

Sleep Disorders in Parkinson's Disease: Present Status and Future Prospects

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Key words: Parkinson's Disease; Sleep Disorders; Management

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world. In China, approximately 48–89% of Chinese patients with PD have been shown to be affected by sleep disorders. In recent decades, there have been major advances in our understanding of the relationship between sleep disorders and PD, yet many questions remain unanswered.

Epidemiological studies have demonstrated that sleep disorders are associated with a decline in cognitive performance, productivity, mood, and quality of life, as well as with major social, medical, and economic impacts. At present, the pathophysiology of sleep-wake disturbances in PD remains largely unknown, although the etiology is most likely multifactorial. Alterations of pathophysiological mechanisms are thought to underlie several processes, including sleep-wake regulatory centers, overnight emergence of motor symptoms, adverse effects of antiparkinsonian medications, psychiatric symptoms, and sleep fragmentation caused by multiple factors.^[1,2] However, recent genetic studies of PD had identified multiple genes and loci which might be associated with sleep disorders. Genetic studies of rapid eye movement sleep behavior disorder (RBD) offered some new insights that glucocerebrosidase mutations and microtubule-associated protein tau loci were associated with RBD. Moreover, some genes and genetic loci were associated with restless legs syndrome (RLS) as follows: *MEIS1*, *BTBD9*, *PTPRD*, *MAP2K5/SKOR1*, *TOX3*, and *RLS1-8*.^[3]

Sleep disorders in PD can be classified into two categories: disturbances of sleep and disturbances of wakefulness.

The most common disorders include insomnia, RBD, excessive daytime sleepiness (EDS), RLS, sleep-disordered breathing (SDB), and disruptions of circadian rhythms.

Insomnia

Insomnia is defined as a persistent difficulty with sleep initiation, duration, consolidation, or quality. The patient might report some of the following symptoms related to nighttime sleep difficulty, such as fatigue, memory impairment, and daytime sleepiness. It is the most common sleep disorder in PD cases, and these patients usually report difficulties with sleep onset and sleep maintenance. Sleep fragmentation is a key indicator of sleep maintenance insomnia. Psychiatric symptoms have been shown to have a negative impact on sleep quality, particularly with respect to depression, which commonly results in early-morning awakenings. Recently, there has been an increase in the amount of researches that explore cognitive behavior therapy for insomnia – a promising potential method of insomnia treatment for patients with PD.^[4]

Rapid eye movement sleep behavior disorder

RBD is a parasomnia, characterized by loss of the atonia that normally occurs during rapid eye movement sleep, and is associated with dream enactment behavior. These vocalizations or behaviors often correlate with dream mentation, leading to the frequent report of “acting out one's dreams.” RBD has been estimated to affect 22–60% of Chinese patients with PD. While

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Received: 26-02-2018 **Edited by:** Yi Cui

How to cite this article: Shen Y, Liu CF. Sleep Disorders in Parkinson's Disease: Present Status and Future Prospects. Chin Med J 2018;131:883-5.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.229903

this disorder has been an area of intensive investigation over the past few decades, the mechanisms underlying it remain poorly understood. At present, the diagnosis of RBD requires polysomnography, although there is no consensus on the best standard for diagnosing the rapid eye movement sleep without atonia that occurs before or during RBD.

Importantly, RBD can act as a window into long-term brain health, as it is both a symptom of early-stage α -synucleinopathy and a potential marker of more severe disease manifestations in PD. Therefore, RBD will likely be a priority in future research. Moreover, based on our previous research, we hypothesize that rapid eye movement sleep without atonia is associated with the severity of PD illness and might continue to develop as PD progresses.^[5]

Both idiopathic and symptomatic RBD are more strongly associated with neurodegenerative diseases than other sleep disorders. Idiopathic RBD can have subtle prodromal neurodegenerative abnormalities, including hyposmia, constipation, orthostatic hypotension, autonomic dysfunction, and abnormalities in gait, neuroimaging, and neurophysiological tests. In addition, 74% of patients with RBD may meet the Movement Disorders Society criteria for a diagnosis of prodromal PD.^[6] Furthermore, up to 90.9% of RBD cases ultimately develop a neurodegenerative disease over the course of longitudinal follow-up. Finally, RBD is associated with more severe motor and nonmotor manifestations in patients with PD than other groups. Therefore, clinicians should pay attention to the clinical course of RBD and its rate of phenocconversion and need to administer future neuroprotective therapies that can modify the course, delay the onset, or prevent the development of the disabling manifestations of PD.^[7]

Excessive daytime sleepiness

EDS is defined as an inability to maintain wakefulness and alertness during the major waking episodes of the day which results in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. It affects approximately 13–47% of Chinese patients with PD and has an annual incidence of 6%. EDS can affect both the motor and nonmotor symptoms of patients with PD. At present, there are few options for the pharmacological management of EDS in PD. However, in these cases, clinicians should note the impact of dopaminergic therapy, especially any adverse effects of dopamine agonists. Future studies are needed to develop long-term therapies for the management of EDS in PD patients.

Restless legs syndrome

RLS diagnosis requires that patients have an urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs. These symptoms often begin or worsen during periods of rest or in the evening. The prevalence of RLS in Chinese patients with PD is approximately 8–35%. RLS can be difficult to distinguish from similar disorders in a clinical setting; therefore, the full profile of RLS must be investigated to establish a diagnosis. Importantly, there are

numerous confounders that can result in false positives for RLS, such as dystonia, akathisia, painful neuropathy, and biphasic dyskinesia. Further studies are needed to understand the potential overlap between the symptoms, co-occurrence, and temporal order of occurrence of RLS in patients with PD, as well as to investigate the conversion of RLS to PD.^[8]

Sleep-disordered breathing

SDB is characterized by abnormalities of respiration during sleep. The disorders are grouped into obstructive sleep apnea (OSA) disorders, central sleep apnea disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders. The prevalence of OSA in patients with PD is estimated to be around 20–60%. It is characterized by upper airway narrowing or closure during sleep while respiratory effort continues. The consequences of OSA include cardiac arrhythmias, nighttime confusion, EDS, and functional decline. Some studies have found that OSA worsens cognitive functioning. Although the most effective treatment for OSA is continuous positive airway pressure, this may not result in overall cognitive improvement in patients with PD.^[9] Hence, future research should include development of screening tools and better management of this disorder.

Circadian rhythm disruptions

The 2017 Nobel Prize in Physiology or Medicine was awarded to Jeffrey C. Hall, Michael Rosbash, and Michael W. Young for elucidating the molecular mechanisms controlling circadian rhythms. Circadian rhythms are biological rhythms that can affect mood, cognition, and autonomic and motor functions. In addition, there is increasing evidence of circadian disruption in PD. The circadian rhythm disorder is caused by alterations of the circadian time-keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm and the external environment. Hence, understanding how circadian rhythms function, and which mechanisms can affect them, offers an opportunity to explore the pathophysiology of PD and potential treatments. For example, a recent *JAMA Neurology* article introduced light therapy as a treatment for disturbed sleep and wakefulness associated with PD.^[10] Light therapy caused an alteration in circadian rhythms wherein the light stimulated melanopsin-containing retinal ganglion cells through the retinohypothalamic tracts. This suggests that, while chronobiology has long been neglected, in the future, we need to build systematic clinical investigations of circadian rhythm disruption in PD.

OPTIONS FOR THE MANAGEMENT OF SLEEP DISORDERS IN PATIENTS WITH PARKINSON'S DISEASE

In general, management of sleep disorders in patients with PD is complex as these conditions are heterogeneous; therefore, treatment plans must be individualized and directed at the underlying cause(s).^[11] Prior to treatment, a comprehensive battery of clinical, neuropsychological, neuroimaging, and electrophysiological assessments should

be conducted, and the sleep disorder cause and subtype need to be carefully evaluated. As examples, patients with PD that also experience insomnia should be treated based on the defined etiology (e.g., akinesia and drugs), whereas EDS often occurs secondarily as a symptom of another sleep disorder and can be treated with drugs, surgery, and/or increased nocturnal sleep. In addition, when PD occurs in conjunction with RLS, other secondary factors and contributing comorbidities should be excluded, such as metabolic disorders (e.g., iron, folic acid, and vitamin B12 deficiency), end-stage renal disease, diabetes, pregnancy, and serotonergic antidepressants and, for RBD, the institution of appropriate safety measures is a key component of any management plan.

Importantly, the influence of dopaminergic and other PD medications on sleep needs to be accounted for when designing a treatment plan. Each of the sleep disorders discussed above can potentially be affected (either positively or negatively) by antiparkinsonian medications. For example, dopaminergic medications, particularly dopamine agonists, affect subjective sleepiness, and many dopaminergic agents can be effective for treating RLS in patients with PD. In addition, dopaminergic therapy can improve dream-enactment behavior in PD patients with RBD.

As previously mentioned, circadian-based therapies, such as timed-light exposure and melatonin, should be a focus of current research. In addition, promoting behavioral interventions including proper sleep hygiene habits, increased activity during the day, and restriction of daytime napping that improve the consolidation of sleep-wake cycles can also be effective.^[2] To this end, management of nighttime sleep quality may also be beneficial for motor symptoms in patients with PD.^[11] Finally, transcranial magnetic stimulation and deep brain stimulation are novel treatments that might improve sleep disorders.

CONCLUSIONS

While recent reports have shown a clear association between sleep and PD, it is still unclear if primary sleep disorders increase the risk of developing PD and/or enhance the rate of progression, or if they arise as a consequence of PD. In addition, there are numerous unanswered questions regarding effective diagnostic assessments and management of sleep disorders in these cases, as well as the epidemiology, pathophysiology, clinical impact, and implications of the underlying disease and its manifestations. Future work should address these issues using longitudinal studies that

employ large cohorts of patients with PD and identify high-risk patients for neuroprotective interventions.

The field of research focusing on sleep and PD has made enormous and exciting strides, and it is likely that future research at a molecular level will provide better therapies in this progressive disease. Therefore, the genetic study of sleep-related disorders still lags behind other medical fields. At present, the challenges of this field are improving our understanding of sleep-wake regulation and function, disseminating knowledge on sleep and sleep disorders to physicians and the general population, and educating neurologists with the aim of improved diagnosis of sleep disorders for early detection. Finally, we need to develop better treatment options and devise up-to-date guidelines for the management of PD patients with primary or comorbid sleep disorders.

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