

“Spectrum of Sleep Disturbances in Parkinson’s Disease”

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ABSTRACT Sleep disturbances are one of the most common non motor symptoms in patients with Parkinson’s disease. It affects the quality of life of PD patients adversely. Sleep disorders in PD are diverse and have complex pathophysiology, however it can be diagnosed clinically by most of the neurologist if diligently asked for. Treatment of the sleep disturbances in PD may result in improved motor functions and better quality of life. Here we review the various sleep disorders, its pathophysiology and treatment.

Keywords: Parkinson’s disease, Sleep disorders, Excessive daytime sleepiness, Quality of life

Introduction

Parkinson’s disease (PD) is a chronic, progressive, disabling neurodegenerative disorder with a prevalence of approximately 360 per 100,000 and an incidence of 18 per 100,000 per year. As the average age of the population increases, the prevalence of PD can be expected to rise. The motor symptoms in PD result from degeneration of dopaminergic neurons in substantia nigra. The pathological process in PD is even more extensive to involve serotonergic, noradrenergic and cholinergic systems responsible for development of nonmotor symptoms (NMSs) of PD. NMSs such as depression, anxiety, psychosis, sleep disturbances, cognitive impairment and autonomic dysfunctions are commonly seen in PD and they adversely affect the quality of life. One large series has reported that almost every patient with PD exhibit at least one nonmotor symptom.¹ Sleep disorders are among the most common non-motor symptoms in Parkinson’s disease. The overall prevalence of sleep disturbances in PD varies from 68%-98%.² Sleep disturbances in PD is multifactorial and have negative impact on quality of life (QoL) of PD patients. Clinicians and PD patients may not recognize the sleep disturbances and its relation with PD so the prevalence

may be underestimated. However it can be diagnosed clinically with the help of questionnaires and very occasionally polysomnography is required. Treatment options are diverse and depend upon the diagnosis of sleep abnormality which is present in patient.

Parkinson’s Disease and sleep disturbances:

The whole gamut of sleep disorders may occur in PD. Sleep in PD patients may be disturbed because of the neuronal degeneration of sleep regulating areas in brain, motor (difficulty in turning inside bed) and non-motor symptoms such as autonomic dysfunction, hallucinations, depression and due to effects of drugs used for treatment of PD. The various sleep abnormalities in PD are as below:

1. *Insomnia*

Nocturnal symptoms with sleep disturbances are well known in PD.^{3,4} Frequent night-time awakenings and sleep dis-ruptions are the most common sleep problems in PD. In addition, periodic leg movements in sleep, fragmentary nocturnal myoclonus, sleep apnea, REM sleep behavioral disorders, and parasomnias may all disrupt sleep in PD. Reversal of sleep rhythm with sun downing also is common in PD. Upto 80% of patients with PD complain of sleep fragmentation, insomnia, and nocturia. A nationwide German study has recently included 1449 PD patients and reported sleep disturbances in 49% of patients.⁵ Another study (PRIAMO study) done on 1072 PD patients showed frequent occurrence of nonmotorsymptoms fatigue being commonest (58%) followed by insomnia, (37%), urgency and nocturia (35%), RBD (30%), EDS (21%), and restless legs syndrome (RLS) (15%).¹

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Insomnia can be due to problem with onset or maintenance of sleep. Impaired sleep maintenance is one of the major factor for poor nighttime sleep quality in PD. Sleep benefit has been observed in patients with PD even prior to start of treatment denoting the importance of maintenance of sleep quality in PD. A good nighttime sleep reduces the severity of daytime parkinsonism, and many patients describe better mobility the morning after a restful night. Polysomnographic studies have demonstrated increased sleep latency and frequent awakenings, with as much as 30-40% of the night spent awake in patients with PD. Drug induced hallucinations also disrupt night time sleep in patients with PD. Apart from dopaminergic drugs, depression, anxiety, and autonomic dysfunction also contribute to poor sleep quality in PD. On the other hand insufficient dopaminergic treatment causing nocturnal akinesia, nocturia, muscle cramps, and various other nonmotor symptoms may cause sleep disruption. There are various scales to measure the subjective sleep quality and they are validated for use in PD.

2. Excessive Daytime Somnolence

Prevalence of Excessive daytime sleepiness (EDS) varies in different studies from 15.5 to 74% of PD patients.⁶ EDS is considered to be a risk factor for development of PD and it may be present even at premotor stage of disease. The prevalence of EDS increases as the disease progresses and its prevalence varies according to the assessment method. Excessive daytime somnolence may occur due to fragmentation of nighttime sleep and sleep apnoea but it is thought to be integral part of disease itself. PD patients with EDS do not correlate with variables such as disease severity, total sleep time or sleep stage percentages, but rather found to be related to primary impairments of waking arousal and REM-sleep expression. In PD, sleepiness is associated with cognitive decline and hallucinations suggesting EDS to be a poor prognostic marker. Although infrequent but sudden, unforeseen sleep is also reported in PD known as sleep attacks. Significant number of PD patients may be unaware of their sleepiness despite being involved in accidents. Dopaminergic drugs used to treat PD also contribute to excessive daytime sleepiness. Dopamine agonists have been found to be associated with EDS but total dose of dopamine is reported to be the main predictor of EDS. A multicenter study reported correlation between ESS and levodopa equivalent dose irrespective of drug class selected.⁷ EDS can be assessed subjectively by using the Epworth sleepiness scale (ESS)⁸ and is recommended by the Movement Disorders Society, for the evaluation of EDS in patients with PD. ESS >10 is indicative of pathological sleepiness. In a recent review on polysomnographic studies in PD

has shown lack of objective sleepiness by multiple sleep latency test despite significant subjective sleepiness in patients.⁹

3. Circadian Rhythm Sleep Disorders

Circadian rhythm disturbances are also present in PD mainly imparted by the degenerative process. There may be alteration in levels of hormones especially melatonin, changes in heart rate, blood pressure due to the process of neurodegeneration in hypothalamus, sleep regulating centers in brain stem, autonomic dysfunction and levodopa therapy. PD patients with depression have been found to exhibit circadian rhythm abnormalities more compared to patients without depression. Suprachiasmatic nucleus is intact in PD but presence of circadian rhythm abnormalities indicates involvement of hypothalamus and brainstem.

4. Rapid Eye Movement Sleep Behaviour Disorder

Rapid eye movement sleep behaviour disorder (RBD) is present in 25-50% of patients with PD. RBD is characterized by a loss of muscle atonia during REM sleep that results in dream-enacting behaviour, and sometimes even leads to injury to the individual or bed partner. It is more common in males and its association with neurodegenerative diseases especially synucleinopathies has been found. Locus coeruleus, pedunculopontine nucleus and cholinergic nuclei are pathologically involved in RBD. Early manifestations of PD preceding even the onset of typical motor symptoms, impaired visual and olfactory discrimination have also been observed in idiopathic RBD patients. In the survey of their PD patients, Scaglione and colleagues (2005) found that only 33% had RBD. Of these, PD preceded RBD in 73%, an average of 8 years before onset of RBD. However not all patients with RBD develop PD but early detection of RBD can be used as a preclinical marker and a basis for intervention. PD patients with RBD are non tremor type, have more tendency to fall and less responsive to dopaminergic medications. American Academy of Sleep Medicine (AASM) 2001, proposed criteria for RBD includes intermittent loss of REM sleep electromyographic atonia and by the appearance of motor activity associated with dream enacting behaviour. The motor activity involves kicking, punching severe enough to hurt the bed partner along with emotional outbursts.

The gold standard for diagnosis remains a polysomnography with audiovisual recording. Video-PSG is more specific which also shows increased muscle activity during REM sleep.

5. Restless Legs Syndrome (RLS)

RLS is an urge to move the legs due to uncomfortable sensation in legs during period of inactivity or rest. RLS is commonly observed along with motor symptoms, and sleep disturbances of PD. In 80% of RLS patients have periodic limb movement during sleep. Response to dopaminergic therapy indicates similar pathophysiology of PD and RLS. The pathophysiology of RLS is not known but a central dopaminergic dysfunction has been proposed based on responsiveness to dopaminergic therapy and decreased dopamine D2 receptor binding observed in the RLS patients by SPECT.

Diagnostic criteria for RLS

Required criteria

- Uncomfortable and unpleasant sensations in the extremities (prickling, stinging, itching, 'like crawling ants,' sometimes described as pain), with an urge to move
- The sensations begin or worsen during inactivity
- The sensations and/or urge to move are partially or totally relieved by movement
- The sensations and/or urge to move display a circadian pattern: worse in the evening or night compared than the early morning; or only occurring in the evening or night

Supportive features of RLS

- Positive family history
- Clear beneficial response to dopaminergics
- Presence of periodic limb movements during sleep

6. Periodic Limb Movement Disorder

Periodic limb movement disorder often co-occurs with RLS but it is a distinct disorder. PLM is more common in PD compared to control and it is thought to be a factor causing nocturnal sleep disturbances and excessive daytime sleepiness.

7. Sleep Apnoea Syndrome (SAS)

Studies have reported 20-60% incidence of SAS in PD, attributing it to nocturnal akinesia or hypokinesia of respiratory and pharyngeal muscles. However, polysomnographic studies did not find difference in apnoea-hypopnea index (AHI) in patients with PD and control. The relation between PD and SAS is still not clear.

Pathophysiology:

Sleep dysfunction in PD is multifactorial, primarily due to neurodegenerative process impairing the

thalamocortical arousal and affecting sleep regulating centres in the brainstem. Other factors responsible are nocturnal hypo or akinesia, nocturia, bizarre dreams, comorbid anxiety and depression and side effects of the pharmacological treatment. Finally, there can be overlapping with independent age-related sleep disturbances.

It has been hypothesized that mesocorticolimbic dopaminergic system modulates sleep and wake cycle.¹⁰ Impairment in this pathway leads to fragmentation of night sleep and excessive daytime somnolence. Dopamine maintains sleep homeostasis and its role is independent from nigrostriatal dopaminergic system. It has been postulated that degeneration of mesocorticolimbic dopaminergic system is imparting sleep disturbances in PD. Apart from mesocorticolimbic system, degeneration of serotonergic, cholinergic, and noradrenergic system also play an important role in sleep disruption in PD. These neurons form a flip-flop switch model of sleep-wake regulation. This model was proposed by Saper, which includes an ascending arousal system regulated by noradrenergic locus coeruleus, glutaminergic parabrachial nucleus, serotonergic dorsal raphe, dopaminergic ventral periaqueductal gray matter and histaminergic tuberomammillary nucleus and a sleep inducing system controlled by ventrolateral preoptic nucleus. The axons of ascending arousal system run through hypothalamus where they contact lateral hypothalamic orexin neurons and maintain thalamocortical arousal. During wake state arousal system inhibits preoptic sleep promoting cell groups. There is a complex relationship between hypothalamic hypocretin system and dopaminergic system in basal ganglia and it functions as an external regulator of the flip-flop switch promoting wakefulness. PD patients have fewer dopaminergic neurons in cell groups of arousal system than controls.¹¹ Other foci of arousal such as noradrenergic and cholinergic nuclei are also depleted in PD. It has been hypothesized that dopaminergic dysfunction and neuronal degeneration can destabilize this switch and its regulators, promoting rapid transitions to sleep intruding on wakefulness and also disrupting nocturnal sleep. Hallucinations also have a disruptive effect on sleep, as they show a clear nocturnal preponderance and mostly visual.

However, sleep disturbances themselves, in particular, REM sleep abnormalities, represent the strongest predictor for the occurrence of hallucinations. Interestingly, hallucinations in PD may reflect intrusions of dream content into wakefulness, possibly due to degeneration of brainstem areas specifically involved in REM sleep regulation. This hypothesis is supported by increased nighttime RBD and abnormal REM sleep during

daytime napping in PD patients with hallucinations. EDS is very common symptom in PD. Gjerstad et al, & Boddy et al, 2007 proposed that excessive daytime sleepiness (EDS) is frequent in Parkinson's disease and its presence has been associated with longer disease duration and dementia.^{12, 13} EDS is currently part of the proposed criteria for Parkinson's disease related dementia as a supporting feature. EDS is due to multilayered causes primarily due to degeneration of sleep regulating centres, fatigue caused by the motor disability, night time awakenings due to akinesia, nocturia, hallucinations and RBD, dopaminergic treatment especially dopamine agonists. The presence of daytime rapid eye movement (REM) sleep intrusions associated with visual hallucinations and sleep onset REM periods in the multiple sleep latency test (MSLT) in some PD as seen in narcolepsy suggests that both disorders may share similar pathology. Like in narcolepsy, role of orexin/hypocretin system has also been postulated in development of EDS in PD and it has been hypothesized that degeneration of hypocretin neurons in hypothalamus is causing excessive daytime somnolence in patients with PD. However, cerebrospinal fluid (CSF) levels of hypocretin-1, which are typically low in narcolepsy have been normal in various studies in Parkinson's disease.¹⁴ In addition to hypocretin system, noradrenergic, cholinergic, and serotonergic system in pedunclopontine, raphe nucleus and locus coeruleus respectively causes disruption of sleep structure and EDS. Other comorbid conditions such as depression and anxiety also have negative impact on sleep quality. In polysomnography recordings destructuring of sleep has been observed in PD mainly the duration of NREM 2, 3

and REM.

Dopaminergic therapy and sleep

Chronic medication with levodopa may be one of the important factor resulting in poor night time sleep quality and excessive daytime somnolence. Levodopa induces sleep at lower doses but disruption of sleep and wakefulness at higher dose. However, because of alleviating effect of levodopa on motor symptoms may lead to improvement in sleep. Therefore the relationship between dopaminergic therapy and sleep is more complex. Studies have reported that dopaminergic drugs result in better sleep architecture due to improvement in nocturnal akinesia, nocturia and some of the dopa responsive nonmotor symptoms. However, worsening of nighttime sleep quality and daytime somnolence has also been reported in patients taking dopaminergic therapy. Some of the drugs such as ropinirole has beneficial effect on sleep quality while amantadine, selegiline may result into sleep disruption. One recent study has reported subjective sleep impairment in patients taking high doses of levodopa but there was no correlation with objective polysomnographic findings. Excessive daytime sleepiness rather improves after dopaminergic therapy due to improvement in motor symptoms.¹⁵

Management of sleep problems

Sleep disturbances in PD are multifactorial. Treatment requires detection of responsible factors and their management. There are various drugs also which help in improving sleep quality in PD patients. (table no. 1)

Table 1: Etiology and management of sleep disturbances in PD

SLEEP DISORDER	ETIOLOGY	MANAGEMENT
Nocturnal sleep disturbances	<ol style="list-style-type: none"> 1. Difficulty in turning inside bed 2. 'Off' dystonia 3. Dyskinesias 4. Nocturia 5. Restless leg syndrome 6. Drug effects: hallucinations 7. Rapid eye movement disorder of sleep 8. Sleep disordered breathing 9. Depression, anxiety 	<p>Titration of dopaminergic therapy Slow release levodopa preparation, Doudopa, apomorphine Management of autonomic symptoms Dopaminergic therapy for RLS and PLMS</p> <p>Modification of drug therapy</p> <p>Clonazepam</p> <p>Continuous positive airway pressure Antidepressants and anxiolytics</p>
Excessive daytime somnolence	<ol style="list-style-type: none"> 1. Disturbed nocturnal sleep 2. Dopamine agonists(Sleep attacks) 3. Degeneration of primary brain regions regulating sleep 	<p>Improvement of nocturnal sleep Removal of medication if possible Stimulants: modafinil, methylphenidate</p>

Conclusion

Sleep disorders are commonly found in patients with PD. It is often ignored due to prominent motor symptoms in PD. However diagnosis and treatment of sleep disturbances may lead to improvement in both motor symptoms and quality of life of PD patients.

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