Sleep-Wake Disturbances in Parkinson's Disease: Current Evidence regarding Diagnostic and Therapeutic Decisions

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Key Words

Parkinson's disease • Rapid eye movement sleep behavior disorder • Restless legs • Sleep apnea • Insomnia • Circadian disorder

Abstract

Sleep disorders have been frequently reported in patients with Parkinson's disease (PD). However, there is insufficient evidence to guide precise recommendations on some diagnostic and treatment strategies. Here, we review clinical studies dealing with sleep abnormalities in PD and present clinical recommendations. Previous studies describing insomnia, excessive daytime sleepiness, narcolepsy-like episodes, circadian changes, sleep-disordered breathing, rapid eye movement sleep behavior disorder, vivid dreams and restless legs syndrome are evaluated. Longitudinal studies associating sleep disorders with PD onset or clinical deterioration are rare: only one longitudinal study associated daytime sleepiness with PD onset. Evidence suggests that clinical investigations must include direct questioning about depressive symptoms, nocturnal cramps, pain, nocturia and nighttime off periods. A patient interview must be conducted regarding sleep symptoms, including nightmares, abnor-

mal behavior during sleep, snoring, restless legs syndrome and daytime sleepiness. Initial evidence indicates that light therapy improves motor function and depression. Advice on sleep hygiene, the treatment of concomitant depression and the careful use of dopaminergic drugs and hypnotic agents should be considered. To date, very few controlled studies are available to make a recommendation for the management of sleep-wake disturbances in PD.

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Introduction

Parkinson's disease (PD) is a progressive nervous system disease occurring most often after the age of 50 years and affecting all ethnic groups, with an estimated worldwide prevalence of 1.6–1.8% in persons over 65 years of age [1–4]. Although supporting evidence exists for genetic and environmental etiologies, the cause of PD is unknown [5, 6]. Clinical pathological studies indicate that PD occurs secondarily to the degeneration of dopamine-producing cells in the substantia nigra. Nigrostriatal alpha-synucleinopathy plays a central role in the pathogenesis of PD, multiple system atrophy and dementia with

Lewy bodies. In spite of the fact that defective dopaminergic neurotransmission is central in PD, many studies show that other neurotransmitter alterations also affect multiple brain areas [7, 8]. The cardinal clinical features of PD include an asymmetric onset of bradykinesia, rigidity and resting tremor. Most idiopathic PD patients present with one or more of these motor features. At the beginning of the illness or as the disease progresses, postural instability and falls manifest, which adds to the disability and severity of the illness [9]. Despite advances in therapy, PD is still a progressive disorder frequently leading to motor disability and dementia. Given the recognized heterogeneous symptom presentation and progression of PD, the complex therapeutic aspects of this illness need to be better understood.

Most PD patients progressively develop non-motor symptoms during the course of the disease. Depression, cognitive deterioration, dementia, postural hypotension and sleep abnormalities are some of the frequently reported non-motor symptoms [10]. It has recently been shown that in advanced stages of the disease, motor fluctuations, mood changes, drooling, tremors and sleep problems (described most commonly as middle- and late-night insomnia followed by daytime sleepiness) are the most troublesome symptoms from the patient's perspective [11]. Nocturia has also been reported as a disturbing symptom in PD. It is generally agreed that the disease worsens with the duration of illness [12] and old age. It has been demonstrated that non-motor symptoms can be disabling and significantly impair a patient's quality of life [10, 13, 14]. However, complications, both motor and non-motor, and responses to treatment differ widely between individuals [15]. It is possible that sleep alterations have a deleterious effect on motor performance and the clinical evolution of PD. More longitudinal studies on this subject may help to clarify this issue. Furthermore, understanding the interactions between motor and non-motor symptoms can be useful as a guide to therapy.

Though often clinically neglected, sleep disorders are more frequently seen in PD patients than in the general population, with estimates ranging from 25 to 80% of patients [16–19]. The interactions between sleep and dopaminergic function and their implications for PD are far from understood. First, it has been demonstrated that sleep deprivation is related to increased dopaminergic sensitivity, and it is generally agreed that insomnia can precede manic episodes [20, 21]. On the other hand, some PD patients have reduced symptoms in the morning, indicating a favorable effect of sleep on motor function [22, 23]. This apparent paradox remains unexplained, as does

the question of why only a subgroup of patients benefit from sleep. These unsolved issues have been further challenged by a recent report confirming that sleep deprivation improves motor function in a subgroup of PD patients [24]. One possible explanation is that the influence of sleep or sleep deprivation on PD depends on some particular aspects of the disease in the patient. Sleep disorders such as insomnia, excessive daytime sleepiness, narcolepsy-like episodes, sleep-disordered breathing, circadian rhythm disorders, restless legs syndrome (RLS) and sleep-disordered rapid eye movement (REM) have all been reported in PD patients. To understand the magnitude of the problem, it is vital to note that insomnia and depressive symptoms are important and independent predictors of a poor quality of life due to health problems [25]. It has been shown that PD patients with sleep disorders are at an increased risk for mood disturbances, which can also affect the quality of life of spousal caregivers [26]. In spite of many studies on sleep disorders in PD, many questions remain. For instance, longitudinal studies can help to establish the cause-and-effect relationship between sleep abnormalities and clinical outcomes. Also, controlled studies evaluating therapies for sleep disorders in PD are scarce. Two important questions need to be answered: does PD predispose a patient to sleep disorders, and do sleep disorders influence the clinical evolution of PD?

A literature search of MEDLINE using the words 'sleep' and 'Parkinson's disease' found 1,530 studies extending back to 1956; with the inclusion of the term 'randomized', 63 studies were found, and among these, 16 were reviews. The evaluation of sleep in 44 studies was performed using the Parkinson's Disease Sleep Scale (PDSS), while 83 used the Epworth Sleepiness Scale (ESS), 31 the Pittsburgh Sleep Quality Index (PSQI) and 18 the Scales for Outcomes in PD (SCOPA)-sleep scale. Recently, a task force evaluating PD sleep scales recommended that (1) the PDSS and the PSQI should be used for screening, rating and measuring the severity of overall sleep problems; (2) the SCOPA-sleep scale should be used for rating overall sleep problems for the purposes of screening and measuring their severity; (3) the ESS should be used to screen for and measure severity of sleepiness; (4) the Inappropriate Sleep Composite Score (ISCS) should be used for screening and measuring daytime sleepiness or sleep attacks, and (5) the Stanford Sleepiness Scale (SSS) should be used for rating sleepiness and for measuring its severity at a specific moment [27]. This study also highlighted the lack of a need for new scales. It has been shown that problem-specific subitems of the PDSS are

more accurate in predicting polysomnography-related changes when compared to the PDSS as a whole [28].

The aim of this article is to review our current knowledge about sleep and wake abnormalities in PD. We will discuss the most common sleep abnormalities, clinical phenomenology, neuropathological bases, clinical trials, longitudinal studies and the important questions for guiding future studies. We also aim to increase the awareness of sleep abnormalities in PD, discuss the complex evidence about the relationship between sleep and brain structure abnormalities and recommend directions for further research. In light of the fact that an evidence-based recommendation for the treatment of sleep-wake abnormalities in PD cannot be made presently, we review the available diagnostic and therapeutic options.

Sleep Disorders

Insomnia

Insomnia is defined as 'repeated difficulty with initiation, duration and/or maintenance of sleep, despite adequate opportunity with consequent daytime impairment such as fatigue, mood disturbances, social and occupational problems, daytime sleepiness, loss of energy, memory impairment, headaches and gastrointestinal complaints' [29]. Insomnia is the most common sleep complaint in PD [17, 30]. A variety of processes can be responsible for insomnia in PD patients such as the inability to move in bed, stiffness, nocturia, dystonic movements, cramps, medication effects, comorbid conditions such as depression and dementia, primary sleep disorders such as RLS and obstructive sleep apnea (OSA), and the neuropathological changes related to the disease itself [17, 31–35]. Therefore, it is necessary to conduct an investigative sleep anamnesis interview about nocturnal cramps, disturbing off periods, pain, depressive symptoms, sleep-related breathing disorders, RLS and REM sleep behavior disorders. It has been reported that familial cases have the same level of non-motor symptoms as non-familial cases [36]; conversely, it has been shown that familial cases have more sleep disturbances [37].

Structural abnormalities of the brain have been suspected to play an important part in the genesis of sleep abnormalities in PD. Previously, connections have been made between sleep abnormalities and structural brain damage [38, 39]. Recent studies using more advanced tools, such as functional MRI, SPECT and PET, have shed more light on the understanding of this complex subject [40–42]. However, at the present time, sleep fragmenta-

tion and poor sleep quality have not been associated with specific brain abnormalities.

The effects of medication on sleep in PD are a much more controversial subject. Table 1 examines the effects of medications on sleep in PD. Generally, dopaminergic agents, particularly dopamine agonists, have been connected with somnolence and associated sleep attacks [43, 44]. Micallef et al. [45] showed that pramipexole induces sleepiness as assessed by the Multiple Sleep Latency Test (MSLT) in healthy young subjects, independent of disease-related sleep dysfunction. Other studies have indicated a beneficial effect of dopaminergic agents on sleep, probably as a consequence of improved functional ability [46–48]. Conversely, a large randomized trial has shown that both levodopa and sustained-release levodopa preparations are associated with insomnia [49]. In fact, the role of sustained-release preparations on sleep fragmentation has not been totally clarified. A 12-week open-label trial of 14 PD patients using low doses of quetiapine showed a generally good tolerance and improvement of sleep quality and excessive daytime sleepiness [50]. Despite the great number of reports, controlled studies on the treatment of insomnia in PD are scarce. Consequently, an evidence-based recommendation cannot be made presently. Advice about sleep hygiene, the treatment of concomitant depression and the careful use of dopaminergic drugs and hypnotic agents are all considered common-sense measures [51]. Insomnia increases with very high doses of dopaminergic agents; Watts et al. [52] reported that insomnia is equally worse after high doses of levodopa or ropinorole. Recently, several dopaminergic agents have been reported to improve sleep in PD (table 1) [50, 53–59]. A study involving 6 patients revealed that insomniac PD patients have an increased total sleep time after subthalamic nucleus stimulation [60]. A follow-up of 30 patients showed that bilateral high frequency subthalamic stimulation improved insomnia symptoms [61]. Insomnia has been reported as a side effect of rotigotine [62], selegiline [63], tolcapone [64] and reboxetine [65]. In summary, controlled trials involving a large number of patients that evaluate nocturnal performance and daytime consequences are required to reach any conclusions.

Excessive Daytime Sleepiness

Currently, many studies confirm that daytime sleepiness is a frequent and troublesome complaint in patients with PD [66–70]. The estimated prevalence of excessive daytime sleepiness in PD patients varies from 20 to 50% among studies, and this discrepancy may be related to

Table 1. Research articles on therapies for sleep disorders in PD

Authors	Year	Patients n	Drug	Study design	Main findings
Lees [46]	1987	10	L-Dopa HBS	Open-label study	Improvement of nocturnal bradykinesia, rigidity and tremor
Leeman et al. [48]	1987	11	L-Dopa	Randomized, double-blind, placebo-controlled, 4 nights	Improvement of morning motor function
Block et al. [49]	1997	618	Sustained-release or immediate-release L-Dopa	De novo patients randomized – 5-year follow-up	Similar motor benefit; insomnia as a side effect
Waters et al. [59]	1998	298	Tolcapone	Double-blind, placebo-controlled	Insomnia as side effect
Reuter et al. [54]	1999	6	Apomorphine	Observational	Reduction of nocturnal awakenings, off periods, pain, dystonia and nocturia
Arnulf et al. [60]	2000	5	Deep nuclei stimulation	Observational	VIM stimulation reduced tremor without altering sleep or sleep spindles; low frequency did not induce sleep
Sanjiv et al. [82]	2001	160	L-Dopa; L-Dopa + Bromocriptine; L-Dopa + Ropinirole; L-Dopa + Pramipexole	Observational	No significant difference in daytime somnolence
Lemke [65]	2002	16	Reboxetine	Open-label	Insomnia as side effect
Parkinson Study Group [62]	2003	242	Rotigotine	Randomized, double-blind, placebo-controlled	Insomnia as side effect
Romito et al. [61]	2003	33	High-frequency stimulation of the subthalamic nucleus	Observational	Improvement of insomnia
Pacchetti et al. [44]	2003	3	Pramipexole, Ropinirole	Case description	Increased daytime sleepiness (polysomnography)
Juri et al. [50]	2005	14	Quetiapine	Open-label, 12 weeks	PSQI score improved; ESS score was reduced
Micallef et al. [45]	2009	12	Bromocriptine, L-Dopa, Pramipexole	Randomized, double-blind, cross-over with washout period	Pramipexole induced sleepiness (multiple sleep latency test)
Menza et al. [58]	2009	52	Paroxetine CR, Nortriptyline, and placebo	Randomized, placebo controlled trial	Nortriptyline improved sleep
Watts et al. [52]	2010	104	Ropinirole	Observational	Insomnia as side effect
Menza et al. [53]	2010	30	Eszopiclone	6-week, randomized, controlled	Improved quality of sleep
Nodel [55]	2010	40	Pramipexole	Open-label	Improved quality of sleep, reduced sleep latency and sleep fragmentation
Lyons et al. [63]	2010	60	Selegiline	12-week open-label	Insomnia as side effect
Trenkwalder et al. [57]	2011	287	Rotigotine	Double-blind, placebo-controlled	Improved sleep (PDSS)
Ray Chaudhuri et al. [56]	2012	189	Ropinirole	24-week, double-blind	Improved sleep quality (PDSS)

differences in age, disease duration and dopaminergic therapy [66, 70–73]. On the other hand, the reported prevalence of narcolepsy-like episodes and sleep attacks, a common terminology for sudden sleep episodes less frequently reported in PD, varies from 1 to 20%. Most epidemiological studies have used the ESS, a subjective test, for the evaluation of daytime sleepiness [74]. Objective measures of sleepiness such as the MSLT and the Main-

tenance Wakefulness Test are also used; however, these objective measures are not related to the ESS and probably reflect different parameters [75]. The relationship between subjective measures and objective measures of sleepiness have been found to be significant [67], weakly significant [76] and not significant [77]. Two MSLT-based studies showed pathological sleepiness in 19% of PD cases [78, 79]. More information about the relationship be-

tween subjective measures of sleepiness and the MSLT in PD is needed.

Generally, motor disability, presence of depression and dementia, concurrent medical/sleep illnesses and the impact of PD and medications on alertness all contribute to the manifestations of daytime sleepiness in PD. Yet, understanding the role of these symptoms is important for the evaluation of therapy for excessive daytime sleepiness [76]. At present, there is still a need to understand the etiopathogenic mechanisms of excessive daytime sleepiness in PD. Because disease duration and disease severity are predictors of excessive daytime sleepiness and sleep attacks, it has been suggested that specific brain histopathological alterations underlie sudden sleep episodes [71]. The degeneration of hypocretin neurons in PD patients has not been sufficiently studied. A reduction of hypocretin neurons as well as reduced cerebrospinal fluid hypocretin levels have been previously shown in PD patients [80]. Conversely, it has been demonstrated that there is no significant decrease of cerebrospinal fluid hypocretin in PD patients compared to controls [67, 81]. More studies on this issue are warranted. Recently, a reduction of the cerebellar peduncle, possibly indicating ventral tegmental area degeneration, has been associated with excessive daytime sleepiness in PD [41]. These results confirm that brain histopathological alterations underlie the pathogenesis of excessive daytime sleepiness and possible sudden sleep onset. It has also been suggested that all anti-Parkinson drugs can cause daytime sleepiness [82]. It is generally agreed that sleepiness correlates with disease severity and high doses of levodopa or dopaminergic agents [73, 76].

A review of daytime sleepiness in PD highlighted the importance of this symptom and its association with sudden sleep onset. A unique study showed that excessive daytime sleepiness might be associated with an increased risk of developing PD [83]. Narcolepsy-like episodes and sleep attacks occur more frequently in patients with daytime sleepiness and are related to disease severity [71, 84–87]. Sleep attacks can manifest without warning and can be a potential cause of car accidents [88]. In contrast to these findings, one study showed that PD patients do not have more car accidents than controls [85].

Very few controlled studies on the effects of medication on sleepiness in PD have been published. The effect of modafinil on sleepiness in PD patients remains controversial. Studies have shown significant improvement [89], modest improvement [90] and no improvement of sleepiness [89]. Weintraub et al. [91] showed that atomoxetine significantly improved cognition and daytime

sleepiness and was well tolerated. Nocturnally administered sodium oxybate has also been shown to improve daytime sleepiness and fatigue in PD [92]. It should be noted that fatigue has not been related to daytime sleepiness or nighttime sleep dysfunction and has been strongly influenced by the presence of depression and lower functional status [93].

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders potentially influence daytime and nocturnal dysfunctions. It is common to find that PD patients go to bed and wake up very early; therefore, a phase advance may occur [94]. Advanced sleep phase is usually associated with older age [95] and characterized by involuntary sleep and waking times that are generally more than 3 h earlier than usual sleep times. For patients with PD, both age-related changes and brain damage can provoke circadian rhythm sleep abnormalities. This relationship deserves more careful clarification, although it is complex. For instance, a slower absorption rate of levodopa during nighttime, possibly related to delayed gastric emptying, has been reported in PD patients [96]. In agreement with this example, it has been documented that phase advance in PD is possibly influenced not only by age but also by dopaminergic therapy and disease severity [97, 98]. Given the complexity of this issue, an abnormal pattern of daily activities [99] and associated comorbidities, such as depressive symptoms and daytime sleepiness, could also influence circadian rhythms [70, 76]. Thus, the analysis of this complex issue must take all of these variables into careful consideration.

Recently, Cai et al. [100] showed that there are abnormalities in the molecular clock in PD. They studied 17 patients and showed a difference in the expression pattern of brain and muscle Arnt-like protein-1 (*BMAL1*) but not in the expression pattern of the period circadian protein homolog 1 (*PER1*) during the nighttime in PD patients. The relative abundance of *BMAL1* was significantly lower in PD patients versus control subjects and, furthermore, the expression levels of *BMAL1* correlated with the Unified Parkinson's Disease Rating Scale (UPDRS) score and with the PSQI [100]. These results show that there are abnormalities in the molecular clock in PD. The role of clock gene abnormality on sleepiness, sleep abnormalities and circadian changes in PD is of interest. In the same vein, an uncontrolled study of 12 patients showed that bright-light therapy at dusk improved motor function and sleep [101]. In a randomized, placebo-controlled study, 36 PD patients received 30 min of 7,500-lux bright-light therapy over 15 days and showed a significant im-

provement of tremor, UPDRS parts I, II and IV, and depression [102]. Currently, only these two studies have shown that light therapy at dusk and in the morning improves motor dysfunction, depression and agitation. Other studies on this subject are warranted. This preliminary evidence needs more clarification but offers new possible therapeutic perspectives, not only for sleep problems but also for motor and non-motor symptoms such as cognition and mood.

REM Behavior Disorder

Idiopathic REM behavior disorder (RBD) is characterized by a loss of normal atonia during REM sleep [103, 104]: simple or complex behavior, potentially violent, corresponding to enacted dreams [105]. Approximately 50% of RBD individuals will develop PD, dementia with Lewy body or multiple system atrophy within 10 years, suggesting that the alpha-synuclein pathogenic process may start decades before the first symptoms [106]. RBD is predominant in elderly men. However, Ju et al. [107] recently showed that in younger individuals, RBD has a lower male-to-female ratio. Other gender differences have also been found. In elderly men, RBD is more often associated with neurodegenerative disorders; in women, the idiopathic form is more frequent. It has been suggested that in women, RBD is frequently associated with a high rate of antidepressant use and autoimmune disease [107].

Cognitive impairment has been observed in idiopathic RBD and in RBD associated with degenerative diseases [108]. A 2-year follow-up has shown a progressive deterioration of memory in RBD, indicating 'an underlying evolving degenerative process' [109]. PD patients with clinically probable RBD are older, have a longer disease duration, more disability, a longer duration of anti-Parkinson medication and lower tremor scores in the UPDRS [110]. Interestingly, it has been shown that movements recorded in PD subjects with RBD during REM sleep have better speed (but less coordination) compared with the pattern of movements seen in the same subjects during wakefulness, suggesting that the movements during RBD are generated by the motor cortex and projected downstream via the pyramidal system bypassing the basal ganglia [111]. Postuma et al. [112] also showed that PD patients with RBD were less likely to be tremor predominant, had more falls and had lower amplitude response to their medication. The latter findings are indicative of a more severe form of PD. A unique and challenging study showed that patients with left-sided PD onset or predominant right hemisphere dysfunction have more nocturnal hallucinations and daytime dozing [113]. It has been sug-

gested that visual hallucinations may be dream imagery coinciding with daytime episodes of REM sleep. Therefore, psychotic episodes could be narcolepsy-like REM sleep disorders [114]. A longitudinal evaluation has indicated that the presence of RBD in PD could be a warning sign for the development of cognitive impairment [115]. Most of the studies showing that PD patients with RBD have more cognitive impairment are cross-sectional, which makes a cause-and-effect relationship difficult to establish [108, 116, 117]. Previously, visual hallucinations have been described as a common symptom in PD patients with RBD [115]. Forsaa et al. [118] performed a 12-year prospective evaluation of 130 patients and showed that psychotic symptoms in PD manifest at an older age of onset, require higher doses of dopaminergic drugs and occur in association with probable RBD. Interestingly, the same authors also showed that psychotic symptoms, age at onset, chronological age, motor severity and dementia independently predicted an increased mortality in PD patients [119]. Connections among psychotic symptoms, dementia and RBD have been previously established [120]. These results corroborate the evidence that RBD is a noxious manifestation of PD.

According to the International Classification of Sleep Disorders (ICSD) Minimal Criteria, a diagnosis of RBD can be made when limb or body movement is associated with dream-enacting behavior and at least one of the following occurs: (1) harmful or potentially harmful sleep behaviors; (2) dreams appear to be acted out, and/or (3) sleep behaviors disrupt sleep continuity. Polysomnographic abnormalities are additional criteria to confirm the diagnosis in dubious cases. In contrast, the 2nd edition of the ICSD requires the following for the clinical diagnosis of RBD: (1) presence of REM sleep without atonia on polysomnography; (2) at least one of the following: (a) sleep-related, injurious, potentially injurious, or disruptive behaviors by history (i.e. dream-enacting behavior) and/or (b) abnormal REM sleep behavior documented during polysomnographic monitoring; (3) absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder, and (4) the sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder [121]. It has been shown that the majority of RBD patients report symptoms only in response to specific questioning; thus, investigative questioning during sleep anamnesis is necessary [122].

Clonazepam is efficacious in and well tolerated by the majority of patients afflicted by RBD and should be con-

sidered as an initial treatment [123]. Careful surveillance of side effects, such as increased risk of falls, daytime sleepiness, confusional arousal, concomitant cognitive impairment or worsening of OSA, should be considered when using clonazepam. Melatonin or other benzodiazepines such as zopiclone and alprazolam may be good alternatives [124–126]. Monoamine oxidase inhibitors, tricyclic antidepressants, serotonergic synaptic reuptake inhibitors and noradrenergic antagonists can induce or aggravate RBD symptoms and should be avoided [123]. Results from a double-blind clinical-polysomnography study have shown that quetiapine improves visual hallucinations in PD [127].

RLS

RLS is a sensorimotor disorder. Its prevalence increases with age, and the incidence rates vary from 2 to 12% [128–130]. A preference for female gender [131] and a familial form with more precocious manifestations [132] have been described. RLS is characterized by an irresistible urge to move the legs and is usually accompanied by uncomfortable sensations. It manifests or worsens at rest, is exacerbated in the early evening or at night and is alleviated or partially alleviated by movement. End-stage renal disease [133, 134], iron deficiency [135], multiple sclerosis [136, 137] and the use of some drugs, such as antidepressants and antipsychotics [138], have been associated with RLS. Doubts remain about whether diabetic patients have a higher incidence of RLS [139, 140]. Despite high prevalence rates of RLS in PD, there is no evidence that RLS symptoms early in life predispose to the subsequent development of PD [141–143]. Patients with RLS frequently have periodic limb movements that can be diagnosed by polysomnography [144]. In similarity to RLS, periodic limb movements may involve dopamine mechanisms [145]. Few studies have addressed the issue of periodic limb movements in PD: it remains to be clarified whether periodic limb movements are more frequent in PD patients with RLS than in patients without.

Therapeutic options for RLS associated with PD are the same as in other clinical conditions and include palliative measures such as trying to maintain a regular sleep pattern, moderate exercise, massaging the legs, taking a hot bath or using a heating pad or ice pack. Dopaminergic agonists are the preferred drugs, and other medications such as levodopa [146], benzodiazepines, opioids, gabapentin and pregabalin can also be used [147].

Sleep Disordered Breathing

Previous studies indicate that OSA prevalence varies from 24 to 65% [148–151]. Contradictory evidence can be found showing both a higher prevalence of OSA in PD patients than in the general population [67, 149, 151] and no increased risk of OSA in PD patients [152, 153]. Studies suggest a relationship between daytime sleepiness and OSA in PD [67, 154]. Conversely, findings have also shown no relationship between daytime sleepiness and OSA in PD [152, 153]. In fact, very few studies about sleep in PD involved polysomnography. Presently, there are no conclusive data regarding the prevalence of OSA in PD patients compared to the general population. Of greater importance is the need to clarify the possible deleterious effects of OSA in PD; studies on the effects of OSA therapy in PD are virtually non-existent.

Conclusion

Sleep abnormalities are common and significantly impair the quality of life of PD patients. Clinical investigations must include direct questioning about depressive symptoms, nocturnal cramps, pain and nighttime off periods. An interview about sleep symptoms, nightmares, abnormal behavior during sleep, RLS and daytime sleepiness must also be conducted. PD patients commonly have reduced daytime social activities and tend to go to bed early and wake up early. Preliminary evidence indicates that sleep hygiene measures and bright-light therapy could benefit sleep, cognitive performance and motor ability. It is important to diagnose and treat RBD in PD, and the majority of patients will benefit from the use of clonazepam. In cases with excessive daytime sleepiness, an emphasis on sleep hygiene and a warning about accidents are advised. Medications that promote alertness can be used, though this is not an evidence-based recommendation. The treatment of RLS with nighttime dopaminergic agonists is similar to other clinical situations. The results of continuous positive airway pressure therapy in PD are unknown. To date, very few controlled studies are available to make a recommendation for the management of insomnia in PD. Generally, for the treatment of sleep abnormalities in PD, the implementation of sleep hygiene, the treatment of concomitant depression and the careful use of dopaminergic drugs and hypnotic agents should be considered. More prospective studies are necessary to clarify whether the onset of PD predisposes a patient to sleep abnormalities or if sleep abnormalities aggravate the course of illness.

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