45.7 (14.3)	—
Motor UPDRS	25.0 (14.1)	19.3 (13.2)	20.6 (8.7)	—
PD duration (years)	5.3 (5.2)	5.6 (2.7)	6.9 (5.9)	—
MOCA score	25.4 (3.7) *(Range: 18 to 30)*	24.9 (3.1) *(Range: 20 to 29)*	25.0 (2.9) *(Range: 22 to 30)*	—
Levodopa equivalence dose (mg/day)	701.2 (902.3)	804.9 (522.1)	609.1 (210.0)	—
Proportion (%) on negative chronotropic medication°	17.8	22.2	14.3	—
Proportion (%) with dysautonomia¶	42.9	66.7	42.9	—
FVC (L)	4.0 (1.0)	3.6 (1.0)	3.2 (0.9)	—
FVC % pred.	109 (26.2)	102.6 (11.6)	99.3 (10.5)	—
FEV1 (L)	3.0 (0.8)	2.7 (0.7)	2.3 (0.7)	—
FEV1 % pred.	103 (25.7)	95.9 (11.3)	87.0 (17.0)	—

°Negative chronotropes include either beta-blockers or calcium channels blockers.
¶The dysautonomia score is based on a question from the first part of the UPDRS (see Section 2), regarding light-headedness on standing. Patients with reported dysautonomia have slight to severe symptoms, whereas patients with no reported dysautonomia have no symptoms of light-headedness.
PM: portable monitoring.
PD = Parkinson's disease.
UPDRS: Unified Parkinson's Disease Rating Scale.
PD duration: number of years since PD diagnosis.
MOCA: Montreal Cognitive Assessment.
FVC: forced vital capacity.
FEV1: forced expiratory volume in one second.

control group. The PM had generally low sensitivity but high specificity for various cut-offs of AHI, making it an adequate tool to "rule in" but not "rule out" OSA in PD patients. Overall, the RDI was an underestimate of the AHI. The PM had an excellent sensitivity for ODI ≥ 5/h.

The failure rate among subjects who attempted an initial PM study was 27.0% in our group of PD patients. This is higher than the rate of 10.3% previously reported in the general sleep clinic population [11] and than in our clinical laboratory, 1% to 7% per month for the same time period [23]. Moreover, 7 of 44 (16%) PD patients who were offered PM testing declined and only 30% of those who had a technical failure agreed to repeat the study. Most patients declined because they felt self-installation of the PM was too overwhelming. Psychiatric symptoms associated with PD such as anxiety or depression could be another factor related to the high noncompletion rate. Of note, these patients also underwent PSG as part of the study protocol. In the clinical setting, patients might theoretically prefer to undergo or repeat a PM study rather than undergoing PSG.

Although the quality of the airflow and pulse oximetry signals was overall adequate, there was a significantly lower airflow signal quality for PD patients compared to controls. It is possible that motor symptoms or cognitive dysfunction present in PD could impede the proper installation of the device or more readily lead to displacement of the nasal cannula during the night. However, neither the PD motor severity variables nor the MOCA score correlated with signal quality (Table 7, supplementary materials). Age appears to play a role in PD patients but not in control subjects (Table 4) with respect to signal quality. However, this does not appear to affect performance of the PM as RDI/AHI ratio was no different in younger versus older patients (Table 6). We did not systematically assess whether the patients installed the PM device themselves or if a caregiver helped them, but this might have affected willingness to undergo PM testing as well as signal quality.

Our data suggest that PM is a good tool to rule in OSA in PD patients with a prior clinical suspicion, as the specificity and the PPV were high. Specificities for PM in PD patients were roughly equivalent to those reported in the general population [11]. Patients with a PM recording suggestive of moderate or severe OSA are most likely to have OSA. This is consistent with the current AASM recommendation that PM may be used to rule in OSA in patients with a high pretest probability of moderate to severe OSA [9]. However,

Table 2: Polysomnographic data.

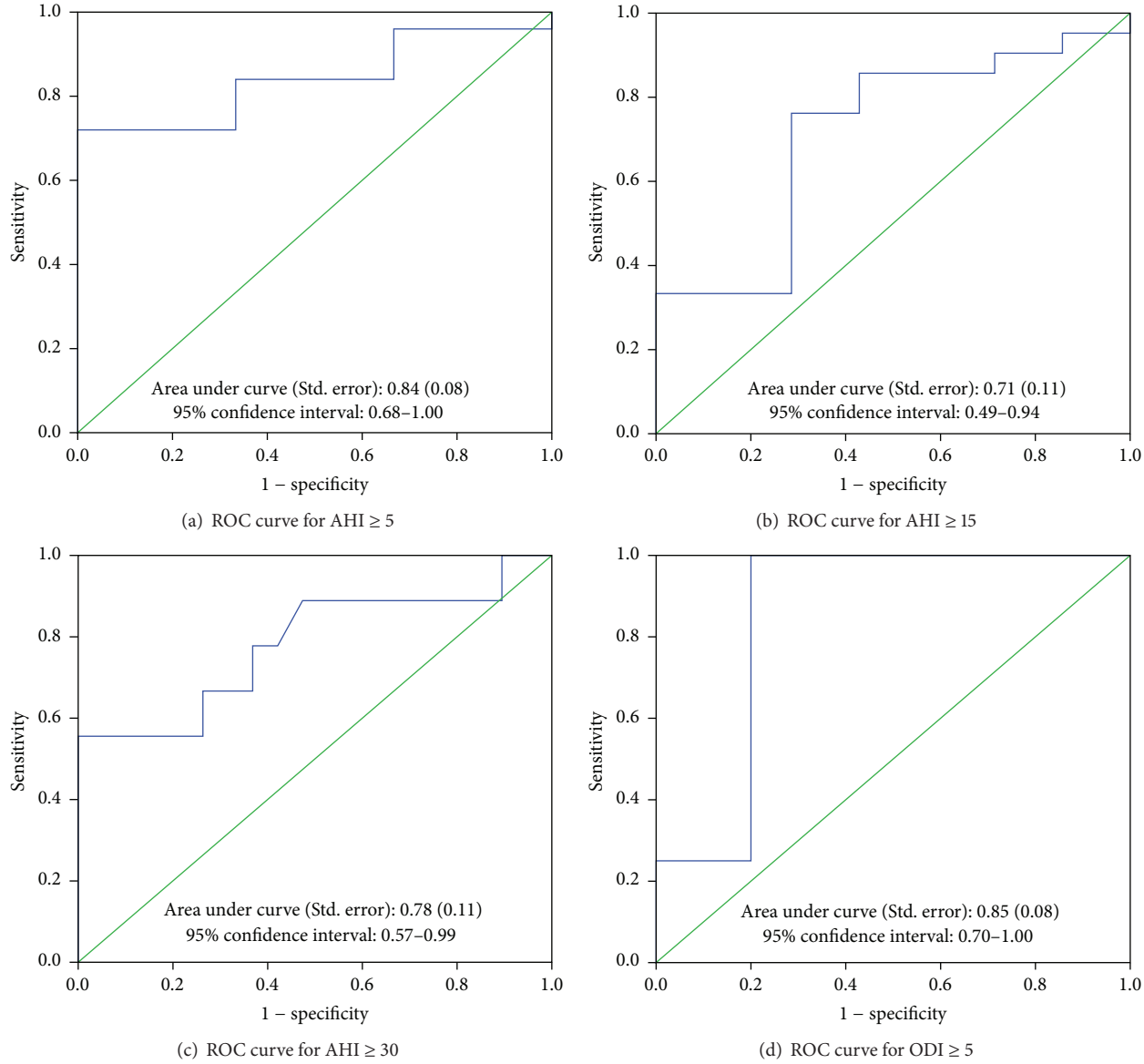
	PD patients with successful PM recording ($n = 28$)	PD patients with PM recording failure ($n = 9$)
Polysomnographic data		
Total sleep time (min)	333.3 (59.9)	334.3 (56.9)
Sleep efficiency (%)	76.3 (12.5)	78.5 (14.0)
Wake after sleep onset (min)	89.5 (57.2)	90.5 (67.1)
Stage changes	177.9 (65.9)	161.6 (40.3)
Stage 1 (% TST)	13.8 (11.6)	10.0 (5.2)
Stage 2 (% TST)	50.9 (14.5)	51.4 (15.3)
Stage 3 (% TST)	23.3 (16.4)	26.0 (17.8)
Stage REM (% TST)	12.0 (8.1)	12.7 (9.4)
% Total sleep time in supine position	59.9 (29.5)	47.1 (18.7)
Total arousal index (events/h)	43.0 (17.7)	37.6 (13.6)
Respiratory arousal index (events/h)	24.3 (15.8)	16.9 (11.3)
Periodic limb movements of sleep index (events/h)	19.6 (21.5)	59.1 (65.3)
Periodic limb movements arousal index (events/h)	2.8 (3.5)	5.6 (5.8)
Spontaneous arousal index (events/h)	15.5 (6.2)	15.0 (4.6)
AHI (events/h)	28.2 (19.5)	20.4 (13.0)
Proportion (%) with AHI ≥ 5	89.3	87.5
Proportion (%) with AHI ≥ 15	78.6	62.5
Proportion (%) with AHI ≥ 30	35.7	25.0
ODI (events/h)	7.3 (12.4)	3.6 (3.2)
Obstructive apnea index (events/h)	2.5 (4.6)	1.1 (2.3)
Central apnea index (events/h)	1.1 (2.8)	0.5 (0.7)

AHI: apnea hypopnea index.
ODI: oxygen desaturation index.
No significant differences were found between those with successful versus failed recordings.

Table 3: PM data for PD patients and non-PD controls.

	PD patients ($n = 28$)	Controls ($n = 56$)	Adjusted p values*
Quality variables			
Recording time	470.7 (75.7)	439.9 (84.6)	0.11
Airflow signal quality (%)♯	91.1 (14.2)	98.3 (5.2)	0.001
Oxygen saturation signal quality (%)♯	93.4 (16.6)	95.7 (14.6)	0.51
Pulse signal quality (%)♯	93.9 (16.2)	95.8 (14.6)	0.58
OSA variables			
RDI (events/h)	15.0 (15.1)	22.3 (19.5)	—
Supine RDI (events/h)	18.8 (24.4)	24.2 (21.7)	—
Nonsupine RDI (events/h)	9.6 (12.4)	15.6 (17.6)	—
Time in supine (%)	52.6 (30.8)	48.2 (35.3)	—
Mean saturation (%)	93.7 (4.6)	93.6 (2.5)	—
Oxygen desaturation index (events/h)	6.5 (8.1)	12.6 (13.7)	—

Values are mean (SD) unless specified.
♯(%) Percentage of optimal signal quality as provided by the RemLogic software.
* Adjusted p value was obtained by performing linear regression, adjusted for age and gender.
PD: Parkinson's disease.
RDI: respiration disturbance index.



(a) ROC curve for AHI ≥ 5

(b) ROC curve for AHI ≥ 15

(c) ROC curve for AHI ≥ 30

(d) ROC curve for ODI ≥ 5

Figure 2: Receiver operating characteristics curve analysis of PM for AHI ≥ 5, AHI ≥ 15, AHI ≥ 30, and ODI ≥ 5. ROC referred to an AHI cut-off from PSG, which shows the sensitivity and specificity of each observed value of the RDI obtained from the PM in relation to the given PSG cut-off.

Table 4: Correlation of signals quality with age in PD patients and controls.

	Cases		Controls	
	r	*p*	*r*	*p*
Airflow signal quality	−0.36	0.06	−0.14	0.32
Oxygen saturation signal quality	−0.36	0.07	−0.11	0.41
Pulse signal quality	−0.34	0.09	−0.10	0.45

r: Pearson correlation coefficient.
p: *p* value.

it does not seem to be an adequate tool to rule out OSA. The sensitivities and NPVs of the PM were poorer for PD patients. There was a high rate of false negatives, higher than the 4 to 8% of false negative reported by the AASM for unattended type III PM [9]. The PM tends to underestimate severity of OSA, as seen on the Bland-Altman plot. The mean bias (AHI-RDI) was 12.4 ± 20.1/h. Discrepancy between RDI and AHI was significantly greater in patients with more marked motor dysfunction (Table 6). Scoring of respiratory events on PM recordings in these patients may be more challenging in the absence of EEG.

An important factor that could contribute to the increased PM false negative rate is the type of OSA found in PD patients. In our population, most events on PSG were hypopneas with arousals but few desaturations. This is likely in part due to lower BMI of our study subjects compared to general population with OSA, which has been shown to result in less desaturation in association with apnea and

Table 5: Performance of PM for multiple AHI cut-offs and ODI.

Parameters (n = 28)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
AHI ≥ 5/h (n = 25)			**RDI ≥ 5/h**		
	0.84 (0.64–0.95)	0.67 (0.09–0.99)	0.95 (0.77–0.99)	0.33 (0.04–0.78)	0.82 (0.63–0.94)
AHI ≥ 15/h (n = 21)			**RDI ≥ 10/h**		
	0.62 (0.38–0.82)	0.71 (0.29–0.96)	0.87 (0.59–0.98)	0.38 (0.14–0.68)	0.64 (0.44–0.81)
			RDI ≥ 15/h		
	0.33 (0.14–0.57)	0.71 (0.29–0.96)	0.78 (0.40–0.97)	0.26 (0.09–0.51)	0.43 (0.24–0.63)
			RDI ≥ 20/h		
	0.33 (0.15–0.57)	1.00 (0.59–1.00)	1.00 (0.59–1.00)	0.33 (0.15–0.57)	0.50 (0.31–0.69)
AHI ≥ 30/h (n = 9)			**RDI ≥ 30/h**		
	0.56 (0.21–0.86)	1.00 (0.82–1.00)	1.00 (0.48–1.00)	0.83 (0.61–0.95)	0.86 (0.67–0.96)
ODI_{PSG} ≥ 5/h (n = 5)			**ODI_{PM} ≥ 5/h**		
	0.88 (0.47–0.99)	0.80 (0.56–0.94)	0.64 (0.31–0.89)	0.94 (0.71–1.00)	0.82 (0.63–0.94)

RDI (respiration disturbance index) was used for home portable monitoring.
AHI (apnea hypopnea index) was used for polysomnography.
ODI: oxygen desaturation index.
95% CI: 95% confidence interval.
PPV: positive predictive value.
NPV: negative predictive value.

Table 6: Assessment of patient characteristics in relation to discrepancies between RDI and AHI.

	RDI/AHI ratio		p value	95% CI
Age*	<Median (n = 14)	>Median (n = 14)		
	0.78 (0.84)	0.71 (0.54)	0.82	−0.49; 0.61
MOCA	<26 (n = 12)	≥26 (n = 16)		
	0.70 (0.82)	0.77 (0.61)	0.81	−0.52; 0.66
Motor UPDRS	<Median (n = 14)	>Median (n = 14)		
	1.02 (0.85)	0.46 (0.32)	0.03	0.05; 1.08
Dysautonomia¶	Yes (n = 12)	No (n = 16)		
	0.57 (0.31)	0.87 (0.87)	0.22	−0.20; 0.79
Neg. chronotropic med.	Yes (n = 6)	No (n = 22)		
	0.53 (0.28)	0.79 (0.75)	0.21	−0.17; 0.68
Either dysautonomia or neg. chronotropic med.	Yes (n = 18)	No (n = 10)		
	0.58 (0.30)	0.89 (0.90)	0.24	−0.22; 0.82

*Groups of age were separated according to the median age (63.5 years). Patients with younger age are <63.5 years and patients with older age are ≥63.5 years.
MOCA: Montreal Cognitive Assessment.
UPDRS: Unified Parkinson's Disease Rating Scale.
¶The dysautonomia score is based on a question from the first part of the UPDRS (see Section 2), regarding light-headedness on standing. Patients with reported dysautonomia have slight to severe symptoms, whereas patients with no reported dysautonomia have no symptoms of light-headedness.
Neg. chronotropic med.: Negative chronotropic medication (i.e., calcium channel blockers and/or beta-blockers).
RDI: respiratory disturbance index (measured with PM).
AHI: apnea hypopnea index (measured with PSG).
95% CI: 95% confidence intervals.

hypopnea during sleep [24]. However, on PM, EEG is not recorded and arousals are not scored. Cascon et al. found that heart rate increases associated with autonomic hypopneas considered as a surrogate marker of cortical arousals could improve the diagnostic accuracy of OSA with PM [15]. This has been standard in our sleep laboratory for some years. However, PD patients frequently have dysautonomia, which could undermine the accuracy of the PM by blunting heart rate responses. In our cohort, 43% had dysautonomic features, with self-reported light-headedness. Although this is a subjective and imprecise assessment of dysautonomia, those patients appeared to have greater discrepancy between RDI and AHI. Moreover, Lachapelle et al. have suggested that negative chronotropes could interfere significantly with "autonomic hypopnea" detection and consequently with PM accuracy [25]. Of our patients, 18% were on either beta-blockers or calcium channel blockers. Although we did not have sufficient power to demonstrate a statistically significant effect, our data suggest that these two factors could affect the accuracy of PM recordings by impeding measurement of pulse accelerations needed to score some hypopneas causing underestimation of events. It is also important to note that

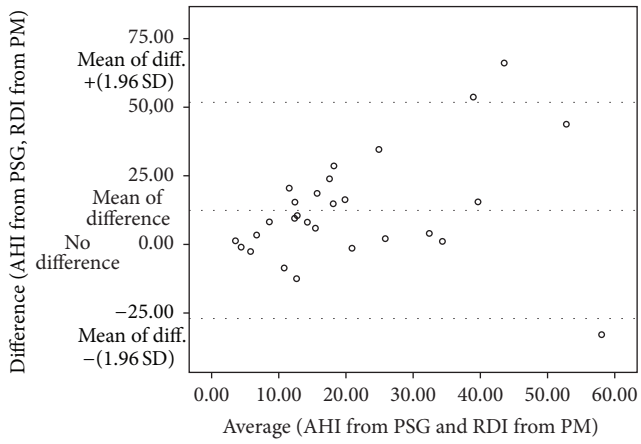


Figure 3: Bland-Altman plot comparing AHI from PSG and RDI from PM.

laboratories that do not score "autonomic hypopneas" and rely solely on oxygen desaturation to score hypopnea events on PM would most likely significantly underestimate the AHI, resulting in lower sensitivity for OSA diagnosis.

None of the patients in our study had any hypoventilation or predominant central sleep apnea. This is similar to the findings of Cochen De Cock et al. [3]. However, others [26] have found a number of PD patients with predominant central sleep apnea. This may depend on the patient population, comorbidities, and PD medications [26].

Overestimation of AHI occurred in 14% of the PM studies. This could be due to artefacts that would be more difficult to appreciate on PM recordings than on PSG. Sleep staging is not performed with PM, and respiratory fluctuations in wakefulness may have been scored as sleep-disordered breathing. Moreover, the PM and PSG studies were run on separate nights, so the night-to-night variability in OSA severity may have contributed to discrepancies [27].

Strengths and Limitations. We studied the PM in its site of intended use, the patient's home, which aimed at representing performance in real practice. PSG and PM studies were scored by the same sleep technician, in a blind manner, helping to prevent interscorer variability and observational bias. Our experimental design simulated the clinical use of PM in our sleep laboratory, with instructions regarding the installation of the PM identical to the standard clinical setting. This makes our results generalizable to the average sleep laboratory setting.

There were some limitations to our study. PSG and PM in the PD patients were done on two different nights, in two different environments. Although these are more "real-life" conditions, differences in results may be explained at least in part by night-to-night variability which is known to occur in OSA in the general population [27]. However, a previous study suggested OSA in PD appears to be relatively stable across different nights [28]. Further research with simultaneous PM and PSG on the same night could be relevant to better assess this factor. In this study, we have not excluded patients with RLS. We had a relatively high number of positive questionnaires for RLS, but we did not have clinical confirmation of RLS diagnosis. The questionnaire may overestimate RLS due to inclusion of RLS mimics by the questionnaire. We found that the periodic limb movements of sleep index (PLMS) and the PLM-related arousal index (PLMAI) were relatively low (Table 2). Therefore, we expect PLM to only have a minor influence on our data. The study sample was relatively small and our population may not be entirely representative of all PD patients, which can affect external validity. We excluded patients that could not undergo in-laboratory PSG, thereby excluding most advanced PD patients. Patients could also decline to undergo PM if they did not feel capable of doing it. Hence, our results apply to a selected population of PD patients. This study was observational and not experimental and there remains the potential for unknown and unmeasured bias.

Clinical Relevance. Our results can be applied to a clinical population of PD patients with sleep complaints. When a PM study is positive for moderate or severe OSA in a PD patient, it is likely that the patient has clinically significant OSA and could benefit from treatment, such as CPAP. Treating OSA in PD could help improve NMS, such as excessive daytime sleepiness [2, 29]. Conversely, when a PM study is negative, mild and moderate OSA have not been excluded, although severe OSA is less likely. A full PSG should then be considered in this case. PSG should also be performed when other sleep disorders are suspected.

5. Conclusion

To our knowledge, this is the first study attempting to validate the use of PM in PD patients and as such it addresses a knowledge gap in the literature. There is recently a trend for increased use of PM for OSA diagnosis. It is important to understand implications of using this type of sleep testing in PD. Additionally, PM use may help simplify access to OSA diagnosis in PD, since PSG has limited availability and may represent a significant burden in PD patients. Our study suggests that PM is feasible in some PD patients, although the failure rate was higher and the signal quality was lower than in a general sleep clinic population. Increasing age was associated with poorer signal quality but this did not affect the agreement between RDI and AHI. However, in patients with greater motor dysfunction and in those with dysautonomia or on negative chronotropic medications, the severity of OSA was underestimated by the PM (lower RDI/AHI ratio). Overall, PM is a good tool to rule in OSA in PD patients with moderate or severe OSA. In the context of increasing evidence implicating OSA as a potentially harmful and frequent comorbidity in PD, increasing the use of home testing in clinical practice when appropriate could facilitate a prompt diagnosis and treatment of OSA. The limitations of PM performance have to be taken into account when deciding on its use and when interpreting PM recordings, including its inability to detect sleep disorders other than OSA. Additional studies with larger cohort are needed to confirm these findings and to assess the cost-effectiveness of strategies employing PM testing among PD patients.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This was a secondary analysis of an observational cohort study. No details revealed in this paper disclose the identity of the subjects.

Consent

All persons gave their informed consent prior to their inclusion in the study.

Conflict of Interests

Anne-Louise Lafontaine has served in advisory boards for Abbvie and has received honoraria from Teva, Allergan, Merz, and Norvatis. Marta Kaminska was consultant and member of advisory board at Biron Laboratoires du Sommeil.

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Research Article

Minimal Clinically Important Difference on Parkinson's Disease Sleep Scale 2nd Version

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Background and Aims. The aim of the present study was to determine the estimates of minimal clinically important difference for Parkinson's Disease Sleep Scale 2nd version (PDSS-2) total score and dimensions. *Methods*. The subject population consisted of 413 PD patients. At baseline, MDS-UPDRS, Hoehn-Yahr Scale, Mattis Dementia Rating Scale, and PDSS-2 were assessed. Nine months later the PDSS-2 was reevaluated with the Patient-Reported Global Impression Improvement Scale. Both anchor-based techniques (within patients' score change method and sensitivity- and specificity-based method by receiver operating characteristic analysis) and distribution-based approaches (effect size calculations) were utilized to determine the magnitude of minimal clinically important difference. *Results*. According to our results, any improvements larger than −3.44 points or worsening larger than 2.07 points can represent clinically important changes for the patients. These thresholds have the effect size of 0.21 and −0.21, respectively. *Conclusions*. Minimal clinically important differences are the smallest change of scores that are subjectively meaningful to patients. Studies using the PDSS-2 as outcome measure should utilize the threshold of −3.44 points for detecting improvement or the threshold of 2.07 points for observing worsening.

The present scientific contribution is also dedicated to the 650th anniversary of the foundation of the University of Pécs, Hungary

1. Introduction

The nonmotor symptoms of Parkinson's disease (PD) have been increasingly recognized as major burden of quality of life [1, 2]. Sleep-related problems are one of the most frequent and troublesome nonmotor aspects of PD. Sleep-related problems are certainly multidimensional. The recently developed Parkinson's Disease Sleep Scale 2nd version (PDSS-2) was designed to be simultaneously able to capture the multidimensional aspects of sleep-related problems and any changes in sleep quality [3]. It consists of 15 items evaluating three domains (motor symptoms at night, PD symptoms at night, and disturbed sleep) [3]. Symptoms on each domain can be scored in the range of 0–20 points, higher scores representing more nighttime sleep-related problems. The sum of the three domains gives the total score of PDSS-2 with the maximum value of 60 points. PDSS has been translated and validated into several languages [4, 5] and has good clinical validity [6]. The threshold indicating sleep problems is 11 points for the Hungarian version of PDSS-2 [7].

Even though the PDSS-2 has been utilized in several pharmacological [8–12] and neurosurgical [13] studies to identify

any improvement in nocturnal sleep quality, the magnitude of change required to represent a clinically meaningful improvement has not been evaluated yet.

One of the major issues in recent biomedical research is the evaluation of clinical meaning of changes on patients' reported outcomes (PROs). As some changes may be statistically significant but clinically irrelevant, statistical significance does not necessarily imply clinical importance: interventions with small effect size, for example, may have no clinical importance for the patients or clinicians.

To overcome this issue, the concern of minimal clinically important difference (MCID) was introduced in late 1980s. Jaeschke et al. defined the MCID as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate. . .a change in the patient's management" [14]. In other words, MCID is the smallest change in an outcome measure that a patient would identify as important. Therefore, MCID offers a threshold above which outcome is experienced as relevant by the patient avoiding the problem of mere statistical significance.

Evaluation of MCIDs for different outcome measures not only is important because of clinical decision-making and the labeling claims of medical products but also is required for study design as it is essential for calculating the sample sizes required for different trials and surveys.

However, there are some important issues with the MCID thresholds. First, thresholds for detecting minimal clinically meaningful improvement and worsening may be asymmetric. Therefore, different threshold values may exist for detecting improvement and deterioration on the same outcome measure [15].

A more troublesome concern is the methodology- and sample-dependent nature of MCID. At the moment numerous different approaches are available for MCID calculations (e.g., anchor-based and distribution-based techniques). For example, application of different methods even on the same sample can result in different MCID values [15, 16]. On the contrary, the usage of the same outcome measures and methods for MCID calculation on different study population can also yield different MCID thresholds [15, 17]. To overcome these problems, an article summarizing the recommendations on methods for evaluating MCID was recently published [18]. According to its proposals, the estimation of MICD for a specific outcome measure should be based on multiple approaches. Because the PRO measures should correlate with the appropriate clinical anchor used for determining MCID, the value of correlation coefficient should be at least 0.3 between them.

The aim of the present study was to determine the estimates of MCID for Parkinson's Disease Sleep Scale 2nd version (PDSS-2) in a longitudinal observational setup. Our protocol fully complied with the recommendations for determining MCIDs [18] and simultaneously multiple techniques were assessed for the calculations.

2. Materials and Methods

2.1. Patients. In this prospective study 413 consecutive patients fulfilling the UK Brain Bank criteria for PD were enrolled [19] at Department of Neurology, University of Pécs, Hungary, between 2013 and 2015. The patients were examined by neurologists specialized in movement disorders. Each subject gave written informed consent in accordance with the ethical approval of Regional and Institutional Ethical Committee (3617.316-24987/KK41).

2.2. Obtained Rating Scales. Besides PDSS-2 sociodemographic and PD-related data were obtained and the patients were screened for dementia by the means of Montreal Cognitive Assessment and Mattis Dementia Rating Scale [20] at baseline. Patients with atypical parkinsonism or dementia (receiving ≤125 points on Mattis scale and/or fulfilling the criteria of DSM-5 for major neurocognitive disorder in PD [21, 22]) were excluded from the study. Severity of Parkinson's disease was assessed by the Hungarian validated version of Movement Disorders Society-Sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [23, 24], the Hoehn-Yahr Scale (HYS) [25], and the Schwab-England Scale (SES) [26]. Implying the recommendations of the Movement Disorders Society Task Force, the original HYS was obtained and treated as ordinal values [27]. Baseline characteristics of the study population are demonstrated in Table 1.

Patients were reexamined 9 months (275 ± 21 days) later after receiving standard clinical care. After completing the PDSS-2 questionnaire, the patients were asked to describe if their sleep quality was either "very much better," "much better," "a little better," "the same," "a little worse," "much worse," or "very much worse" since the last visit. These answers were identical with the Hungarian validated version of Patient-Rated Global Impression of Improvement (PGI-I) items adjusted for sleep problems.

2.3. Anchor-Based Methods to Determine MCID. The anchor-based approaches utilize either patient-based or clinician-based external indicator to assign subjects into several groupings reflecting no change, small negative changes, large negative changes, small positive changes, or large positive changes. Two different types of anchor-based approaches were applied to determine CIDs. These types of methods require an independent standard or anchor that is simultaneously interpretable by itself, clinically relevant, and correlated with the instrument being evaluated [28, 29]. For this study, the above-mentioned PGI-I items served as the anchors for calculating the MCID estimates for PDSS-2.

2.3.1. Within-Patients Score Change Method. This approach defines MCID as the change between the PRO scores of a group of patients selected according to their answer to a global assessment scale (anchor). Therefore, in this study we calculated the mean change on the PDSS-2 dimensions and the total score for those subjects who indicated "no change" at follow-up or for those who indicated "a little worse" or "a little better" change.

2.3.2. Sensitivity- and Specificity-Based Approach. This second anchor-based method is useful in calculating the threshold that allows for the best discrimination between groups of patients. For example, the score that produces the greatest

Table 1: The demographic and disease-specific characteristics of the study population (n = 413) at baseline examination.

	Mean or number of patients	Standard deviation	Median	Percentile 25	Percentile 75
Age	64.83	9.20	65.00	59.00	72.00
Sex	285M/128F				
Education (years)	11.9	3.4	12.0	11.0	16.0
Disease duration	9.91	5.99	9.00	5.00	13.00
HYS (number of patients at stage 1/2/3/4/5)	68/125/170/35/15				
Patients on levodopa (baseline)	215 (52.1%)				
Patients on levodopa (follow-up)	265 (64.2%)				
Levodopa dosage (baseline, in LED, mg)	585.4	472.1	520.0	200.0	812.5
Levodopa dosage (follow-up, in LED, mg)	735.3	490.4	620.0	350.0	912.5
Patients on dopamine-agonists (baseline)	165 (39.9%)				
Patients on dopamine-agonists (follow-up)	324 (78.5%)				
Dopamine agonist dosage (baseline, in LED, mg)	215.6	244.9	160.0	.0	320.0
Dopamine agonist dosage (follow-up, in LED, mg)	323.2	234.4	324.0	98.5	420.0
Patients on benzodiazepines (both baseline and follow-up)	44 (10.7%)				
Schwab-England	74.2	13.9	80.0	70.0	90.0
MDS-UPDRS nMEDL	14.8	6.5	14.0	10.0	19.0
MDS-UPDRS MEDL	17.0	8.3	16.0	10.0	23.0
MDS-UPDRS ME	40.3	14.8	39.0	29.0	48.0
MDS-UPDRS MC	5.2	3.6	5.0	2.0	7.0
MDS-UPDRS total score	77.2	25.8	74.0	58.0	91.0
PDSS-2 motor symptoms domain	4.7	3.9	5.0	2.0	7.0
PDSS-2 PD symptoms domain	3.6	3.3	4.0	1.0	5.0
PDSS-2 disturbed sleep domain	7.3	4.1	7.0	4.0	10.0
PDSS-2 total score	15.6	9.6	16.0	8.0	21.0

HYS: Hoehn-Yahr Stages; LED: levodopa equivalent dosage; MDS-UPDRS: Movement Disorders Society Sponsored Version of Unified Parkinson's Disease Rating Scale; MDS-UPDRS MC: Motor Complications (Part 4 of MDS-UPDRS); MDS-UPDRS ME: Motor Examination (Part 3 of MDS-UPDRS); MDS-UPDRS MEDL: Motor Experiences of Daily Living (Part 2 of MDS-UPDRS); MDS-UPDRS nMEDL: Non-Motor Experiences of Daily Living (Part 1 of MDS-UPDRS).

sensitivity and specificity for discriminating patients with minimal change from patients without any change can be considered as the MCID. Generally sensitivity is the proportion of subjects with a positive test out of the group of subjects who were truly positive. Likewise, specificity is the proportion of subjects with a negative test out of the group of subjects who were truly negative. Used in conjunction with MCID estimations, sensitivity is the proportion of the patients who report a change on the external criterion (i.e., PGI-I) and whose PRO score (e.g., PDSS-2) change exceeds the threshold MCID value. Similarly, specificity is the proportion of subjects who do not report a change on the external criterion (anchor) and whose PRO score changes are below the threshold MCID value. A sensitivity of 100% indicates that all true positives are identified, whereas a specificity of 100% indicates that all the true negatives are identified.

In our study, we applied receiver operating characteristic (ROC) curve technique to find the most suitable MCID values. Because the recommendations for desirable MCID sensitivity and specificity levels have yet to be determined [18], we followed the method described by Hauser et al. [15, 17]. Assuming that false-positive and false-negative identifications are equally unwanted, we determined the cutoff value with the most optimal balance between sensitivity and specificity. The optimal cutoff points to distinguish changes on PDSS-2 between subjects rated as minimally worsened or minimally improved and subjects rated as unchanged on the PGI-I score were estimated as the point on the ROC curve closest to the point of (0, 1). It was calculated as the minimum value of the square root of $(1 - \text{sensitivity})^2 + (1 - \text{secificity})^2$. For the most optimal cutoff values the positive (LR+) and negative (LR−) likelihood-ratios were also determined using the following formulas:

$$\begin{aligned} \text{LR+} &= \frac{\text{True positive rate}}{\text{False positive rate}} = \frac{\text{Sensitivity}}{(1 - \text{Specificity})}, \\ \text{LR−} &= \frac{\text{False negative rate}}{\text{True negative rate}} = \frac{(1 - \text{Sensitivity})}{\text{Specificity}}. \end{aligned} \quad (1)$$

2.4. Distribution-Based Method to Determine MCID. The distribution-based methods compare the changes in PRO scores to some measure of variability. However, the distribution-based estimates provide no direct information about the MCID. They are simply a way of describing the observed differences in a standardized metric [18].

Effect size is generally a measure of exactly how strong the relationship that was being examined is. Common effect sizes are mean differences, correlation coefficients, regression coefficients, odds ratios, and hazard ratios. The value of the effect size represents the number of standard deviations (SDs) by which the scores have changed from baseline to the follow-up. By convention, an effect size of 0.2 is considered as small, 0.5 as moderate, and 0.8 as large [18]. Used in conjunction with anchor-based methods, effect size ascertains the responsiveness of the external criterion. With regard to MCID, for example, the change in scores corresponding to small effect size should estimate the MCID value [18, 29].

2.5. Statistical Analysis. All statistical analyses were carried out using IBM SPSS software package (version 21, SPSS Inc., Chicago, USA). We calculated Spearmen's correlation coefficients to assess the relationship between the PGI-I and the changes in PDSS-2 scores. Comparison of baseline and follow-up scores was performed by paired t-tests. Statistical significance level was set to 5%. Because the SPSS Suite did not have built-in functions for calculating positive and negative predictive values, we utilized the syntax available on the IBM website (http://www-01.ibm.com/support/docview.wss?uid=swg21483380, assessed on Jan 15, 2013).

3. Results

During the observational period the levodopa dose in LED increased from 585.4 ± 472.1 mg to 735.3 ± 490.4 mg and the dopamine-agonist dose (measured in LED) increased from 215.6 ± 244.9 mg to 323.2 ± 234.4 mg, whereas the number of patients on dopamine-agonist therapy increased from 165 to 324 (Table 1).

3.1. Anchor-Based MCID Estimation. The Spearman correlation coefficient assessing the correlation between the PGI-I and the change in PDSS-2 was 0.364 ($p < 0.001$). As a correlation coefficient higher than 0.3 between the anchor and the PRO is required for detecting MCID [18], our study setting can be considered as a suitable dataset for detecting MCID for PDSS-2.

3.1.1. Within-Patients Score Change Method. Because we aimed to determine only the magnitude of minimal clinically important difference, only the data for those judged minimally improved ($n = 142$), unchanged ($n = 126$), and minimally worse ($n = 154$) are presented in Table 2.

Mean changes (±SD) for PDSS-2 for subjects rated minimally improved, unchanged, or minimally worse on PGI-I scale are demonstrated in Table 2. The mean change for patients rating the same sleep quality was −0.54 (±3.24), whereas for minimal improvement it was −3.44 (±6.40) and for minimal worsening it was 2.07 (±7.72) points on the total score of PDSS-2 (Table 2).

3.1.2. Sensitivity- and Specificity-Based Approach. Subsequently we performed ROC analysis between the changes in the total score of PDSS-2 compared and the PGI-I as state variable. The most optimal cutoff value discriminating the minimal improvement was ≤−3 points on the total score of PDSS-2, whereas the best cutoff to identify the minimal worsening was ≥2 points (Table 3).

3.2. Effect Size Method. The estimates calculated by anchor-based methods for detecting minimal clinically meaningful improvement and worsening represent the effect size of 0.21 and −0.21, respectively.

Because both anchor-based and distribution-based calculations gave similar results, we could estimate that the threshold representing minimal clinically important difference for improvement was −3.44 points and for worsening it was +2.07 points.

4. Discussion

Following the recommendations of Revicki et al. [18], our aim was to evaluate the magnitude of minimal clinically important difference on PDSS-2. By the utilization of the combination of both anchor- and distribution-based methods, we were able to estimate the MCID thresholds for the total score of PDSS-2 congruently. Based on our results, the magnitude of MCID is asymmetric for improvement and worsening. According to our results, any improvement larger than −3.44 points and any worsening larger than +2.07 points can represent clinically important changes for the patients. This asymmetry is probably due to the asymmetric perception of sleep quality. According to our data relatively larger improvements are required to be judged by the patients as positive improvement, whereas a relatively smaller worsening can elicit the perception of worsening.

One of the limitations of our study may be that we utilized only patient-derived anchors for assessing MICD and our data is not based on the objective (e.g., polysomnographic or actigraphic) findings. Because sleep quality is very subjective, in our opinion the severity of sleep problems can only reliably be described by the patients. There is no objective physical or instrumental examination which could reliably measure the sleep quality of the patients. Not even the sleep labs can describe all dimensions of the sleep. Polysomnography (PSG), for example, can objectively detect the presence and measure the severity of PMLS in an artificial setup, but it is still unable to capture several other aspects of sleep quality [30, 31]. Although the PDSS was validated against PSG [30, 31], not even the original (English) version of PDSS-2 was validated against any sleep lab tests [3]. This was the reason why we applied a patient-derived (and not a clinician-based) anchor to assess the MICD. Because similar approach was utilized for pain outcomes [32], our method is acceptable for detecting MICD for PDSS-2.

Since its publication in 2011 [3], a growing number of studies utilized the PDSS-2 to evaluate changes in sleep

Table 2: Mean changes of PDSS-2 scores with respect to Patient-Rated Global Impression of Improvement scores.

	PDSS-2 total score					PDSS-2 motor symptoms domain					PDSS-2 PD symptoms domain					PDSS-2 disturbed sleep domain				
	Mean	SD	Median	25th percentile	75th percentile	Mean	SD	Median	25th percentile	75th percentile	Mean	SD	Median	25th percentile	75th percentile	Mean	SD	Median	25th percentile	75th percentile
PGI-I (sleep problems)																				
A little better	−3.44	6.40	−3.00	−5.00	2.00	−.92	2.98	0.00	−2.00	1.00	−.92	2.48	0.00	−1.00	0.00	−1.60	2.87	−2.00	−3.00	1.00
The same	−0.54	3.24	−1.00	−3.00	3.00	−.15	4.02	0.00	−3.00	2.00	−.15	3.38	0.00	−2.00	1.00	−.21	3.35	0.00	−3.00	1.00
A little worse	2.07	7.72	2.00	0.00	7.00	0.53	4.01	1.00	−1.00	3.00	0.47	3.62	0.00	−1.00	3.00	1.07	3.12	1.00	1.00	4.00

SD: standard deviation; PDSS-2: Parkinson's Disease Sleep Scale 2nd version; PGI-I: Patient-Rated Global Impression of Improvement.

Table 3: Best cutoff values discriminating minimal clinically important differences for PDSS-2 determined by receiver operating characteristic analysis.

	ROC curve cutoff	Sensitivity	Specificity	+LR	−LR	AUC	Significance
PGI-I							
A little better	<−3	54.00	51.40	1.11	0.89	0.523	0.046
The same			NA				
A little worse	≥2	50.98	65.42	1.47	0.75	0.613	0.023

AUC: area under the curve; +LR: positive likelihood-ratio; −LR: negative likelihood-ratio; PDSS-2: Parkinson's Disease Sleep Scale 2nd version; PGI-I: Patient-Rated Global Impression of Improvement; ROC: receiver operating characteristic analysis.

problems of PD patients. However, in the lack of MICD value for PDSS-2, these studies could demonstrate only statistical significance and not clinically meaningful difference.

The first larger study aimed to investigate the effects of rotigotine on nocturnal sleep quality [33]. This was the first study where early morning motor function and nocturnal sleep-disturbances served as the coprimary endpoints. In this double-blind study, the mean PDSS-2 total score had decreased by −5.9 points with rotigotine and by −1.9 points with placebo. Because the difference between the active and placebo arm (−4.0) is larger than our MCID value (−3.56), the observed difference can be considered as clinically meaningful.

Zibetti et al. demonstrated that 2–4 months' long levodopa/carbidopa intestinal gel (LCIG) treatment can improve the nighttime sleep quality in PD measured by PDSS-2 (improvement from 34.0 points to 20.9 points) [10]. Similar efficacy was observed by Kovács et al. [12]. They observed 7-point improvement (from 25 points to 18 points) on PDSS-2 total score after 6-month long LCIG treatment [12].

Recently, Deli et al. demonstrated the beneficial effects of bilateral subthalamic deep brain stimulation on the sleep quality in PD. In that study the total score of PDSS-2 decreased from 24 (median, IQR: 17–32) to 10 (median, IQR: 7–18) points ($p < 0.001$) in the population of 25 advanced PD patients [13]. Meanwhile, the number of patients having clinically troublesome sleep problems also decreased from 13 to 3. Based on our MCID estimations, all of these reported changes are also clinically meaningful.

5. Conclusions

Minimal clinically important differences are the smallest change of scores that are subjectively meaningful to patients. The results of our study estimate the minimum magnitude of change that should be sought when studies are designed using the PDSS-2 to evaluate the change over time in the sleep quality in PD. Studies using the PDSS-2 as outcome measure should utilize the threshold of −3.44 points for detecting improvement or the threshold of +2.07 points for observing worsening.

Abbreviations

CID: Clinically important difference
HYS: Hoehn-Yahr Stage
LED: Levodopa equivalent dosage
LCIG: Levodopa/carbidopa intestinal gel
LR: Likelihood-ratio
MCID: Minimal clinically important difference
MDS-UPDRS: Movement Disorders Society Sponsored Version of Unified Parkinson's Disease Rating Scale
MDS-UPDRS MC: Motor Complications (Part 4 of MDS-UPDRS)
MDS-UPDRS ME: Motor Examination (Part 3 of MDS-UPDRS)
MDS-UPDRS MEDL: Motor Experiences of Daily Living (Part 2 of MDS-UPDRS)
MDS-UPDRS nMEDL: Non-Motor Experiences of Daily Living (Part 1 of MDS-UPDRS)
PD: Parkinson's disease
PDSS-2: Parkinson's Disease Sleep Scale 2nd version
PGI-I: Patient-rated Global Impression of Improvement
PRO: Patients' reported outcome
ROC: Receiver operating characteristic
SD: Standard deviation
SEM: Standard error of measurement
SES: Schwab-England Scale.

Conflict of Interests

Krisztina Horváth reported no financial disclosure. Béla Faludi reported no financial disclosure. Zsuzsanna Aschermann received <1000 EUR consultation fees from Hungarian subsidiaries of Novartis, GlaxoSmithKline, UCB, and Teva Pharmaceutical Industries Ltd. Regarding this study the author did not receive any corporate funding. Sámuel Komoly received <1000 EUR consultation fees from Hungarian subsidiaries of Biogen, TEVA, Astellas, Pfizer, and Novartis. Regarding this pilot study the author did not receive any corporate funding. Gabriella Deli reported no financial disclosure. Péter Ács reported no financial disclosure. József Janszky received <1000 EUR consultation fees from Hungarian subsidiaries of UCB, Valeant, and Eisai. Regarding this pilot study the author did not receive any corporate funding. Norbert Kovács received <1000 EUR consultation fees from Hungarian subsidiaries of Medtronic, Boehringer Ingelheim, Novartis, GlaxoSmithKline, UCB, Krka, and Abbvie. Regarding this study the author did not receive any corporate funding.

Authors' Contribution

Krisztina Horváth participated in the research project: conception, organization, and execution; statistical analysis: design, execution, review, and critique; paper: writing of the first draft and review and critique. Béla Faludi helped in the research project: execution; statistical analysis: review and critique; paper: review and critique. Zsuzsanna Aschermann participated in the research project: organization; statistical analysis: review and critique; paper: review and critique. Sámuel Komoly helped in research project: organization; statistical analysis: review and critique; paper: review and critique. Gabriella Deli participated in research project: organization; statistical analysis: review and critique; paper: review and critique. Péter Ács participated in research project: organization; statistical analysis: review and critique; paper: review and critique. József Janszky helped in research project: conception; statistical analysis: review and critique; paper: review and critique. Norbert Kovács participated in the research project: conception, organization, and execution; statistical analysis: design, execution, review, and critique; paper: writing of the first draft and review and critique.

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Review Article

The Interaction between Obstructive Sleep Apnea and Parkinson's Disease: Possible Mechanisms and Implications for Cognitive Function

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Parkinson's disease (PD) is a relentlessly progressive neurodegenerative disorder associated with hallmark motor and nonmotor symptoms (NMS) such as sleep disturbances and cognitive dysfunction. While dopaminergic treatments have improved the motor aspects of PD, progression remains inevitable. Research has recently increasingly focused on strategies to modify disease progression and on nonmotor manifestations of PD, given their impact on patients' quality of life. Obstructive sleep apnea (OSA) is a treatable sleep disorder, common in the general population, associated with excessive daytime sleepiness and neurocognitive deficits. Neuroimaging has demonstrated structural and functional changes in OSA patients; in animal models, OSA causes brain inflammation and oxidative injury, including in key areas involved in PD pathophysiology such as locus coeruleus. The prevalence of OSA in PD has been variable in studies to date, and potential consequences and interrelationship between the two disorders have not been well studied. There is however emerging evidence that OSA is associated with increased NMS in PD, particularly cognitive dysfunction. This review focuses on the possible interrelationship between OSA and PD. Mechanisms promoting OSA in PD will be reviewed, as well as mechanisms whereby OSA can affect the neurodegenerative process in PD.

1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder, and its prevalence is expected to increase as the population ages [1]. Obstructive sleep apnea (OSA) is a treatable sleep disorder that is common in the general population and is associated with adverse outcomes including cognitive dysfunction [2]. OSA results in sleep fragmentation and intermittent hypoxemia that can have significant detrimental consequences on the brain. However, OSA prevalence in PD has been variable in studies to date in part due to methodological variability, such that until recently, OSA has not been perceived to be a significant issue in PD. Thus, to date, the potential consequences and interrelationship between OSA and PD have not been well studied. However, when already affected by a degenerative process like PD, one could speculate that the brain may be more vulnerable to the effects of OSA due to reduced ability to compensate and also more responsive to OSA treatment. In this paper, we explore the possible bidirectional relationship between OSA and PD (Figure 1). We review the possible pathophysiologic factors predisposing to OSA in the context of PD. We then review the known consequences of OSA on the brain. These data suggest that OSA may play a significant role in the neurodegenerative process of PD, particularly as it relates to cognitive dysfunction.

2. OSA Overview

OSA is characterized by recurrent complete (apnea) or partial (hypopnea) upper airway obstruction resulting in intermittent hypoxemia and arousals from sleep. Pathophysiologic

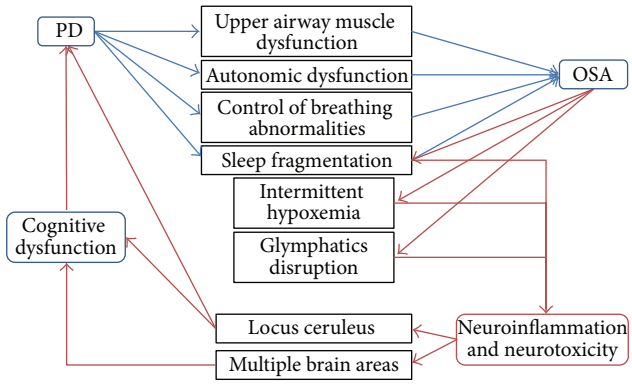

Figure 1: Hypothetical mechanistic relationship between PD and OSA. Legend. PD: Parkinson's disease; OSA: obstructive sleep apnea.

factors include reduced airway dimensions, altered central control of breathing, sleep-wake instability, altered arousal responsiveness, and upper airway dilator muscle dysfunction. The latter maintain upper airway patency and are modulated by neuronal inputs related to sleep-wake state, mechanoreceptor input, blood gases, autonomic activity, and other factors [3]. The prevalence of OSA depends on the definition of respiratory events used [4, 5] and significantly increases with age. In the general population, OSA prevalence has been estimated at 9–47% of women and 17–52% of men aged 50–70 years [6, 7]. Indeed, hypopneas in the original Wisconsin cohort study were scored as such only in the presence of a drop in hemoglobin oxygen saturation [6]. Currently recommended criteria include hypopneas associated with arousal only [8], which would lead to higher prevalence estimates [9]. OSA has been associated with a range of adverse outcomes including cognitive impairment, increased risk of hypertension, diabetes, fatal and nonfatal coronary events, arrhythmias such as atrial fibrillation and nonsustained ventricular tachycardia, congestive heart failure, stroke, and mortality (reviewed in [10]).

3. OSA in Other Neurological Disorders

OSA risk is increased with male sex, older age, and higher body mass index (BMI), but also in conditions such as neuromuscular disorders [11], epilepsy [12], multiple sclerosis [13], and stroke [14]. Moreover, in CNS disorders, OSA appears to modify the manifestations or disease course, which suggests a bidirectional relationship. For example, OSA is associated with an increased incidence of stroke [15, 16]. In turn, OSA appears to be associated with poorer outcome at discharge and up to 12 months and increased mortality at 12 months after stroke [17]. Furthermore, despite the difficulty in applying continuous positive airway pressure (CPAP) therapy in patients soon after a stroke, functional outcomes were improved in patients treated for their OSA in two randomized controlled trials (RCT) [18, 19]. In MS, we reported that OSA was associated with increased fatigue [20], which is one of the most frequent, pervasive, and incapacitating symptoms of MS. Treatment of OSA led to improved fatigue [21]. OSA has also been associated with poor seizure control in epilepsy [12]. Patients with OSA who were compliant with CPAP had reduced seizure frequency [22].

4. OSA and Cognitive Function

In addition to sleepiness, OSA in the general population and in the elderly has been associated with impaired cognition and psychomotor performance [2, 23–26]. In women, this relationship is more pronounced among carriers of the APOE 4 genotype [26]. Most commonly reported deficits in OSA are reduced executive function and attention capacity deficits such as reduced information processing speed and short-term memory span, as well as deficient verbal fluency and impaired vigilance [27, 28]. Data from prospective studies have also demonstrated that individuals with OSA at baseline were more likely to develop cognitive impairment [29, 30] and frank dementia [31] at follow-up.

The response of neurocognitive dysfunction to CPAP therapy in the general population has been variable and incomplete [32–35]. This has been suggested to stem from near-normal cognitive function before CPAP, lack of statistical power [32, 35], poor compliance with treatment [36], or irreversible brain damage from long-standing OSA [37].

A recent meta-analysis evaluating the effect of CPAP on various subtypes of executive function found a significant beneficial effect [38]. However, the APPLES trial [35], a large multicenter RCT of CPAP versus sham CPAP which evaluated three domains of cognitive function in OSA (attention and psychomotor function, learning and memory, executive, and frontal lobe function), failed to show the expected benefits. In this study, individuals with a Mini-Mental State Examination score ≤ 26 (normal cutoff in healthy adults) were excluded. Hence, only those with scores within the normal range were included, and there was little room for further improvement. The authors advanced the "cognitive reserve theory" to explain lack of positive results. That is, some individuals may have greater preexisting flexibility in neural function and capacity to cope with disruption, or better compensatory mechanisms [39]. Possibly, then, a detrimental effect of OSA on cognition may only become apparent in individuals with reduced cognitive reserve, or with another predisposing condition to cognitive dysfunction.

In Alzheimer's disease (AD), data is relatively scant and inconclusive regarding a relationship with OSA. There is a suggestion that OSA is more prevalent in AD patients than in controls [40], and severity of dementia correlates with severity of OSA [41], but not all studies have found this and the magnitude of the effect does not appear to be very large [42]. Moreover, directionality of the relationship is unclear from these cross-sectional studies. A small trial of OSA treatment with CPAP in AD found that cognition improved with CPAP use in the treated group [43] and that there appeared to be slowed deterioration of cognition with sustained use of CPAP in the observational follow-up [44].

5. OSA Prevalence in PD and Possible Pathogenic Mechanisms

Sleep disturbances are frequent in PD and include insomnia, hypersomnia, sleep architecture and circadian abnormalities, restless legs syndrome, and REM Sleep Behavior Disorder (RBD) [45]. OSA is reported to occur in 20–60% of PD subjects [46–51]. This wide range likely reflects differences in patient populations, small sample sizes with selection bias, and most importantly differences in scoring of respiratory events between laboratories [5]. In particular, studies suggesting a low prevalence of OSA in PD have included only hypopneas with desaturations [48], overlooking entirely respiratory events causing sleep fragmentation without hypoxemia. It has also been suggested that OSA prevalence in more advanced PD might be reduced compared with the general population due to lower body mass index of PD patients [52]. However, this may depend on the criteria used to define OSA, as hypoxemia is more likely to be associated with a higher BMI. OSA in PD may not follow the same pattern as in the general population. Trotti and Bliwise did not find BMI to be correlated with OSA severity in PD [51]. Correlation between OSA severity and PD severity has been found in two studies [47, 50] and in our own work [53], though causality cannot be inferred from these cross-sectional studies. While OSA does not appear to be more common in PD than the general population, it is clear that the two conditions do not uncommonly coexist, either because OSA is frequent in the general population and thus coincides with PD, or due to PD-related changes predisposing to OSA, or both.

Biologic plausibility exists for PD itself being involved in OSA pathogenesis. The upper airway musculature may be affected by involuntary movements resulting in abnormal spirometry consistent with upper airway obstruction [54], which improves with levodopa [55]. These disturbances may be exacerbated in sleep, resulting in OSA. Our group has found that PD patients on night-time long-acting levodopa had less sleep-disordered breathing than those not on such medication [56]. This further supports the notion that the upper airway is responsive to levodopa and may thus be affected as part of the movement disorder, predisposing to OSA. Levodopa may also produce disordered breathing as a form of dyskinesia [57, 58].

PD is also associated with autonomic dysfunction, which may impair control of breathing, particularly during non-REM sleep where respiration is predominantly dependent on chemical drive. Such a mechanism has been suggested as a partial explanation of the high prevalence of sleep-disordered breathing in the Shy-Drager syndrome [59, 60]. Abnormal afferent chemosensitive feedback control to the central respiratory generator has been implicated [59]. This is consistent with reports of sleep-disordered breathing, occasionally fatal, occurring in patients undergoing cervical cordotomy for pain relief, which is associated with other manifestations of autonomic dysfunction [61]. OSA itself can alter autonomic function with consequences beyond the sleep period, particularly increased sympathetic tone that is associated with baroreflex and chemoreflex changes [62, 63]. Control of breathing is affected, potentially further promoting OSA. In PD, chemosensitivity to hypoxia was found to be reduced, despite normal pulmonary function, and this was associated with reduced dyspnea in hypoxic conditions [64]. Respiratory drive in response to hypercapnia was also found to be reduced [65], possibly as a result of involvement by the PD neurodegenerative process of the brainstem [66], where the central chemoreceptor and respiratory centers are located. An abnormal hypercapnic response can predispose to hypoventilation, especially in sleep. Moreover, activity of upper airway dilator muscles, a key element in OSA pathophysiology, is modulated by respiratory drive and CO_2 levels [67, 68]. How these mechanisms affect the upper airway and respiration during sleep in patients with PD has not been directly studied.

Sleep fragmentation may itself induce respiratory disturbances. A change in sleep state such as the transition from wakefulness to sleep is associated with a change in respiration manifesting as periodic breathing, usually transient. However, in individuals with a low arousal threshold, a modest fluctuation in breathing may trigger an arousal. Arousals from sleep following a respiratory event lead to hyperpnea and hypocapnia, which in turn may trigger another respiratory pause upon return to sleep, triggering a cycle of respiratory instability, further promulgating OSA [69]. In mice, sleep fragmentation resulted in impaired arousal responses to hypercapnia [70], which could prolong apneas and hypopneas. In humans, sleep fragmentation led to increased upper airway collapsibility in sleep [71], increasing propensity for OSA. In PD, sleep fragmentation and dysfunction occur as part of the disease. This is thought to be multifactorial, due in part to dysfunctional sleep circuits but also to medications and comorbidities [72]. Hence the intrinsic sleep fragmentation in PD may be a factor in progression of OSA in this condition.

6. Mechanisms of Deleterious OSA Effects on the Brain

6.1. Intermittent Hypoxemia. The mechanisms involved in the effects of OSA on the brain in general and on cognitive function in particular have not been clearly elucidated, but several factors could play a role. OSA is increasingly being incriminated as causing neural injury. Intermittent *hypoxemia* in particular has been implicated, possibly through mechanisms of ischemia/reperfusion [73], and oxidative injury [74]. OSA with hypoxemia is also associated with delayed peripheral nerve conduction [75] and treatment of OSA partially reverses the dysfunction [76]. In animal models, exposure of rodents to intermittent hypoxemia resulted in impaired learning and memory that did not normalize after a recovery period. Increased astrocytes and neuronal apoptosis were found in frontal cortex areas (including cingulate gyrus) and certain hippocampal regions, implying differential neuronal susceptibility [77]. Reduction in striatal norepinephrine concentration was also shown as a result of intermittent hypoxemia [78], as well as injury in specific catecholaminergic neuron groups, notably the dopaminergic periaqueductal gray and locus coeruleus [79]. NADPH

oxidase [80] and iNOS [73] were found to mediate this injury and the associated proinflammatory response. The proinflammatory transcription factor NF-κB is also induced by intermittent hypoxemia in OSA [81, 82] causing systemic inflammation. Evidence of systemic inflammation in OSA was found with elevated plasma levels of C reactive protein [83], TNF-α, interleukin- (IL-) 6 [84, 85], and IL-8 [86]. IL-6 and TNF-α levels correlated with OSA severity [87]. This likely contributes to neuroinflammation [88] which promotes neurodegeneration [89, 90]. Although these OSA-related mechanisms might theoretically exacerbate PD neuropathology, they have not been studied to date in PD.

Intermittent hypoxemia in mice has also been found to be associated with reduced expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and reduced long-term potentiation [91]. This could explain some cognitive deficits, as reduced BDNF levels have been associated with impaired cognition [92, 93]. However, in humans, serum BDNF levels were no different in OSA versus control subjects [94].

It should be noted that while OSA-related hypoxemia in humans has been associated with cognitive deficits in some studies [95, 96], others have found a paradoxical apparently protective effect [97]. Recent data suggest that there may be an ischemic preconditioning effect in some OSA patients [98]. Hence the exact role of hypoxemia as a cause of cognitive deficit in humans remains to be clarified, though severity of the intermittent hypoxia likely plays a role [88]. In PD hypoxemia associated with OSA is less marked as compared with non-PD individuals [48]. This is due to the lower BMI of PD patients with OSA. However, individuals earlier in the course of their PD may have a higher BMI, including before diagnosis, and hypoxemia might be a more important factor in that setting. Moreover, it is unknown what level of hypoxemia might be considered "safe" in PD. It is possible that what is inconsequential or protective in an otherwise healthy brain may be deleterious in PD. More research will be needed to clarify these relationships.

6.2. Sleep Fragmentation. In addition to hypoxemia, OSA is associated with *sleep fragmentation*, which appears to be a key factor in brain dysfunction and cognitive outcomes. Some deficits in OSA are similar to those occurring in sleep deprivation [99]. In a longitudinal study of elderly individuals, sleep fragmentation related to OSA, but not hypoxemia, was associated with cognitive decline [30]. Sleep fragmentation due to OSA was also found to be the best predictor of episodic memory deficits [100]. In mice, sleep fragmentation results in learning deficits. This was found to be associated with increased gene expression and activity of NADPH oxidase in the hippocampus and cortex of wild type mice [101]. However, mutant mice lacking NADPH oxidase activity were protected from the learning deficits. Chronic sleep fragmentation was also found to selectively increase cortical expression of TNF-α [102]. Moreover sleepiness and learning deficits associated with sleep fragmentation were absent in TNF-α double receptor knockout mice and in mice treated with a TNF-α neutralizing antibody [102]. Hence, sleep fragmentation appears to induce oxidative stress and inflammation just as intermittent hypoxia does. Interestingly, in a sleep fragmentation animal model of OSA, there was reduced neuronal excitability in the locus coeruleus [70], an area implicated in PD pathophysiology (compare with below).

6.3. Glymphatics. Recently a novel waste clearance system operating in the brain has been characterized, termed the glymphatic system [103]. It involves transport of CSF along periarterial spaces, via convective flow through the brain parenchyma and perivenous spaces into the cervical lymphatic system, eliminating soluble proteins and metabolites. Its function declines with age and this has been suggested to contribute to the accumulation of abnormal proteins in the extracellular space, such as β-amyloid or α-synuclein, rendering the brain more vulnerable to neurodegenerative pathologies. The particularity of this system is that it is activated only during sleep. Therefore, any process leading to sleep fragmentation can disrupt this system, resulting in potentially adverse consequences on brain homeostasis. It is known that dementia in PD often results from an "admixture of pathologies" [104–106], including Lewy body but also Alzheimer-related pathologies, with a smaller component of cerebrovascular pathology. One could therefore speculate that glymphatic abnormalities may be a nonspecific mechanism predisposing to cognitive dysfunction in PD. Glymphatics could be affected by sleep fragmentation or hemodynamic changes occurring in OSA. Intermittent hypoxia has also been implicated in potential blood-brain barrier dysfunction and alteration in brain water and solute fluxes, through a number of mechanisms stemming from a chronic maladaptive response [88].

6.4. Role of the Locus Coeruleus. The locus coeruleus has been implicated in cognitive decline in the general population. A recent autopsy study from a longitudinal clinical-pathologic cohort study on aging found that lower locus coeruleus neuronal density was associated with lower baseline level of cognition and faster cognitive decline [107]. An imaging study showed that locus coeruleus connectivity was correlated with memory scores and was reduced in patients with mild cognitive impairment [108]. With regards to PD, a recent case series and review by Del Tredici and Braak [104] focused on the role of noradrenergic defects in the locus coeruleus in development of dementia in PD.

The effects of intermittent hypoxemia and sleep fragmentation on the locus coeruleus and other specific brain regions, as described above, may have significant implications in PD. While the key abnormality in PD pathophysiology is loss of dopaminergic neurons of the substantia nigra, resulting in depletion of dopamine from the basal ganglia, other regions of neurodegeneration have been identified, which may better correlate with the nonmotor symptoms of PD [109, 110]. Locus coeruleus neurons specifically have been implicated in pathophysiology of PD: loss of their trophic influences may increase sensitivity of dopaminergic neurons to neurotoxic insults [111, 112]. The currently emerging concept of PD pathogenesis revolves around a combination of genetic, cellular, and environmental factors

that independently or concomitantly result in cell death, possibly by triggering mitochondrial dysfunction and oxidative stress, abnormal protein degradation, and other forms of subcellular dysfunction [113]. After disease onset, regardless of the initial insult, the progression of cell loss may result from common pathways that include oxidative and nitrosative stress and neuroinflammation [113–115]. Neuroinflammation appears to play a key part in pathogenesis of PD. Nonsteroidal anti-inflammatory drugs decrease the risk of PD [116], and inflammatory cytokines are increased in the serum and/or cerebrospinal fluid of PD patients [IL-2, TNFα, IL-6, RANTES, osteopontin, and IL-1β]. In PD animal models, intranigral infusion of TNFα blockers attenuated dopaminergic neurodegeneration, while mice lacking TNF receptors 1 and 2 had attenuated striatal damage after injection of MPTP [115]. In the process of neuroinflammation, microglia became activated and capable of antimicrobial and toxic functions: damage to dopaminergic neurons can occur through reactive oxygen and nitrogen species, produced, respectively, by NADPH oxidase and inducible NO synthase (iNOS) [90]. As described above, activation of oxidative and nitrosative processes has been described in OSA. OSA, therefore, could be an additional insult on an already vulnerable brain, promoting the inflammatory neurodegenerative mechanisms and accelerating functional decline.

While no human studies exist looking at the locus coeruleus in OSA, animal data suggest OSA may reduce the noradrenergic locus coeruleus neuronal population and impair its function [70, 79, 117] (compare with sections on Intermittent hypoxemia and Sleep Fragmentation). While the focus of this review is on cognitive function, it can be inferred from the above that OSA, through its effects on the locus coeruleus, could affect the pathogenesis of PD. The implication is that OSA may not only promote decline in cognitive function, but also accelerate the overall disease process. This could include worsening of motor dysfunction in those with established PD and promoting development of overt PD in those with subclinical disease or with another predisposing factor (e.g., genetic). Indeed, recent epidemiological evidence suggests that OSA increases the risk of PD [118, 119].

7. Sleep and Cognitive Function in PD

Cognitive dysfunction is found in 20–40% of patients with early PD but is a major cause of long-term disability [113]. In one large study, after 20 years' follow-up, 83% of survivors had dementia [120]. The most commonly documented deficits in early PD are in executive "frontal" functions [121, 122] and memory [123, 124].

Sleep is a state that is crucial for proper cognitive function. It allows for consolidation of declarative memory [125] and of "implicitly" learned motor skills [126]. Implicit learning is dependent on attention [127] and is sensitive to sleep effects [128]. Poor sleep quality affects memory consolidation [129] and executive function [130, 131] in older adults. Changes in sleep EEG characteristics (sleep spindles and slow waves) with aging have been implicated in reduction in sleep-dependent memory consolidation in older adults [129].

Studies looking at sleep and sleep disorders in PD have found that subjective daytime sleepiness and fatigue are linked with cognitive impairment [132]. Presence of RBD is also linked with worse cognitive function [133, 134]. Poor sleep efficiency as measured by actigraphy has been variably associated with executive dysfunction [135] and memory deficits [136]. A recent meta-analysis has found multiple cognitive domains to be affected by poor sleep in PD [137], though most studies relied on self-reported sleep quality. Regarding implicit learning, PD patients appear not to have the expected improvement in motor skill following sleep [138, 139]. Hence, disrupted sleep, though a nonspecific symptom, appears to be an important factor in poor cognitive function and learning in PD. A recent study has found that specific sleep EEG (sleep spindle) alterations in PD are associated with subsequent development of dementia [140]. These alterations may be a marker of future dementia but it is unclear if sleep changes could be a causative factor in cognitive decline. Further work will need to be done to assess whether strategies aimed at improving sleep quality can reduce the risk of dementia.

8. Neuroimaging in relation to Cognitive Function in OSA and PD

Structural and functional changes on brain imaging associated with neurocognitive deficits have been found in OSA patients [23, 33, 141–143]. They include decreased grey matter in the hippocampus and temporal lobe, anterior cingulate, and cerebellum, as well as in the frontal and parietal lobes. CPAP therapy appears to increase gray-matter volume in hippocampal and frontal structures [33]. In PD, cortical atrophy in the hippocampus and frontal areas has been found in patients with mild cognitive impairment (MCI), but not in cognitively intact PD patients [144]. Most studies report a correlation of temporal lobe atrophy with poor memory in PD [145, 146], but some find a correlation between memory problems and frontal regions [147], or with medial temporal and frontal lobes [145]. It is conceivable that the variability in results is related at least partly to confounding effects of OSA, which was not accounted for in those studies. In that similar brain regions have been found to be affected in OSA, particularly temporal and frontal areas [33, 141]; OSA may contribute significantly to the cortical atrophy patterns identified in PD-MCI.

Functional neuroimaging in OSA has revealed decreased brain activation in cingulate, frontal, and parietal regions during performance of sustained attention and memory tasks [23, 141, 148]. In PD, poor performance on memory and executive function tests was associated with metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei, using FDG PET [149]. Other studies also report recruitment of additional pathways for the performance of certain cognitive tasks in PD, suggesting an adaptive compensatory response [150, 151], which has also been found in OSA [152, 153]. CPAP therapy, in one study [153], decreased OSA-related overactivation of prefrontal and hippocampal structures. Hence, both OSA and PD are independently associated with altered CNS activation

during cognitive tasks, which may be reversible in the context of OSA. Activation patterns in patients with PD and OSA have not been studied.

9. Preliminary Data on Impact of OSA in PD

Little literature exists on outcomes related to OSA in PD. In one study, OSA was found to have a greater influence on memory consolidation in subjects with PD than in otherwise healthy OSA controls [154]. In another, working memory improvements after sleep showed a negative correlation with hypoxemia [155]. Our own preliminary data suggest that OSA is associated in PD patients with self-reported hypersomnolence and lower Montreal Cognitive Assessment (MoCA) scores [53], after adjusting for possible confounders. In an observational study, we have found that CPAP treatment of OSA led to an improvement in MoCA scores in PD patients with OSA but not those untreated or without OSA [156]. Neikrug et al., in the only RCT of OSA treatment in PD published to date, found that CPAP therapy was well tolerated and resulted in improved sleep architecture, as well as in reduced daytime sleepiness [157]. Despite the potential difficulties in applying CPAP therapy to PD patients, these promising results support further studies in this area.

10. Conclusion

Clearly, many questions remain and further work in this area will be necessary to clarify the role of OSA in PD. In a possible bidirectional relationship, OSA is potentially both a manifestation of PD, as well as a factor contributing to its signs and progression. Large prospective cohort studies will be needed to evaluate the impact of OSA on progression of PD-related cognitive dysfunction, as well as motor dysfunction. OSA has the merit of being largely correctable, such that effective treatment can readily improve its symptoms. RCTs will be needed to assess the effect of OSA therapies in PD. Treatment typically includes CPAP, though possibly other modalities could be more effective in PD than in the general population, given the somewhat different pathophysiology of OSA in PD. Moreover, if a deleterious effect of OSA on PD progression is confirmed, OSA treatment could be evaluated as a disease-modifying therapy, which could potentially delay cognitive decline or motor dysfunction.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Restless Legs Syndrome and Leg Motor Restlessness in Parkinson's Disease

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Sleep disturbances are important nonmotor symptoms in Parkinson's disease (PD) that are associated with a negative impact on quality of life. Restless legs syndrome (RLS), which is characterized by an urge to move the legs accompanied by abnormal leg sensations, can coexist with PD, although the pathophysiology of these disorders appears to be different. RLS and PD both respond favorably to dopaminergic treatment, and several investigators have reported a significant relationship between RLS and PD. Sensory symptoms, pain, motor restlessness, akathisia, and the wearing-off phenomenon observed in PD should be differentiated from RLS. RLS in PD may be confounded by chronic dopaminergic treatment; thus, more studies are needed to investigate RLS in drug-naïve patients with PD. Recently, leg motor restlessness (LMR), which is characterized by an urge to move the legs that does not fulfill the diagnostic criteria for RLS, has been reported to be observed more frequently in de novo patients with PD than in age-matched healthy controls, suggesting that LMR may be a part of sensorimotor symptoms intrinsic to PD. In this paper, we provide an overview of RLS, LMR, and PD and of the relationships among these disorders.

1. Introduction

Sleep disturbances are one of the major nonmotor symptoms in Parkinson's disease (PD) that affect a significant number of patients and result in an impaired quality of life. These disturbances can occur in the early or even in the premotor phase of PD but are often underrecognized by patients and physicians. The evaluation of sleep disturbances in PD is complicated by complex, overlapping nocturnal problems including nocturnal motor and nonmotor problems in addition to disease-related alterations of the sleep/wake cycle [1]. Restless legs syndrome (RLS), which is characterized by an urge to move the legs accompanied by abnormal leg sensations, can coexist with PD. A significant number of PD patients who suffer from RLS exhibit delayed sleep onset [2], and PD patients with RLS are reported to have more severe sleep problems than PD patients without RLS [3]. The prevalence of RLS in the general adult population in Europe and the USA is approximately 7–10% [4], while the prevalence in Asia is reported to be 1–4% [5–7]. The marked clinical response to dopaminergic agents in RLS, together with the results of a lesioning study that examined the effects of 6-hydroxydopamine injections into A11 dopaminergic neurons in rats [8], suggests that central dopaminergic dysfunction plays a role in RLS; however, pathological evidence supporting dopaminergic involvement in the brain is lacking. In contrast, PD is characterized by resting tremor, bradykinesia, rigidity, and postural instability, which are caused by dopaminergic cell loss in the substantia nigra, as demonstrated by both pathological and imaging studies. Dopaminergic treatment improves motor symptoms and several aspects of nonmotor symptoms in PD patients. Several studies have reported that the prevalence of RLS is more frequent in PD patients compared with control subjects, suggesting a significant link between the two disorders. However, the reported prevalence of RLS in PD patients ranges from 0 to 50%, depending on the study [9]. Importantly, no valid RLS criteria exist for PD patients, and whether RLS criteria for the general population are also suitable for PD patients has yet to be determined [10]. Immobility due to parkinsonism may augment subtle RLS symptoms,

and several motor and sensory symptoms related to PD are difficult to distinguish from RLS. When dopaminergic therapy effectively treats RLS symptoms in PD patients, the prevalence of RLS in PD may be underestimated; thus, RLS in PD may be confounded by chronic dopaminergic treatment. Despite the similarly positive response to dopaminergic treatment and presumed central dopaminergic dysfunction in both RLS and PD, different mechanisms are suggested to be involved in the pathogenesis of PD and RLS. A recent study reported that leg motor restlessness (LMR) that does not fulfill the diagnostic criteria for RLS is more prevalent in de novo patients with PD than in healthy controls [11]. To examine the occurrence and characteristics of RLS and LMR in PD and understand the relationships between these disorders, we have conducted a literature search for articles published between January 1984 and November 2014 using MEDLINE and the terms "Parkinson's disease," "restless legs syndrome," and "leg motor restlessness." Among the 364 articles identified, we included articles based on their relevance to RLS and LMR in PD and important papers cited within these articles. In this paper, we provide an overview of RLS, LMR, and PD and of the relationships among these disorders.

2. The Diagnosis of RLS

In accordance with the NIH/IRLSSG diagnostic criteria published in 2003, RLS is diagnosed when four essential symptoms are present: (1) an urge to move the legs is usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity, such as when lying down or sitting; (3) the urge to move or the unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, as long as the activity continues; and (4) the urge to move or the unpleasant sensations are worse in the evening or at night than during the day or only occur in the evening or at night [12]. Additional findings that support the diagnosis of RLS include a positive family history of RLS, a positive therapeutic response to dopaminergic drugs, and the presence of periodic limb movements during wakefulness or sleep. The revised IRLSSG criteria for RLS, published in 2014, added a fifth diagnostic criterion that the occurrence of the four other diagnostic criteria cannot be accounted for solely by symptoms of another medical or behavioral condition as shown below [4]. This additional criterion increases the specificity of the RLS diagnostic criteria. In addition, hyperarousal producing poor sleep without daytime sleepiness has been described in patients with RLS, which is reflected in the fourth finding that supports the diagnosis of RLS, a "lack of profound daytime sleepiness" as shown below.

IRLSSG Consensus Diagnostic Criteria for Restless Legs Syndrome/Willis-Ekbom Disease (RLS/WED) [4]

(a) Essential Diagnostic Criteria (All Must Be Met). Consider the following

(1) An urge to move the legs is usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs.

(2) The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.

(3) The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

(4) The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.

(5) The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, and habitual foot tapping).

(b) Supporting Features. Consider the following

(1) Periodic limb movements (PLM): presence of periodic leg movements in sleep (PLMS) or resting wake (PLMW) at rates or intensity greater than expected for age or medical/medication status.

(2) Dopaminergic treatment response: reduction in symptoms at least initially with dopaminergic treatment.

(3) Family history of RLS/WED among first-degree relatives.

(4) Lack of profound daytime sleepiness.

RLS patients usually complain of fatigue, reduced concentration, and depressive symptoms, which are suggestive of the consequences of sleep deprivation; however, excessive daytime sleepiness is uncommon in RLS patients, except in patients with severe RLS symptoms [4]. In contrast, according to the international classification of sleep disorders (third edition) [13], for RLS to be diagnosed, patient's symptoms must affect his or her sleep and daytime functioning, although this criterion may be omitted for certain research applications, such as genetic or epidemiological studies.

3. The Pathophysiology of RLS

The pathophysiology of idiopathic RLS remains unclear; however, the following mechanisms have been postulated: dopamine-related mechanisms, including reductions in striatal D2 receptor levels; iron-related mechanisms, including reductions in iron and ferritin levels in the cerebrospinal fluid (CSF) and genetic factors associated with altered brain iron levels; and altered microvascular flow in the legs [14–16]. Importantly, iron is a cofactor of tyrosine hydroxylase, which is the rate-limiting enzyme in the synthesis of dopamine. A study measuring oxygen and carbon dioxide partial pressures in the legs showed that peripheral hypoxia is associated

with the appearance of RLS symptoms [15]. RLS patients exhibit lower ferritin levels and higher transferrin levels in the cerebrospinal fluid compared with control subjects; however, in the serum, ferritin and transferrin levels do not differ between RLS patients and control subjects [17]. Mizuno et al. [18] also reported no difference in serum iron, ferritin, and transferrin levels between RLS and non-RLS patients (psychological insomnia without RLS); in contrast, CSF iron and ferritin levels were significantly reduced and CSF transferrin levels were significantly increased in the RLS group compared with the non-RLS group. However, a weaker correlation between the CSF and serum ferritin levels in the RLS group suggests that impaired iron transport from the blood to the central nervous system may contribute to low brain iron concentrations in idiopathic RLS. These studies support the hypothesis that reduced CSF ferritin levels play a role in RLS. In addition, the endogenous opiate system may be involved in the pathogenesis of RLS, considering its ability to affect RLS symptoms [19].

According to a hypothesis about the pathogenesis of RLS reviewed by Clemens et al. [20], the hypothalamic dopaminergic A11 cell group projects to the neocortex, the serotonergic dorsal raphe nucleus, and the spinal cord, most strongly to the sensory dorsal horn and the intermediolateral nucleus of the spinal cord. The A11 nucleus exerts inhibitory controls in these areas; thus, dysfunction of the A11 nucleus or of these pathways is thought to lead to an increased sympathetic drive and the occurrence of abnormal sensations, focal akathisia, and muscle restlessness, contributing to the emergence of RLS. However, Earley et al. [21] investigated the A11 cell bodies in 6 RLS and 6 aged-matched control autopsy cases and found no dramatic cell loss or neurodegenerative process in the A11 hypothalamic region of patients with RLS. In the 4 autopsy cases of RLS, Lewy bodies were not found, and immunohistochemistry did not reveal accumulations of alpha-synuclein [22]. Connor et al. [23] reported that, in RLS autopsy cases, decreases in D2 receptor levels that correlated with RLS severity were observed in the putamen, and increased tyrosine hydroxylase levels were found in the substantia nigra but not in the putamen compared with controls. The authors suggested that their results were consistent with the finding that dopaminergic systems are activated in an animal model of iron insufficiency.

A study by Allen et al. [24] using proton magnetic resonance spectroscopy has demonstrated that increased glutamatergic activity is associated with the arousal sleep disturbance in RLS. This nondopaminergic abnormality may be responsible for sleep disruption in RLS patients and the observation that RLS patients rarely exhibit excessive daytime sleepiness despite sleep loss.

4. Imaging in RLS

Allen et al. [25] assessed brain iron concentrations in 5 RLS and 5 control patients using a specific MRI measurement and showed that the iron content in the red nuclei and the substantia nigra was decreased in the RLS patients compared with the controls. The study, conducted using 3.0-Tesla MRI and T2 relaxometry, found that the iron index in the substantia nigra was lower in patients with late-onset RLS (onset age ≥45 years) than in controls, whereas no difference in the iron index was found between the controls and patients with early-onset RLS (onset age <45 years) [26]. Brain imaging studies evaluating dopaminergic dysfunction in RLS patients have yielded inconclusive results. SPECT/PET studies have shown that nigrostriatal functions and ligand binding to the striatal dopamine transporters (DAT) and D2 receptors are normal in RLS [27–30], while other studies have found a reduced ability of D2 receptors to bind ligands and reduced 18F-dopa uptake in the striatum and putamen [31, 32]. In a study that examined real-time DAT binding potentials, RLS patients exhibited decreased DAT binding in the striatum in both day and night scans, suggesting that membrane-bound striatal DAT but not total cellular DAT is decreased in RLS [33]. Reduced echogenicity in the substantia nigra has been reported in RLS patients compared with healthy controls and PD patients [34, 35].

5. RLS and PD

In view of the marked response to dopaminergic treatment in both RLS and PD, the relationship between PD and RLS has been investigated previously. Although the prevalence of RLS among PD patients varies widely (0–50%), depending on the study [9], several studies have found an increased prevalence of RLS in PD patients compared with controls. Several conditions observed in PD, including sensory symptoms, pain, motor restlessness, akathisia, and the wearing-off phenomenon, should be differentiated from RLS. However, no specific diagnostic criteria for RLS exist for PD patients; thus, an immobilization test to diagnose RLS in PD patients may be useful [36].

Similarities between PD and RLS include a marked response to dopaminergic agents, aggravation by dopaminergic antagonists, and an association with periodic limb movements in sleep. The differences between the two conditions include normal presynaptic nigrostriatal dopaminergic function, as shown by neuroimaging, and no neuronal loss in the substantia nigra in idiopathic RLS patients, whereas in PD, substantial neuronal loss in the substantia nigra and abnormal neuroimaging findings in the nigrostriatal dopaminergic system have been demonstrated [37]. In subjects with both PD and RLS, a significantly increased area of echogenicity in the substantia nigra was found compared with the controls and subjects with idiopathic RLS, suggesting the existence of different mechanisms for regulating brain iron in the idiopathic RLS patients and PD patients with RLS [38, 39]. In addition, significant increased echogenicity was detected in the substantia nigra in PD patients compared with the controls and the idiopathic RLS patients, but no significant difference in substantia nigra echogenicity was found between PD patients with RLS and PD patients without RLS [38, 39].

Table 1 summarizes the prevalence and relevant features of RLS and leg motor restlessness (LMR) in PD patients [2, 3, 11, 40–57]. RLS symptoms appear to be milder in PD-RLS

Table 1: RLS and leg motor restlessness (LMR) in PD.

Author	Year	Country	PD/control	RLS (%) PD/control	LMR (%) PD/control	Characteristics of PD/RLS
Ondo et al. [40]	2002	USA	303/—	20.8/—	—	Lower serum ferritin levels. Older age at RLS onset, less frequent family history
Tan et al. [41]	2002	Singapore	125/—	0/—	15.2/—	1 (0.8%) had RLS-like symptoms correlated with wearing off
Krishnan et al. [2]	2003	India	126/128	7.9/0.8	—	Older, higher rate of depression
Braga-Neto et al. [42]	2004	Brazil	86/—	49.9/—	—	Longer disease duration of PD
Calzetti et al. [61]	2009	Italy	118/110	12.7/6.3	—	Absence of a comorbid association between RLS and PD
Nomura et al. [3]	2006	Japan	165/131	12.1/2.3	—	Insomnia (PSQI), younger age
Gómez-Esteban et al. [43]	2007	Spain	114/—	21.9/—		Sleep disturbance (PDSS)
Loo and Tan [44]	2008	Singapore	200/200	3.0/0.5	—	Slightly younger age
Lee et al. [45]	2009	Korea	447/—	16.3/—	—	Longer disease duration and dopaminergic treatment, more severe disability, and cognitive decline
Peralta et al. [46]	2009	Austria	113/—	24.8/—	—	Younger, earlier onset of PD, lower levodopa-equivalent dosages, and wearing off
Verbaan et al. [47]	2010	Netherlands	269/—	11.0/—	—	No increased frequency of RLS in PD patients RLS severity correlated with PD severity, motor fluctuations, depressive symptoms, daytime sleepiness, cognitive problems, autonomic symptoms, and psychotic symptoms.
Angelini et al.* [48]	2011	Italy	109/116	5.5/4.3	—	No increased frequency of RLS in drug-naïve PD patients
Gjerstad et al.* [11]	2011	Norway	200/173	15.5/9.2	25/8.7	Sleep disturbance (PDSS), depressive symptoms
Suzuki et al. [49]	2012	Japan	93/93	5.5/2.2	32.3/14.0	Higher UPDRS-3 score, depressive symptoms, sleep disturbance (PDSS-2), and impaired QOL
Shimohata and Nishizawa [50]	2013	Japan	158/—	11.4/—	19.0/—	Sleep disturbance, daytime sleepiness
Rana et al. [51]	2013	Canada	127/127	21.3/4.7	—	Pain was reported at a higher rate
Bhalsing et al. [52]	2013	India	134/172	11.9/2.9	—	Sleep disturbance (PDSS)
Shin et al.* [53]	2013	Korea	151/—	16.6/—	—	Severe disease, tremor
Azmin et al. [54]	2013	Malaysia	113/—	9.7/—	—	Younger age of onset of PD, male gender, higher MMSE score, and less advanced HY stage
Rajabally and Martey [55]	2013	UK	37/37	16.2/10.8	40.5/16.2	No correlation with neuropathy or symptomatic neuropathy, cumulative levodopa exposure, or serum vitamin B12 levels in patients with PD
Oh et al.* [56]	2014	South Korea	225/—	16.0/—	—	Supine/nocturnal hypertension
Fereshtehnejad et al. [57]	2015	Iran	108/424	14.8/7.5	—	A higher anxiety score, worse nutritional status, and poorer QOL

*The studies assessing untreated PD patients.

HY: Hoehn and Yahr; LMR: leg motor restlessness; MMSE: Mini-Mental State Examination; PD: Parkinson's disease; PDSS: Parkinson's Disease Sleep Scale; PSQI: Pittsburgh Sleep Quality Index; QOL: quality of life; RLS: restless legs syndrome; UPDRS: Unified Parkinson's Disease Rating Scale.

patients compared with idiopathic RLS patients [40]; among 20 PD patients with RLS, only 3 patients requested treatment for RLS [3]. The risk factors for RLS in PD patients vary and include insomnia, depressive symptoms, cognitive impairment, longer disease duration, a higher dose of dopaminergic treatment, younger/older age, younger-onset PD, older-onset RLS, and severe or mild severity of PD, depending on the study (see Table 1). A family history of RLS appears less frequently in PD patients with RLS than in idiopathic RLS patients [40]. A recent study found correlations between RLS and both nocturnal/supine hypertension and blood pressure fluctuations in newly diagnosed PD patients, suggesting the existence of cardiovascular and autonomic impairments in PD patients with RLS [56]. Peralta et al. [46] reported that, in 113 PD patients, comorbid RLS was associated with younger PD age of onset, lower levodopa-equivalent doses, and the presence of the wearing-off phenomenon (61%). Verbaan et al. [47] found that 11% of 269 patients with PD had RLS, and no differences were observed between the PD with RLS and PD without RLS groups, with the exception of female predominance in the PD with RLS group. The authors speculated that dopaminergic treatment may have led to the RLS prevalence being underestimated in PD patients. In contrast, Lee et al. [45] found that a longer duration of dopaminergic treatment was the most significant factor related to the presence of RLS in PD patients. RLS severity, as rated by the International RLS Scale, was significantly improved following subthalamic nucleus deep brain stimulation (STN-DBS) together with a reduction in dopaminergic treatment in PD patients [58], suggesting that dopamine receptor overstimulation may result in the emergence of RLS in PD. In RLS patients, prolonged dopaminergic treatment may result in augmentation, characterized by an overall increase in the severity of RLS symptoms [59] in which overstimulation of the D1 dopamine receptors compared with the D2 receptors in the spinal cord by dopaminergic treatment has been proposed as the mechanism [60]. In contrast, in PD patients, chronic dopaminergic treatment is associated with the development of dyskinesia and motor fluctuation rather than RLS, which are not observed in RLS patients. Chronic dopaminergic treatment may lead to augmentation of previously unrecognized RLS in PD patients; however, this hypothesis should be confirmed by additional studies comparing the incidence of RLS between untreated PD patients and treated PD patients prospectively.

A questionnaire-based study of a large sample of PD patients ($n = 661$) showed that the presence of RLS, nightmares, hallucinations, and sleep talking was associated with probable REM sleep behavior disorder (RBD), as defined by an RBD screening questionnaire score ≥ 6 [62]. A negative impact of RLS on the quality of life in PD patients has been described previously [57].

The effect of STN-DBS on RLS symptoms in patients with PD is difficult to interpret, considering the reductions in dopaminergic medication dosages following surgery. Kedia et al. [63] found that 5.6% of 195 PD patients who underwent STN-DBS experienced new, problematic RLS. The total daily amounts of PD medications were reduced after DBS by a mean of 74%, suggesting that reductions in PD medication doses may have unmasked RLS in DBS-treated PD patients. In contrast, 6 advanced-stage PD patients with RLS reported significant improvements in RLS symptoms following STN-DBS surgery, despite a mean 56% decrease in the levodopa-equivalent dose postoperatively [64]. Similarly, Chahine et al. [58] observed that STN-DBS ameliorated not only RLS symptoms but also other symptoms, such as daytime sleepiness and sleep quality.

Thus, an assessment of RLS in drug-naïve patients with PD may provide a more accurate understanding of the associations between PD and RLS. Two case-controlled studies showed that the prevalence of RLS in drug-naïve PD patients was not significantly greater than that observed in healthy controls [11, 48]. In two other studies that investigated drug-naïve PD patients, the prevalence of RLS was found to be approximately 16%, which appears to be greater than the prevalence of RLS in the general population in Asia [53, 56]; however, those studies did not include control subjects. Further studies including large samples of drug-naïve PD patients are required to determine whether a significant association between RLS and PD exists.

Most studies have suggested that the onset of RLS follows the onset of PD (70–95%) [3, 40, 46], and, unlike the situation with RBD, there is insufficient evidence to suggest that RLS is a risk factor for the subsequent emergence of PD. Wong et al. [65] have reported the development of PD in men following severe RLS symptoms (>15 times/month). However, this study suggests that severe RLS symptoms may represent an early feature of PD rather than a risk of developing PD.

Rios Romenets et al. [66] investigated the relationship between RLS and the use of domperidone, a peripheral dopamine blocker that does not cross the blood-brain barrier, and found that RLS was more prevalent in PD patients taking domperidone than in PD patients not taking domperidone (48% versus 21%). The authors speculated that dopaminergic receptors located outside the blood-brain barrier or circumventricular organs in the brain may be involved in the pathogenesis of RLS in PD.

6. RLS Mimics in PD

In PD, the following conditions can mimic RLS: akathisia, the wearing-off phenomenon, pain, dystonia, inner tremor, and sensorimotor symptoms related to PD, as well as restlessness in the legs, such as LMR [37, 60, 67, 68]. It is important to distinguish wearing-off-related restlessness from RLS. Akathisia, a condition typically associated with exposure to neuroleptic medications, is characterized by inner restlessness affecting the whole body rather than only the legs and does not vary diurnally. Patients with akathisia feel compelled to move because of inner restlessness rather than an "urge to move the legs" [69]. In 100 patients with PD, 68% experienced a need to move and an inability to remain still due to parkinsonism and sensory complaints, and 26 patients experienced a state of true akathisia [70]. Another study found that among 56 consecutive PD patients, 45% exhibited akathisia, and the presence of akathisia in these patients was associated with disease severity and the age of onset of PD

[71]. Akathisia can be observed in untreated PD patients, but it is usually associated with the initiation of treatment with PD medications and is more common in treated PD patients [68]. Importantly, in PD patients, the overlap between RLS, wearing-off-related lower limb discomfort and restlessness, and akathisia may complicate the clinical assessment and diagnosis of true RLS [68].

7. Variants of RLS in PD

In RLS, body parts other than the legs, such as the arms and trunk, may also be involved [12]. With the exception of severe RLS cases, the involvement of these regions as an isolated or initial sign is rare. Patients with restlessness in body parts other than the legs, including the arms [72], bladder [73], chest [74], back [75], abdomen [76], and genital regions [77], with or without restlessness in the legs, have been described. We reported an 82-year-old man with PD who presented with an abnormal sensation limited to his "lower back" [75]. The patient complained of an urge to move his lower back, and symptoms occurred in the evening and while at rest. His symptoms completely resolved following the administration of a low-dose dopamine agonist at bedtime, and he had no motor fluctuation or dystonia, suggesting that the patient had a variant of RLS, "restless lower back." Aquino et al. [77] described a 65-year-old woman with PD who had disabling discomfort in her pelvis and genital region. The symptoms occurred only during the evening and at night and were triggered by sitting down or lying down, resulting in insomnia. A low-dose dopamine agonist markedly improved her genital symptoms. However, whether restlessness occurring in body parts other than the legs is truly associated with RLS remains to be determined. In view of the dramatic response to dopaminergic medication at bedtime in these patients, recognition and awareness of restlessness in body parts other than the legs are clinically important.

8. Leg Motor Restlessness in PD

Interestingly, Gjerstad et al. [11] found an increased rate of leg motor restlessness (LMR) that did not fulfill RLS diagnostic criteria in drug-naïve PD patients compared with age-matched healthy controls; however, the prevalence of RLS did not significantly differ between the PD patients and healthy controls. LMR was defined as an urge to move the legs that did not fulfill the 4 essential criteria for RLS. These authors concluded that LMR but not RLS occurs with a nearly 3-fold higher risk in early PD compared with the controls. As shown in Table 1, the prevalence of LMR is higher in PD patients than in controls. In our study, we found a significantly higher prevalence of nocturnal restlessness, as measured by the scores on subitems 4 and 5 of the PD sleep scale-2, in PD patients compared with controls, but the prevalence of RLS did not significantly differ between PD patients and controls [49]. When nocturnal restlessness was defined by a sum of the scores for items 4 and 5 equal to or greater than 2, the prevalence of nocturnal restlessness was found to be 32.3% and 14.0% in PD patients and controls, respectively (see Table 1). Nocturnal restlessness was associated with the PDSS-2 total score but not with disease severity, motor function, motor complications, dopaminergic treatment duration, or total levodopa-equivalent dose, suggesting that nocturnal restlessness may be related to endogenous dopamine deficits at nighttime rather than medication-related motor complications. However, it should be noted that nocturnal restlessness as measured by the PDSS-2 may be a reflection of LMR, but a high score response (very often) on items relevant to LMR may reflect symptoms unrelated to LMR. Rajabally and Martey [55] investigated the relationship between LMR, RLS, and neuropathy as evaluated using a validated neuropathy scale in PD patients. They found that although neuropathy was more prevalent in PD patients compared with controls (37.8% versus 8.1%), neuropathy was not associated with RLS or LMR in PD patients and that LMR but not RLS was associated with earlier age at PD onset. Whether LMR in PD eventually develops into true RLS is still unclear [10]. Although the frequency of excessive daytime sleepiness did not significantly differ between PD patients with LMR and PD patients without restlessness, an increased frequency of insomnia and reduced total sleep times were observed in PD patients with LMR compared with PD patients without restlessness [50]. It is important to recognize LMR in patients at early stages of PD. RLS and PD can coexist whether or not they share a common pathophysiology [60], and LMR may be a PD-related sensorimotor symptom.

9. Treatment of RLS and LMR in PD

If serum ferritin levels are below 50 μg/L, treatment should begin with an iron supplement. Subsequently, adding a long-acting dopamine agonist before bedtime should be considered. For PD patients already taking long-acting dopamine agonists, alpha-2-delta ligands (i.e., gabapentin, pregabalin, and gabapentin enacarbil) or clonazepam may be added [78]. For LMR, if the condition represents dopamine deficiency, a long-acting dopamine agonist should be administered first; however, established data for the treatment of LMR in PD patients are currently lacking.

10. Conclusion

We reviewed the literature on RLS and LMR in patients with PD. Longitudinal studies assessing the prevalences of RLS and LMR and their impacts in PD are imperative to clarify the true relationships among PD, LMR, and RLS. In addition, prospective studies comparing the incidence of RLS and LMR between untreated PD patients and treated PD patients are necessary to understand the effects of chronic dopaminergic treatment on LMR and RLS.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

A Polysomnographic Study of Parkinson's Disease Sleep Architecture

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Sleep disturbance is a common nonmotor phenomenon in Parkinson's disease (PD) affecting patient's quality of life. In this study, we examined the association between clinical characteristics with sleep disorders and sleep architecture patterns in a PD cohort. Patients underwent a standardized polysomnography study (PSG) in their "on medication" state. We observed that male gender and disease duration were independently associated with obstructive sleep apnea (OSA). Only lower levodopa equivalent dose (LED) was associated with periodic limb movement disorders (PLMD). REM sleep behavior disorder (RBD) was more common among older patients, with higher MDS-UPDRS III scores, and LED. None of the investigated variables were associated with the awakenings/arousals (A/A). Sleep efficiency was predicted by amantadine usage and age, while sleep stage 1 was predicted by dopamine agonists and Hoehn & Yahr severity. The use of MAO-B inhibitors and MDS-UPDRS part III were predictors of sleep stages 2 and 3. Age was the only predictor of REM sleep stage and gender for total sleep time. We conclude that sleep disorders and architecture are poorly predictable by clinical PD characteristics and other disease related factors must also be contributing to these sleep disturbances.

1. Introduction

Sleep disturbance is a common nonmotor phenomenon in Parkinson's disease (PD) patients with a prevalence reported to vary from 40% to 90% [1]. Sleep patterns and architecture change over time in the aging brain and are thought to decrease in both quality and quantity in the elderly population. The neurodegenerative disease process involves multiple motor and nonmotor networks thought to ultimately contribute to the degeneration of normal sleep cycles beyond that seen in aging alone. The potential result of this degeneration is an increased severity in sleep dysfunction and a heterogeneity in sleep disturbance clinical presentations in the PD patient [1, 2]. Complaints of sleep dysfunction often predate motor symptoms in PD and can include rapid eye movement behavior sleep disorder, excessive daytime somnolence, obstructive sleep apnea, impaired initiation and maintenance of sleep, and restless legs and also can include other parasomnias [3]. Proper vigilance is necessary as the coexistence of disrupted sleep in PD affects quality of life, motor symptoms, cognitive function, and caregiver burden.

Sleep disturbance in the PD population has traditionally been considered to be multifactorial. Contributing factors identified have included the nature of the neurodegenerative

brain changes, aging, dopaminergic medications, disease severity, and comorbid neuropsychiatric disorders [4–6]. However, most of the studies have used subjective sleep measurement. In the present study, we aimed to determine the associations between clinical characteristics with polysomnography (PSG) diagnosed sleep disorders and sleep architecture patterns in a PD cohort.

2. Materials and Methods

The National Institute of Neurology and Neurosurgery (NINN) Institutional Review Board and Ethics Committee approved the study. Written informed consent was provided from study participants for research purposes.

2.1. Study Design. The present study was a cross-sectional and descriptive data/chart review study conducted at the NINN-Movement Disorders Clinic in Mexico City. Data was collected during the period of June 2009 to May 2013.

2.2. Study Participants. Subjects with clinical diagnosis of PD made by a movement disorders fellowship-trained specialist, who fulfilled the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [7], were eligible for inclusion. PD patients who had a PSG study performed within a year for sleep complaints and with a complete data/chart were included in the final analysis.

2.3. Data Sources and Measurements. The following variables of interest were extracted reviewing each subject's chart. Demographics, clinical characteristics, and the Movement Disorders Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) were extracted from each subject's chart [8]. We also documented the presence of motor fluctuations or levodopa-induced dyskinesias (LID); dopaminergic medications such as levodopa (LD), dopamine agonists (DA), levodopa equivalent dosage (LED), and if on monotherapy or polytherapy of dopaminergics; and other medications, such as MAO-B inhibitors, amantadine, antidepressants, benzodiazepines, antipsychotics, and sleep inductors. None of the patients were on wakefulness-promoting agents (e.g., methylphenidate).

PD was clinically divided based on the dominant feature at presentation into postural instability and gait difficulty (PIGD) and tremor-dominant subtypes [9]. The H&Y stage was divided in three groups, mild (stages 1 and 2), moderate (stage 3), and advanced (stages 4 and 5) disease [10]. LED was calculated using the following formula [11]: regular LD dose + LD CR dose × 0.75 + LD × 0.33 if entacapone + pramipexole dose × 100 + ropinirole dose × 20 + rotigotine dose × 30 + pergolide dose × 1 + bromocriptine dose × 10 + selegiline dose × 10 + rasagiline dose × 100 + amantadine dose × 1. For our research purposes, polytherapy was defined as those subjects who were receiving a combination of LD and DA. Any class of antidepressants, benzodiazepines, and antipsychotics were included. Medications considered as sleep inductors in our study were zolpidem, melatonin, or melatonin agonists.

2.4. Polysomnography Technique. All subjects underwent a standardized overnight, single night PSG at the NINN-Sleep Clinic after taking their normal schedule of dopaminergic treatment using a Grass Technologies Twin (version 4.5.0.27) Polysomnographer. Conventional electroencephalography electrodes (F4-M1, C4-M1, O2-M1) were placed in most patients; however, when RBD was clinically suspected, the international 10–20 system for electrode placement was applied in order to rule out epilepsy. Electrocardiography, chin, upper and lower extremities electromyography, electrooculography, pulse oximetry, and abdominal and chest respiratory effort acquisition were also registered according to the recommended specifications of the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events. PSG was later scored and analyzed by a sleep medicine specialist. The diagnosis of any of the above sleep disorders was made according to the International Classification of Sleep Disorders 2nd edition [12].

For the study purposes, subjects were classified into two groups according to the presence or absence of the following sleep disorders, obstructive sleep apnea (OSA), periodic limb movement disorder (PLMD), rapid eye movements (REM), behavioral sleep disorder (RBD), or awakenings/arousals (A/A). Sleep architecture variables were also recorded, such as sleep efficiency, sleep latency, REM latency, periodic limb movement index (PLMI), Apnea-hypopnea index (AHI), sleep stages, and total sleep time. Sleep stages were divided according to the previous classification [13].

2.5. Statistical Analyses. For the analysis of the association between the presence or absence of any sleep disorder and sleep architecture variables (dependent variables) with the clinical and demographic variables (independent variables), a univariate analysis was used followed by a multiple logistic regression analysis. The categorical dependent variables were the sleep disorders: OSA, PLMD, RBD, and A/A. The continuous dependent variables were the sleep architecture variables: sleep efficiency, sleep latency, REM latency, PLMI, AHI, sleep stages, and total sleep time. The independent variables analyzed were the clinical and demographic data collected. The univariate analysis was performed using Student's t-test and a Pearson correlation. For the regression models, the independent variables were selected using the clinical plausibility and bidirectional selection criteria (forward and backward selection).

To identify predictive variables independently associated with the dichotomous sleep dependent variables we used a multiple binary logistic regression analysis. In this analysis, continuous independent variables were categorized to be included in the analysis. The Nagelkerke r^2 coefficients of the final binary regression model that offered the best prediction of the presence of each sleep disorder were calculated. The magnitude of association between the dependent and the independent variables was measured by the odds ratio (OR) and respective 95% confidence interval (CI). A p level < 0.05 was considered significant, but variables with levels < 0.10 were considered relevant in the final model if they showed clinical plausibility.

To identify predictive variables independently associated with the continuous sleep dependent variables we used a multiple linear regression analysis. In this analysis categorical variables were included in the model classified as 0 or 1 (for dichotomous) and 0, 1, or 2 for those showing three categories. The "r" and "r^2" coefficients of the final linear regression models that offered the best prediction of the variability of sleep variables were calculated. The magnitude of independent association between the sleep dependent variables and the independent variables was measured by the B coefficient and respective 95% confidence interval (CI).

A p level < 0.05 was considered significant, but variables with levels < 0.10 were considered relevant in the final model if they showed clinical plausibility. Statistical analyses were performed using commercially available statistical software (SPSS, version 20.0; SPSS, Inc., Chicago, Illinois).

3. Results

3.1. Demographic and Clinical Characteristics. Demographics, clinical characteristics, and sleep variables are shown in Table 1. Among the 55 patients analyzed, 61.8% were males with a mean age of 61.9 (SD = 10.9) years and a mean BMI of 28 (SD = 3.9). The mean disease duration was of 6.5 (SD = 6.7) years, 76.4% had a tremor-dominant PD subtype, 76.4% had mild, 18.2% had moderate, and 5.4% had severe H&Y stage. The mean MDS-UPDRS scores were Part I of 13.9 (SD = 6.1), Part II of 14 (SD = 8.5), Part III of 27.4 (SD = 14.8), Part IV of 2.4 (SD = 3.4), and a total score of 57.8 (SD = 25.4). Forty-seven percent had presence of motor fluctuations or LID. Dopaminergic therapy was carefully documented as follows: 76.4% were receiving levodopa therapy, 81.8% were on a dopamine agonist, and 60% were on polytherapy. The mean LED in our cohort was of 635.4 mg (SD = 428.6). Other medications were also documented: 10.9% were on MAO-B inhibitors, 16.4% on amantadine, 30.9% on antidepressants, 18.2% on benzodiazepines, 1.8% on antipsychotics, and 14.5% on sleep inductors.

3.2. Prevalence of Sleep Disorders. We observed that 56.6% of the patients had OSA, 49.1% RBD, 24.5% PLMD, and 23.6% A/A. Combinations of any of these sleep disorders were observed in 41.6% of the patients. Additionally, 3 subjects had periods of oxygen desaturation, 3 had ventricular extrasystoles, and one had RLS.

3.3. Predictors of Sleep-Related Variables of PD Patients. The final models of multiple binary regressions analysis showing the variables independently associated with OSA, PLMD, and RBD are shown in Table 2. There was a significant association between male gender (adjusted OR 4.4, CI 95% 0.2 to 15.8, $p = 0.02$) and lower disease duration (<5 years) (adjusted OR 4.4, CI 95% 1.1 to 17.4, $p = 0.04$) and the presence of OSA. Lower LED (<600 mg) was more associated with PLMD than higher LED (adjusted OR 6.7, CI 95% 1.5 to 30.4, $p = 0.04$). RBD was more common among patients with MDS-UPDRS Part III scores ≥ 25 (adjusted OR 4.8, CI 95% 1.2 to 18.9, $p = 0.02$) and those using LED ≥ 1000 mg (adjusted OR 11.9, CI

Table 1: Demographic, clinical, and sleep variables of our PD cohort.

Variables	Mean (±SD)
Age	61.9 (10.9)
BMI	28 (3.9)
Disease duration	6.5 (6.7)
UPDRS	
Part I	13.9 (6.1)
Part II	14 (8.5)
Part III	27.4 (18.4)
Part IV	2.3 (3.4)
LED, mg	635.4 (428.6)
Sleep-related variables[a]	Mean ± SD (minimum–maximum)
Sleep latency, min	29.7 ± 39.6 (1–221.5)
REM latency, min	187.3 ± 114.3 (0–468.5)
Sleep efficiency, %	68.1 ± 18.6 (6–94.3)
Total sleep time, min	345.4 ± 109.4 (6–94.3)
Stage 1, %	11.9 ± 9.7 (0–47)
Stage 2, %	61.2 ± 16.9 (16.8–100)
Stage 3, %	13.4 ± 10.2 (0–46.4)
REM, %	13.4 ± 7.6 (0–28.2)
AHI	19.9 ± 21.2 (0–75.4)
PLMI	39.4 ± 105.6 (0–540)
	$n = 55$ (%)
Sleep disorders[b]	
OSA	31 (56.6)
RBD	27 (49.1)
PLMD	13 (24.5)
Awakening/arousals	13 (23.6)
Male	34 (61.8)
Tremor-dominant PD subtype	42 (76.4)
H&Y stage	
Mild	42 (76.4)
Moderate	19 (18.2)
Severe	03 (5.4)
Motor fluctuation of LID	26 (47)
Dopaminergic treatment	
Levodopa therapy	42 (76.4)
Dopamine agonists	45 (81.8)
Polytherapy	33 (60)
Other medications	
Antidepressants	17 (30.9)
Benzodiazepines	10 (18.2)
Amantadine	9 (16.4)
Sleep inductors	8 (14.5)
MAO-B inhibitors	6 (10.9)
Antipsychotics	1 (1.8)

[a]REM: rapid eye movement; AHI: apnea-hypopnea index; PLMI: periodic limb movement index.
[b]Twenty-three patients (41.6%) had more than one sleep disorder. Three patients had oxygen desaturation, three had ventricular extra systoles, and one had restless leg syndrome. OSA = obstructive sleep apnea; RBD = REM behavioral sleep disorder; PLMD = periodic limb movement disorder.

Table 2: Multiple binary logistic regression models showing the independent association among demographic and clinical variables and sleep disorders of PD patients.

Variable	Adjusted OR (CI 95%)	"p" value
OSA[a]		
Male	4.4 (1.2–15.8)	0.02
Disease duration < 5 years	4.4 (1.1–17.4)	0.04
	Nagelkerke $r^2 = 0.30$	
PLMD[b]		
LED < 600 mg	6.7 (1.5–30.4)	0.02
	Nagelkerke $r^2 = 0.20$	
RBD[c]		
≥60 years of age	3.8 (0.9–15.3)	0.06
MDS-UPDRS part III score ≥ 25	4.8 (1.2–18.9)	0.02
LED ≥ 1000 mg	11.9 (1.7–81.9)	0.01
	Nagelkerke $r^2 = 0.30$	

[a]OSA: obstructive sleep apnea; [b]PLMD: periodic limb movement disorder; [c]RBD: REM behavioral sleep disorder.

95% 1.7 to 81.9, $p = 0.001$). There was a nonsignificant trend ($p = 0.06$) for association between RBD and age older than 60 (adjusted OR 3.8, CI 95% 0.9 to 15.3).

The multiple linear logistic regression models showing the independent association among demographic and clinical variables and the sleep parameters of PD patients are shown in Table 3. There was a negative association among amantadine use with older age and sleep efficiency. Taken together, these two variables explain 17% of sleep efficiency of the PD patients ($p = 0.008$). The percentage of sleep stage 1 was negatively associated with dopamine agonist usage and positively associated with severe H&Y stage. These two variables explain 21% of the variation of the percentage of sleep stage 1. The percentage of sleep stage 2 showed a negative association with the MAO-B inhibitors use and MDS-UPDRS III scores. Taken together these two variables explain 14% of the percentage of sleep stage 2 variation among PD patients. The age negatively associated and explained 7% of the percentage of REM stage of our patients. The total sleep time was positively associated with male gender and negatively associated with H&Y severity. Taken together, these two variables explain 9% of the total sleep variation. The final linear regression models showed a fair association (r coefficient between 0.30 and 0.49) with the analyzed sleep parameters.

4. Discussion

A cross-sectional study of 55 PD patients was conducted at the NINN-Movement Disorders Clinic revealing a poor to fair association between clinical characteristics with sleep disorders and sleep architecture, with models explaining only 7% to 21% of the variation of the clinical variables. This study was greatly strengthened by the use of PSG. Limitations should be considered before interpreting our results. It was a cross-sectional study of Mexican patients, where methodological and ethnical biases should be contemplated, and not all described sleep disorders were studied. Nonmotor features of PD as well as social and environmental features, which could have contributed to sleep quality, were not analyzed, and also a relatively low number of patients were analyzed in our cohort. Future studies should include a larger cohort with standardized sleepiness screening scales and PSG.

4.1. Sleep Disorders in PD. Our findings are consistent with previous reported frequencies of sleep disorders in PD [14]. RBD is widely known to be associated with the development of Lewy body pathology and longitudinal studies have shown that eventually patients will develop signs of parkinsonism [15]. We observed that increased age, higher MDS-UPDRS part III, and higher LED were associated with RBD, consistent with previously reported findings [16]. Being male and having a shorter disease duration were associated with OSA. This is consistent with a previous report [17] but differed from other studies reporting no clinical correlations [18]. BMI did not correlate with OSA in our cohort. Variations in results may be explained by the different types of populations studied and the methodological variations applied. Other clinical factors, which could predispose to OSA (e.g., neck circumference, hip-to-waist ratio, or Mallampati score) were not analyzed and should be considered before interpreting our results. We also found that lower LED was associated with PLMD. It has been suggested that striatal dopaminergic nerve cell loss is involved in the increased number of PLMS in PD patients [19]. A previous study reported severity of the disease as clinically associated with PLMD [20] which contradicts our results, since it is common that the LED will increase as disease advances. However, there is a general consensus that the Hispanic populations overall require fewer dosages of medications and the reasons for this are unclear but could be differences in practice. Except for RBD, which is pathologically known to be a predictor of parkinsonism, the poor clinical associations we observed for the sleep disorders in our cohort suggest other factors not considered in the analysis might be better predictors or have stronger associations with these disorders in PD patients. So far, mixed findings regarding sleep disorders and their clinical associations somewhat limit the conclusions.

4.2. Sleep Architecture in PD. The term sleep architecture describes the structure and organization of sleep. Previous reports have shown inconsistent results regarding sleep architecture patterns in PD patients when compared to controls [14]. While some have described changes in sleep efficacy, total sleep time, sleep latency, sleep stages, sleep fragmentation, and/or frequent arousals [5], others have not shown a significant change [21]. Our results are consistent with the literature citing changes in sleep patterns of PD patients. We observed a decrease in total sleep time, in sleep efficiency, and in REM sleep stage. We also observed a prolongation in sleep latency, which can explain the prolongation in REM latency and in sleep stages 1 and 2. We also observed values indicating a moderate sleep apnea and higher PLMI. Recent studies using subjective sleep measurements have found associations between clinical characteristics and changes in sleep patterns, where the disease duration and severity of disease were

Table 3: Multiple linear logistic regression models showing the independent association among demographic and clinical variables and the sleep parameters of PD patients.

Variable	*B* coefficients	95% CI	"*p*" value
Sleep efficiency			
Constant	105.17 (13.57)		<0.0001
Amantadine	−11.37 (6.29)	−24.0 to 1.26	0.07
Age, years	−0.57 (0.22)	−1.0 to −0.14	0.01
		r = 0.41; adjusted r^2 = 0.17	**0.008**
Stage 1%			
Constant	18.49 (2.73)	13.03 to 23.96	<0.0001
Dopamine agonist	−9.08 (3.03)	−15.17 to −2.99	0.004
Severe H&Y stage[a]	15.90 (5.13)	5.57 to 26.24	0.003
		r = 0.49; adjusted r^2 = 0.21	**0.01**
Stage 2%			
Constant	67.22 (2.82)	61.55 to 72.88	<0.0001
MAO-B inhibitors[b]	−16.25 (6.85)	−29.98 to −2.51	0.02
MDS-UPDRS III[c]	−11.67 (0.44)	−20.47 to −2.66	0.01
		r = 0.42; adjusted r^2 = 0.14	**0.007**
Stage 3%			
Constant	10.77 (1.77)	7.23 to 14.32	<0.0001
MAO-B inhibitors[b]	8.75 (4.29)	0.14 to 17.35	0.04
MDS-UPDRS III[c]	4.69 (2.78)	−0.89 to 10.27	0.09
		r = 0.33; adjusted r^2 = 0.07	**0.05**
REM stage %			
Constant	26.2 (5.73)	14.69 to 37.68	<0.0001
Age	−0.21 (0.09)	−0.39 to −0.02	0.02
		r = 0.30; adjusted r^2 = 0.07	**0.03**
Total sleep time, minutes			
Constant	329.05 (18.26)	292.42 to 365.69	<0.0001
Male	58.59 (28.95)	0.48 to −116.70	0.05
Severe H&Y stage[a]	−109.58 (61.95)	−233.90 to −14.73	0.08
		r = 0.35; adjusted r^2 = 0.09	**0.03**

[a]H&Y = Hoehn & Yahr stage. Moderate and severe affected patients were grouped as severe H&Y stage; [b]MAO-B = monoamine oxidase type B; [c]MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale, Part III.

important clinical factors [22]. Insomnia evaluated by the Stavanger sleepiness questionnaire was associated with longer disease duration, female gender, and depression [23]; worse Parkinson's Disease Sleep Scale (PDSS) scores were associated with higher H&Y stages [24]; and excessive daytime sleepiness using the PDSS was also related to longer disease duration [25]. Studies using objective PSG measurements have described an association between higher LED with less REM sleep stage [26] and reduced total sleep time; also age and increased H&Y stage were associated with reduced sleep efficiency [5]. Our results revealed significant associations between age with reduced sleep efficiency and reduced REM sleep stage; male gender, severity of H&Y stage, MDS-UPDRS part III scores, and medications such as dopamine agonists or MAO-B inhibitors associated with reduced sleep stages 1 and 2 and total sleep time. MAO-B inhibitors were also associated with changes in sleep stage 3. Age, gender, and indicators of disease duration were found to be associated with changes in certain variables of sleep architecture as previously described; however we did not observe associations related to the LED. Methodological differences and ethnical backgrounds could explain differences, but the reasons underlying the changes are unknown.

Sleep disorders are commonly reported in PD patients and it has been documented that variations in sleep patterns are multifactorial, suggesting that effects from increasing age, nonmotor symptoms such as depression, and dopaminergic medication may affect the mechanisms of sleep disturbances [16, 27, 28]. In what way MAO inhibitors contribute to sleep architecture is uncertain; however they may indirectly affect sleep patterns by improving depressive symptoms through its adrenocortical axis activity [29]. Our regression models revealed a poor to fair association between variables with the models and this explained only 10% to 30% of the variation. This finding was consistent with previous studies suggesting that other factors not analyzed in our cohort related to

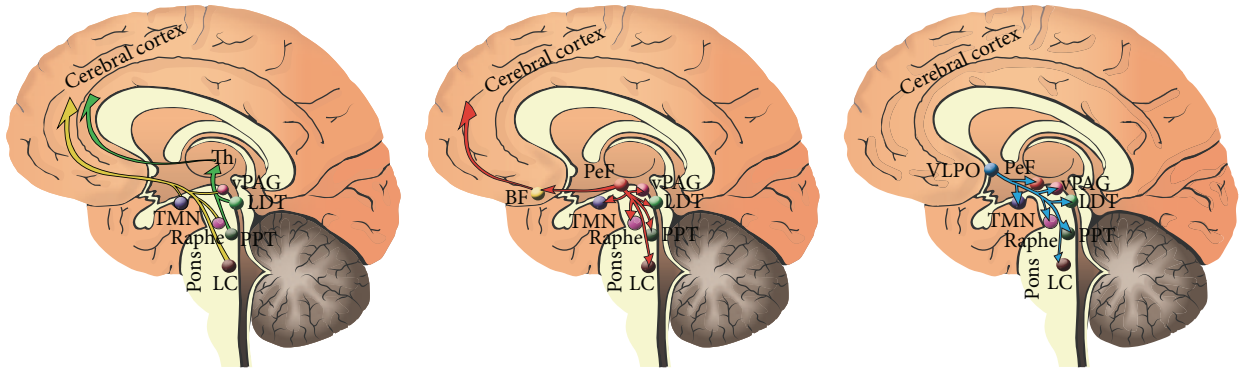

Figure 1: Sleep circuitry drawings of the arousal system affected in PD. Sleep arousal circuit. (a) The monoaminergic arousal system (yellow) includes neurons projecting from the noradrenergic locus coeruleus (LC), the serotoninergic dorsal raphe, the histaminergic tuberomammillary nucleus (TMN), and the dopaminergic ventral periaqueductal gray matter (vPAG). The cholinergic pedunculopontine nucleus (PPT) and the lateral-dorsal tegmental nuclei (LDT) send projections to the thalamus and promote the sensory information (green) to the cortex. (b) These ascending projections will contact the prefornical (PeF) orexin hypothalamic neurons (red) and the cholinergic basal forebrain neurons (BF), before directly innervating the cerebral cortex. Sleep inhibitory circuit. (c) The VLPO send inhibitory projections (light blue) to the components of the arousal circuit inhibiting them during sleep.

changes linked to the disease process itself were impacting sleep quality in PD patients. The exact reasons for this remain to be worked out.

4.3. Monoaminergic Pathway Disruption. A recent study reported a significantly higher burden of alpha-synuclein in brainstem regions (locus coeruleus and raphe nuclei), hypothalamic regions (paramammillary nuclei and the posterior hypothalamus), subcortical/limbic regions (amygdala and thalamus), and also Tau pathology present in cortical regions (entorhinal cortex) of PD patients with sleep disorders when compared to patients without sleep disorders [30]. The weak clinical associations observed in our cohort confirm what previous studies have shown, where sleep quality was independent of motor functions [31]. Additionally, pathological findings observed in brain regions which disturb areas playing roles in arousal and wakefulness suggest that different brain circuits or degenerative brain processes are affecting sleep physiology in PD other than dopaminergic circuitry. Numerous wide projections of neurons release different types of neurotransmitters and neuropeptides to regulate this intricate phenomenon of sleep in the brain. Interestingly, the pathologically alpha-synuclein affected brain regions in PD patients with sleep disorders have been shown in some studies to be consistent with the ascending arousal system monoaminergic pathways, including the noradrenergic locus coeruleus, serotoninergic raphe nuclei, dopaminergic periaqueductal gray matter, and histaminergic tuberomamillary nucleus [32]. Neurons on these sites send projections to basal forebrain and cerebral cortex through the lateral hypothalamus, which is also affected by alpha-synuclein. Overall, these observations suggest that monoaminergic pathways likely have a significant impact on PD sleep related disorders. Figure 1 theoretically represents the possible affected sleep pathways in PD.

In summary, sleep disorders and abnormal sleep architecture are common findings in PD patients despite their clinical characteristics. Other suggested circuits besides the dopaminergic pathways can impact the quality of sleep. It is critical to better understand the complex pathophysiology of sleep in PD patients in order to develop effective treatment strategies to improve a patient and a caregiver's quality of life.

Disclaimer

This paper was run through the iThenticate system provided by the University of Florida and the 1st author takes all responsibility for ensuring originality.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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