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Parkinson's Disease and Sleep –Key Insights

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ABSTRACT

Parkinson's disease (PD) is characterized by motor symptoms such as bradykinesia, rest tremor, rigidity, and postural instability, alongside various non-motor symptoms. The prevalence of PD increases with age, particularly between ages 85 and 89, and exhibits a male predominance. Sleep disturbances affect 64% of PD patients, yet less than half report these issues to healthcare providers. Sleep disorders, including insomnia, restless legs syndrome (RLS), rapid eye movement (REM) sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), sleep-disordered breathing (SDB), and circadian rhythm disorders, substantially worsen non-motor symptoms and reduce quality of life. Neurodegenerative processes and dopaminergic dysfunction play critical roles in these sleep disturbances. Additionally, medications, co-morbidities, and genetic factors contribute to disrupted sleep patterns in PD.

Keywords: Parkinson's disease, sleep disturbances, bradykinesia, rest tremor, rigidity, postural instability, non-motor symptoms, insomnia, restless legs syndrome, rapid eye movement sleep behavior disorder, excessive daytime sleepiness, sleep-disordered breathing, circadian rhythm disorders, dopaminergic dysfunction, neurodegenerative processes

INTRODUCTION

The hallmark of Parkinson's disease(PD),which was first described by James Parkinson, includes bradykinesia, rest tremor, rigidity and postural instability, and a host of other motor and non-motor symptoms[1]. The prevalence increases with age, peaking between ages 85 and 89 years, with a male predominance. Most cases of idiopathic, however there are known genetic and environmental contributions [2]. The Braak hypothesis is the model most frequently used to explain the neuropathological course of Parkinson's disease. This concept proposes that the medulla and olfactory bulb are where the disease begins. This early pathology is linked to symptoms including diminished smell and rapid eye movement sleep behaviour disorder, which occurs before the development of the classical symptoms[3].

Sleep disturbances have been observed in 64% of patients with PD[4]. However less than half of sleep issues are reported to doctors and receive adequate care . Sleep disturbances in PD will raise the burden of non-motor symptoms in addition to motor dysfunction which can lead to reduced cognitive performance, a higher risk of falls, and a lower quality of life[5]. In addition this will also bring significant socio-economic consequences. Sleep is one significant disease-modifying element in this disease.

The most reported sleep disorders in PD include insomnia, restless legs syndrome (RLS), rapid eye movement (Rapid Eye Movement, sleep behaviour disorders (RBD), excessive daytime sleepiness(EDS) sleep disordered breathing (SDB) and circadian rhythm disorders[6].

Pathophysiology

Sleep disturbances in PD are intricately linked to the neurodegenerative process itself, influenced by the deposition of both alpha synuclein in the brain region that regulate sleep such as the locus coeruleus, raphe nuclei, paramammilary and

posterior hypothalamic nuclei, amygdala, and thalamus. Disruption of these structures and their interconnected circuits likely plays a critical role in the sleep disturbances commonly seen in PD, including insomnia, EDS and RBD. Additionally, motor symptoms like RLS, which significantly affect nocturnal sleep, and breathing disorders such as sleep apnoea, further contribute to the fragmented sleep-wake cycle seen in PD patients[7]. These combined factors result in severe disruptions to sleep quality and overall circadian rhythm in PD.

The dopaminergic system is crucial in regulating the sleep-wake cycle. Dopamine within the basal ganglia facilitates sleep through D2 receptors, whereas the dopaminergic pathways outside the basal ganglia support wakefulness via D1 and D2 receptors[8]. So dopaminegic dysfunction in PD can lead to sleep disturbances.

The neuropeptide orexin plays a key role in promoting arousal, and its deficiency may contribute EDS, as well as sleep attacks and narcolepsy-like symptoms in PD [9]. Disruptions in the circadian rhythm have also been observed in PD, which likely contribute to EDS. Patients exhibit a dampened, though still intact, circadian rhythm, characterized by a reduced amplitude in the melatonin cycle and lower overall 24-hour melatonin levels[10].

Histological studies have revealed pathological changes in both the suprachiasmatic nucleus and its afferent pathways originating from the photosensitive retinal ganglion cells in patients with PD which can lead to circadian rhythm disorders[11].

In addition to the impairments in brain function and neurotransmitter activity , several other significant factors also contribute to the sleep disturbances in PD . These include medications like dopamine agonists causing day time sleepiness and 'sleep attacks', antidepressants like SSRIs(Selective Serotonin Reuptake Inhiitors), SNRIs(Serotonin and Norepinephrine reuptake inhibitors), and TCAs(Tricyclic Antidepressants) used to treat the co morbid mood disorders can alter sleep patterns[12]. Other contributing factors are co-morbidities, PD-related symptoms such as nocturnal akinesia that disrupt sleep, and genetic factors that may predispose individuals to specific sleep and wakefulness disturbances [13]. Furthermore, the clinical profile of PD-RLS patients, marked by more severe non-motor symptoms, indicates that neurotransmitter systems beyond dopamine may be involved in the development of PD-RLS. This suggests that factors other than dopaminergic dysfunction could play a role in its etiology, necessitating further exploration of these complex interaction[14].

Clinical features

Insomnia

Insomnia is defined by the International Classification of Sleep Disorders, Third Edition, as difficulty initiating sleep, difficulty maintaining sleep, and/or early morning awakenings [15]. It is, reported in 44% of PD patients and is closely associated with longer disease duration, higher Levodopa equivalent dose, and more severe depression[16].

Rapid eye movement sleep behaviour disorders

RBD is a parasomnia marked by abnormal behaviours and the loss of muscle atonia during REM sleep. This can include vocalizations, jerks, and other motor actions that typically align with the content of dreams with most of the dreams being violent or aggressive, so that they can hurt themselves or bed partners[17].

Meta-analyses report showed that the pooled prevalence of RBD in PD as 42.3% [18] and 46%[19], with RBD occurrence associated with older age, longer disease duration, higher levodopa equivalent daily dose, worse motor and autonomic symptoms, and poorer quality of life[18,19].

Motor manifestations in PD with RBD seem to differ from those without RBD, exhibiting a non-tremor predominant phenotype and perhaps more postural instability and falls[20]. Interestingly, both video-polysomnography (PSG) analysis and reports from bed partners reveal a paradoxical alleviation of parkinsonism during complex RBD episodes. Movements during the episodes were faster, stronger, and smoother and speech was more louder. These suggest a transient restoration of motor function during REM sleep, potentially via bypassing the extrapyramidal system[21]. Additionally, RBD in PD is associated with visual hallucinations[22].It also serves as an early marker of neurodegenerative disease underscoring its potential role in early diagnosis and monitoring of disease progression[23]

Sleep waling which is an NREM parasomia has also been reported in PD patients. In most cases there was associated RBD. So there is still a need for polysomnographic confirmation of these episodes[24,25].

Obstructive Sleep Apnoea

OSA is a sleep-related breathing disorder caused by the repetitive collapse of the upper airway, leading to intermittent hypoxia and impaired ventilation during sleep. Diagnostic criteria for OSA include more than 15 respiratory events per

hour, or more than 5 events per hour when accompanied by typical symptoms such as snoring, fatigue, EDS, or co morbid conditions like hypertension, coronary artery disease, or stroke [26].It is estimated that 20% to 60% of PD patients have concomitant OSA[27]. Studies have shown that PD patients with OSA exhibit worse cognitive functionin[28].

Excessive Daytime Sleepiness

EDS can be defined as the tendency to nod or fall asleep in various situations during daytime. The prevalence of EDS in PD is 35%, with a higher incidence observed in older patients, those with longer disease duration, more severe motor and autonomic symptoms, higher levodopa equivalent daily dose , reduced autonomic functions, and more pronounced neuropsychiatric symptoms[16]. Key factors contributing to EDS include motor complications, such as wearing-off symptoms, the dosage of antiparkinsonian medications, and sleep-disordered breathing. In some cases, severe forms of EDS resembling narcolepsy may occur in PD patients[29].

Restless Legs Syndrome

RLS is characterized by an uncontrollable urge to move the legs, often accompanied by sensory symptoms and discomfort in the lower limbs, particularly around the ankles and knees which gets worsen during periods of rest and tend to subside with movement[30]. However other body parts like arms, abdomen, hips, trunk, genitalia, and even the head and face can also be involved[31,32,33]. It may also serve as a potential preclinical marker of PD[34].

In a recent meta analysis the pooled prevalence of RLS in PD was found to be 20% and was associated with female sex, a mixed motor phenotype, more severe motor symptoms, and non-motor symptoms like RBD, greater cognitive and autonomic dysfunction, increased neuropsychiatric symptoms, higher levels of fatigue, EDS, and poorer sleep quality and quality of life [35].

Periodic leg movement of sleep, which are stereotyped movements of the foot and leg typically recurring every 20-40sec mainly during the first part of night during NREM sleep, occur in more than 80% patient with RLS. However they are also well descried in PD in the absence of RLS[36].

Circadian rhythm disorder

Circadian rhythm disorders involve persistent or recurring sleep disturbances caused by disruptions in the circadian system or a mismatch between the body's internal circadian rhythm and external, socially imposed sleep-wake schedules[37].It can lead to an advanced or delayed onset of sleep in patients and create disruption of normal sleep and wake times[6]. It has been linked to decreased sleep quality during the night, as well as diminished daytime alertness and cognitive function[38].

Diagnosis

Commonly employed methods for detecting sleep disorders in PD include a comprehensive medical history, sleep quality questionnaires, and polysomnography. Recommended questionnaires, among others, include the Parkinson's Disease Sleep Scale (PDSS), the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and the Stanford Sleepiness Scale (SSS)[39] .The multiple sleep latency test (MSLT) is an objective assessment of daytime function in patients with chronic insomnia[40].Actigraphy or dim light melatonin onset may prove useful if a circadian disorder, such as delayed or advanced sleep phase syndrome or non-24-h sleep–wake disorder is suspected[41].

Treatment

The treatment should begin with education on sleep hygiene and non-pharmacological interventions. Pharmacological treatment typically starts by optimizing antiparkinsonian medications. Afterwards, medications tailored to the specific type of sleep disorder are introduced. Managing sleep issues in PD is a continuous process that requires careful attention to choosing the most effective treatment with the fewest side effects for lasting results[42].

Insomnia

Effective treatment for insomnia, whether pharmacological or behavioural, requires accurate identification of the insomnia type (initial, maintenance, or terminal) and the underlying factors. Levodopa–carbidopa controlled-release (LD-CR) may improve sleep-associated motor symptoms in PD, but evidence on its effect on sleep parameters is limited. Studies showed some improvement in nocturnal akinesia with LD-CR, but no significant changes in total sleep time or sleep fragmentation[43].

Certain studies have shown that dopamine agonists like ropinirole and pramipexole have shown modest improvements in insomnia symptoms. Ropinirole prolonged release (PR) improved nocturnal symptoms and sleep quality in advanced PD

patients[44] while pramipexole sustained release (SR) also demonstrated beneficial effects[45].Similarly, rotigotine patches have significantly improved sleep in PD patients with early-morning motor symptoms[46].

Observational studies suggest that treatments providing consistent dopaminergic stimulation, such as apomorphine and levodopa gel infusion, can enhance sleep quality and reduce sleep fragmentation in advanced PD. These findings suggest that medications providing stable dopamine levels may be key in managing PD-related insomnia[47,48].
A prospective observational by Schettino C et al showed that Rasagiline, added to levodopa significantly improved sleep latency and total sleep time[49].

Eszopiclone, FDA(Food and Drug Administration) approved for the treatment of sleep initiation and maintenance insomnia , has shown significant benefits in PD patients. A randomized controlled trial (RCT) involving 30 PD patients found that a dose of 2 to 3 mg of eszopiclone significantly improved several sleep parameters, including reduced nocturnal awakenings and improved sleep quality ratings. However, 13% of patients experienced side effects such as daytime sleepiness and dizziness[50].

Doxepin, at doses of 3-6 mg, was tested in a trial involving 18 participants. Compared to placebo, doxepin (10 mg) resulted in significant improvements in insomnia severity index scores, sleep quality, and fatigue. However, 50% of participants reported side effects such as fatigue, orthostatic dizziness, and nausea[51].

A meta-analysis of 7 studies found that melatonin significantly improved subjective sleep quality in PD patients.[42].
In individuals with PD and psychosis, pimavanserin, a serotonin 5HT2A receptor inverse agonist/antagonist, has shown promise in improving insomnia symptoms. In two RCTs, pimavanserin (34 mg) significantly improved night time complaints compared to placebo, with a notable reduction in insomnia-related issue[52].

Nonpharmacological treatments, such as cognitive behavioral therapy for insomnia (CBT-I) and bright light therapy (BLT), also remain valuable approaches in managing sleep disturbances in PD[53,54].Exercise, including Tai Chi, offer useful non-drug options for managing sleep problems in PD[55].

Studies have shown Deep Brain Stimulation (DBS) significant improvements in sleep quality, sleep latency, sleep efficiency, sleep duration, and insomnia symptoms in PD patients after treatment[56, 57].

RBD
First-line interventions for managing RBD should include a thorough evaluation of environmental safety. To mitigate the risk of injury during episodes, recommendations may include the installation of bed rails to prevent falls from bed. Additionally, it is crucial to remove any dangerous objects or weapons from the patient's immediate surroundings, particularly from within or near the bedroom, to reduce the potential for harm during violent dream enactment behaviors[58,59].

In the treatment of RBD associated PD, several pharmacological interventions have been explored. Clonazepam is one of the most commonly used medications, demonstrating effectiveness in reducing the frequency of violent dream enactment behaviours and improving symptoms in a majority of patients[59,60]. However, long-term use can be associated with side effects such as morning sedation, confusion, dizziness, and falls, particularly in older patients or those with neurodegenerative conditions [61]. Despite some positive case series, the results of large-scale clinical trials, including a recent placebo-controlled study, have been inconclusive regarding the efficacy of clonazepam in treating RBD in PD[62].
An RCT suggested that exogenous melatonin, can be considered as a potential monotherapy or adjunctive therapy for patients with RBD in patients with neurodegenerative disorders [63]. However certain RCTs failed to demonstrate a positive effect of melatonin on RD in PD[64].

Pramipexole, paroxetine, donepezil, and rivastigmine may help in some refractory cases of RBD, though evidence remains inconclusive due to a lack of large RCTs [65]. Rivastigmine has shown some promise in reducing RBD episodes in small studies of PD and mild cognitive impairment patients[66].

Medications that can worsen RBD, including SSRIs, SNRIs, and tricyclic antidepressants, should be discontinued or avoided[67]. Alcohol use can also exacerbate RBD episodes and should be limited in individuals who show a correlation between alcohol use and RBD[68].

“Pseudo-RBD" can occur in patients with OSA, leading to agitated arousals due to obstructive events [69]. Diagnosing and treating OSA with CPAP

(Continuous Positive Airway Pressure) is crucial in patients with both OSA and co morbid RBD to reduce nocturnal behaviours [70].

Restless Legs Syndrome

If RLS is mild, it can often be managed through lifestyle changes alone. Before initiating pharmacological treatment, it is important to assess the frequency, duration, and impact of symptoms on the patient's quality of life. Additionally, screening for secondary causes is essential, including chronic renal failure, deficiencies in iron, vitamin B12, and folic acid, as well as evaluating serum glucose and HbA1C levels. Serum ferritin should be measured, and if it is below 50–75 µg/mL or transferrin saturation is under 20%, oral iron supplementation is recommended. It is also recommended to discontinue medications that may worsen RLS, such as antidopaminergic drugs, antihistamines, and antidepressants (with the exception of bupropion)[71].

Therapeutic options include calcium channel alpha-2-delta ligands (pregabalin, gabapentin, enacarbil) and low-dose dopamine agonists[72]. However dopamine agonist may cause augmentation of RLS.To prevent that long-acting DAs should be preferred [71].

In cases that are resistant to other treatments, low doses of opioids, such as long-acting oxycodone or methadone, may be considered, but should be avoided in patients with a high risk of addiction or those with pre-existing conditions such as severe constipation, sleep apnea syndrome, or prolonged QTc. Additionally, patients may find temporary relief by rubbing or massaging the affected limbs, bathing in hot or cold water, engaging in physical activity, or distracting themselves with mental exercises, such as reading an interesting book when symptoms first appear[73].
DBS of the subthalamic nucleus has shown to provide symptom relief in most PD patients with RLS[74].

Excessive Daytime Sleepiness (EDS)

The first step in the management of EDS is to identify and address any potential sleep disorders that may interfere with nocturnal sleep. Additionally, it is important to review and adjust medications that could contribute to hypersomnia, such as antidepressants, antipsychotics, or sedatives. Educating patients on proper sleep hygiene is also a crucial aspect of treatment. When it comes to medication management, dopamine agonists have been found to cause more EDS compared to levodopa, with the degree of sleepiness directly related to the dose of the dopamine agonists . On the other hand, medications like selegiline, amantadine, and entacapone have shown no significant impact on EDS[75, 76,77,78].
The pharmacological treatment options include , modafinil and caffeine which are the primary wake-promoting agents[79].

Obstructive Sleep Apnoea

PD-related upper airway dysfunction may worsen OSA by reducing airway stability. A study showed that long-acting levodopa at night helped reduce OSA severity in PD[80].

A short-term randomized crossover trial in PD showed that CPAP treatment for OSA improved objective daytime sleepiness, sleep quality, AHI((Apnoea Hypopnoea index), and oxygen saturation [81].Another cohort study a demonstrated improvement in non-motor symptoms overall, subjective sleep quality, anxiety, and cognitive function with CPAP treatment[82]. However due to cognitive deficits, motor issues, and other factors like nocturia, anxiety, and RBD , many patients discontinues treatment[83] .

Alternatives like mandibular advancement devices (MAD) have shown promise, improving sleep and apnoea severity, with better compliance compared to CPAP[84] .

Circadian rhythm disorder

Light therapy demonstrates promising results in improving sleep and alertness in PD, with positive effects on sleep, mood, and other non-motor symptoms associated with the condition[85, 86]. Other treatment options including physical exercise and melatonin may be beneficial but have not been systematically evaluated in patients with PD[6].

CONCLUSION

In conclusion, sleep disorders in PD significantly impact patients' quality of life and are closely linked to motor and non-motor symptoms. Conditions such as insomnia, excessive daytime sleepiness, restless legs syndrome, and REM sleep behaviour disorder are common in PD. These disturbances often worsen with disease progression and complicate the management of PD. While interventions such as dopaminergic therapy optimization and sleep hygiene education are essential, pharmacological treatments show variable efficacy and may have side effects. Ongoing research is needed to better understand the pathophysiology and develop more effective, personalized management strategies for sleep disturbances in PD.

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