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Sleep Disturbances in Parkinson's Disease: A Scoping Review

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Abstract: Neurodegenerative diseases (ND), such as Parkinson's disease (PD) and Alzheimer's disease (AD), are characterized by progressive neuronal loss and degeneration, leading to both motor and non-motor symptoms, including sleep disturbances. Sleep disorders are highly prevalent in PD, affecting between 60% and 98% of patients. These include insomnia, excessive daytime sleepiness (EDS), sleep-disordered breathing, obstructive sleep apnea (OSA), restless legs syndrome (RLS), circadian rhythm disorders, and REM sleep behavior disorder (RBD). This article provides a comprehensive literature review on the pathophysiology, diagnosis, and management of sleep disorders in patients with PD. We highlight the significant impact these disturbances have on quality of life and emphasize the importance of regular screening and individualized treatment plans. Additionally, we discuss the challenges posed by non-motor symptoms in PD, particularly those related to sleep, as they often do not respond well to traditional dopaminergic therapies. Future research should aim to enhance diagnostic techniques and develop more targeted, patient-centered interventions to improve the management of sleep disorders in PD.

Keywords: Parkinson's Disease; Sleep Disorders; Neurodegenerative Diseases; Insomnia; Excessive Daytime Sleepiness; Obstructive Sleep Apnea; REM Sleep Behavior Disorder; Restless Legs Syndrome; Circadian Rhythm.

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1. Introduction

Neurodegenerative diseases (ND) are characterized by a heterogeneous group of complex disorders with characteristics of neuronal loss and progressive degeneration in different regions of the nervous system [1]. Furthermore, ND is becoming increasingly common and a growing cause of death and morbidity worldwide, being more prevalent in the elderly. Some of the main neuropathological features include manifestations of resting tremor, rigidity, postural instability (gait disturbance), bradykinesia, cognitive impairment, depression, sleep problems, and sensory imbalance [2]. In addition, air pollution [3], excessive alcohol consumption [4], and traumatic brain injury [5] have recently been included in the updated dementia prevention model with 12 risk factors across the life course (hypertension, low education, smoking, hearing impairment, obesity, depression, sedentary lifestyle, diabetes, and low social contact) [6], thus Parkinson's disease (PD) and Alzheimer's disease (AD) are currently considered the main neurodegenerative diseases [7].

Furthermore, Parkinson's disease is the second most common neurodegenerative disease, affecting more than 6 million people worldwide. This figure represents a 2.5-fold increase in prevalence compared to the previous generation, making Parkinson's disease one of the leading causes of neurological dysfunction [8]. It is classified as a synucleinopathy, as these are neural inclusions in the form of Lewy bodies and Lewy neurites that show cell loss in the substantia nigra and other areas of the brain [9]. However, PD is highly complex and heterogeneous, and it is difficult to estimate the prognosis of an individual patient. Older age, male gender [10], comorbidity (cancer, metabolic syndrome, low body mass index, vascular risk factors), axial motor dysfunction [11], cognitive and early autonomic dysfunction are indicative of a worse prognosis. In addition, low levels of vitamin B12 have recently been associated with a worse prognosis [12].

However, prodromal symptoms of pre-motor features can precede the motor symptoms of PD by many years. These include constipation, hyposmia (change in sense of smell), REM sleep disturbance, orthostatic hypotension, depression, urge incontinence, and erectile dysfunction [13]. In addition, PD is characterized by "classic" motor symptoms such as resting tremor (initially unilateral), bradykinesia (slowness of movement), rigidity, dragging gait, and postural instability. The symptoms are progressive, but the rate of motor progression is variable [14]. Finally, concomitant with this are non-motor symptoms, which can represent a major challenge to quality of life and appropriate treatment in PD, since they usually do not respond as well to dopamine therapy as motor symptoms [15]. Thus, non-motor symptoms include behavioral/neuropsychiatric changes, autonomic nervous system insufficiency, cognitive changes, and sensory and sleep disorders [16].

In addition, sleep disorders, being one of the most frequent non-motor signs in Parkinson's disease (PD), have the capacity to appear at any stage of the disease, entailing a significant burden for patients and their caregivers. Studies indicate that between 60% and 98% of individuals with PD experience sleep difficulties, with up to 60% facing such problems even before any obvious motor manifestations appear [17]. The most commonly cited sleep disorders in PD include insomnia, restless legs syndrome (RLS), rapid eye movement sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), obstructive sleep apnea (OSA), and circadian rhythm disorders [18]. These conditions can result in decreased sleep quality, as well as causing evident changes in Polysomnography (PSG) [19].

Therefore, the aim of this study is to carry out a broad literature review and evaluate common sleep disorders in patients with Parkinson's Disease including insomnia, excessive daytime sleepiness (EDS), sleep-disordered breathing, obstructive sleep apnea (OSA), restless legs syndrome (RLS), circadian rhythm disorders, and behavioral REM sleep disorders (RBD), since identifying and treating these problems are fundamental given the negative impact they have on the quality of life of people with PD.

2. Method

We searched Medline and PubMed from January 2005 to December 2024 for relevant articles using the keywords “Parkinson’s Disease,” or “neurodegenerative diseases,” or “pathophysiology PD” or “parkinson prodromal symptoms,” or “parksinon sleep disorders”. The initial search produced 801 hits and, after selection based on the abstracts, a total of 19 articles on etiology, diagnosis, pathophysiology or treatment were chosen and reviewed, after excluding articles that followed the first set of criteria - exclusion of articles not included in the 2014-2024 search period, as well as articles that were not originally in English. Additional references were obtained from these articles and from the authors of this review.

3. Results and Discussion

3.1 Insomnia and daytime sleepiness in Parkinson's disease

Difficulty initiating sleep, maintaining it, and waking up earlier than desired for a minimum of 3 days a week over 3 months characterizes insomnia [20]. Sleep initiation problems decrease over the course of PD, while sleep maintenance problems increase, affecting up to 85% of patients [21]. Barone et al. found that, regardless of the severity of the disease, the prevalence of insomnia is reported to be between 37 and 83% [22]. In another study involving 1,447 patients with Parkinson's disease, the authors found that the prevalence of chronic inability to sleep was 36.9% (95% CI 33.3-40.5). Difficulty initiating sleep was 18.0% (95% CI 15.1-20.9), interrupted sleep 81.54% (78.5-84.4), awakenings during the night 31.3% (27.8-34.8), early morning awakenings 40.4% (36.8-44.1), and non-restorative sleep 38.5% (34.8-42.1) [23].

Obstructive sleep maintenance, also known as sleep fragmentation, is the most common subtype of insomnia in PD [24]. In addition, prolonged sleep fragmentation has been associated with problems with executive functions, such as lack of attention, phonemic verbal fluency, and working memory [25]. A study carried out in the community showed that frequent nocturnal awakenings occurred in almost 40% of patients [26]. Furthermore, related to diagnosis, the most recent Parkinson's Disease Sleep Scale (PDSS-2) addresses sleep initiation, sleep maintenance, and daytime sleepiness [27]. The SCOPA Sleep Scale is a questionnaire with two subscales: a nighttime scale that examines sleep onset, sleep fragmentation, sleep efficiency, early morning awakening, and sleep duration, and a daytime scale that evaluates alertness [28].

For the diagnosis of primary insomnia, both in the general population and in PD, polysomnography (PSG) is not indicated because the diagnosis is based on clinical criteria. However, when coexisting sleep disorders related to PD are suspected, such as sleep-disordered breathing, PSG is recommended. Another objective tool is actigraphy, which has gained interest due to its ease of use and ability to monitor rest-activity cycles over a prolonged period of time [29]. In addition, insomnia is linked to autonomic dysfunctions such as gastrointestinal, urinary, pupil motor, and thermoregulatory dysfunctions [23], and also to lower scores on cognitive tests in PD and depression [30]. However, sleep quality is crucial for PD patients. It has long been referred to as the "sleep benefit in PD," which highlights the improved performance and responsiveness to dopaminergic drugs after a good night's sleep [31].

A common symptom of PD is excessive daytime sleepiness (EDS), which can occur in 15-21% of cases early in the disease and up to 46% as the disease progresses [32]. Furthermore, a study on early and untreated PD showed that EDS may be linked to disease progression and independent of other sleep disorders. Other studies have shown that dopaminergic medication appears to increase EDS depending on the dose [33]. However, EDS is still an underestimated feature despite its importance, especially after reports of PD patients (taking dopamine agonists) falling asleep while driving [34]. Studies using the Epworth Sleepiness Scale that assessed daytime sleepiness in PD found varying results, such as 9.3% [23], 33% [35], and 43.2% [36].

Furthermore, a 3-year follow-up showed that in early PD, daytime sleepiness increases significantly over time, with a dose-dependent effect of dopaminergic therapy. This indicates that PD-specific therapy is more relevant than the pathophysiological mechanisms contributing to excessive daytime sleepiness in PD [37]. Finally, advanced age, advanced stage of PD, postural instability and gait disturbances, autonomic dysfunction, and mood disorders are associated with PD [38]. Managing EDS requires identifying potential reversible causes, such as reducing or ceasing dopamine agonists [39].

3.2 Sleep-disordered breathing in Parkinson's disease

Sleep-disordered breathing (SBD) includes obstructive sleep apnea (OSA), sleep hypoventilation, central sleep apnea, and sleep hypoxemia. In PD, OSA is the most common form of SBD [40]. One study identified that manifest or subclinical sleep-disordered breathing is present in up to 50% of people with PD; however, compared to patients without PD, the sleep structure in PD is not resolved by CPAP treatment [41]. OSA has a prevalence in PD of 20-60% [42]. However, there is considerable variability in study methodologies, including the scoring system used by different sleep laboratories [43]. Neikrug et al. reported that the CPAP device is well accepted by individuals with PD who have mild to moderate symptoms [44]. In addition to treating obstructive sleep apnea, CPAP has also shown benefits in improving concentration and the ability to be alert in individuals with OSA [45]. However, Harmell et al. found no evidence of improvements in cognitive ability in individuals with PD due to OSA after undergoing 3 and 6 weeks of CPAP treatment. Another study showed that the MoCA test score increased by an average of 1.6 ± 1.9 points ($p = 0.043$) after 6 months of CPAP use [46].

In addition, high BMI is associated with a higher risk of OSA [47], but it is not related to the severity of OSA in PD [48]. In a group matched by BMI, only 10% of PD patients had severe sleep apnea [49]. Thus, upper airway obstruction, such as laryngopharyngeal motor dysfunction, has been reported as a possible mechanism of OSA [50]. Furthermore, central and obstructive apnea has a high incidence and is found in moderate-severe PD [51]. Various factors can contribute, such as abnormal movement of the glottic-supraglottic structures and stridor, rigidity, and diaphragmatic dyskinesias [52].

Some studies have reported the association of levodopa with OSA [53]. OSA is related to cognitive dysfunction and excessive daytime sleepiness [54]. Thus, the patients with the worst cognitive dysfunction are those with PD, RBD, and OSA [55]. Arnulf et al. found that 20% of 54 PD patients who received levodopa or a combination of levodopa and dopamine agonists referred for somnolence had sleep apnea, which is classified as moderate or severe [56]. Therefore, chronic sleep deprivation caused by disordered breathing during sleep is a risk factor for cardiovascular and cerebrovascular diseases. When left untreated, sleep apnea can cause problems such as sleep deprivation, daytime sleepiness, tiredness, headaches in the morning, and lack of concentration [57]. As a general rule, PD patients with relevant sleep apnea should receive treatment due to the likely long-term negative cardiovascular outcomes [58].

3.3 Circadian rhythm disorders in Parkinson's disease

Circadian rhythm dysfunctions are identified by the constant or repeated occurrence of sleep problems caused by changes in the circadian system or a mismatch between the endogenous circadian rhythm and socially determined sleep-wake schedules [59]. Individuals with PD may experience fluctuations throughout the day in their motor and non-motor symptoms, even when the pharmacokinetics of dopaminergic drugs are stable. In addition, there may also be seasonal variations as the disease progresses [60].

The mechanisms behind these changes are still not fully understood. The deterioration of the centers responsible for sleep and wakefulness is a characteristic of neurodegeneration. Specific changes associated with Parkinson's Disease may impair communication with the hypothalamic suprachiasmatic nucleus (SCN), which is essential for circadian rhythm. For example, the lack of exposure to natural light and the loss of dopamine cells in the retina of Parkinson's patients can interfere with the regulation of light and dark cycles. Dopamine therapy can have both positive and negative effects on the circadian rhythm [61]. Furthermore, dopamine and the circadian cycle have a bidirectional influence of modulation [62]. The motor and non-motor signs of PD show significant variations throughout the day that can be affected by the circadian cycle. Hormonal and molecular indicators of circadian rhythm, such as melatonin and clock genes, show less intensity in their circadian cycles in individuals with PD compared to healthy people [63].

Circadian rhythm-focused approaches, such as the additional use of light (light therapy), show positive benefits on sleep patterns, mood, and motor symptoms in Parkinson's disease [64]. In the context of PD, light therapy (LT) contributes to reducing tiredness during the day, improving sleep quality, ease of sleep, and mood regulation [65]. In addition, studies have shown that light therapy has benefits for motor performance in PD [66]. Individuals with Parkinson's disease have been found to experience disruptions in temperature control throughout the day, with significant decreases in the rhythm-adjusted mean core body temperature (CBT) value and less pronounced CBT rhythms, both of which are strongly associated with severe sleep disturbances [67]. Elements of the endocrine system are seen as the main 24-hour biological markers, and alterations in hormonal cycles have been highlighted in Parkinson's disease. Specifically, individuals with Parkinson's do not show significant changes throughout the day in melatonin levels [68].

Research into alterations in the biological clock has shown a reduction in the expression of BMAL1 mRNA in people with Parkinson's disease. Compared to healthy people, BMAL1 expression levels at night were significantly lower in groups of Parkinson's patients (including those who had previously received treatment or were currently undergoing treatment, as well as those who were not undergoing treatment, known as drug-naive patients) [69]. According to the same research, BMAL1 indices were related to the intensity of PD [69]. Individuals with PD were also found to have increased activity of the PER2 and REV-ERBα genes early in the day [63]. Finally, previous studies have found that dopaminergic therapy can impact sleep and wake patterns in individuals with Parkinson's disease [70]. It has been determined that the use of L-Dopa can advance the stage of the melatonin cycle [71].

3.4 Restless Legs Syndrome in Parkinson's Disease

Restless legs syndrome is characterized by an uncontrollable urge to move the legs, especially during rest. This sleep disorder affects around 30 to 80 percent of people with Parkinson's disease and usually manifests itself very early in the disease. Some scientists argue that the occurrence of Parkinson's disease and restless legs syndrome may be linked to a lack of dopamine in the body [72]. A study analyzing various research studies revealed that the rate of RLS in PD is 14% and is slightly higher in individuals who have previously undergone treatment for PD (15%) compared to those who have not received drug treatment (11%) [73]. One study found that SPI is associated with an increased risk of PD (0.37% incidence of PD in the SPI population versus 0.13% in the control group) [74]. In addition, Lee et al. suggested that the development of SPI in PD was related to the duration of anti-Parkinson's treatment [75]. Similarly, other researchers have reported no association between untreated PD and PIS [76]. Other studies show that PD patients with SPI have older age at PD onset, advanced PD stage, severe limb parkinsonism, depression, anxiety, dysautonomia and worse nutritional status [77].

Ferini-Strambi et al. recently reviewed the literature on three main pathophysiological hypotheses [78]. Firstly, given the common response to dopaminergic therapy, SPI and PD may share a common dopaminergic pathophysiology and possible genetic associations [79]. Secondly, IPS in PD may have a different mechanism to idiopathic IPS, and thirdly, PD and IPS may be two diseases with different correspondences [78]. Otherwise, the interaction between SPI and PD has not been confirmed. In addition, there is evidence of an association between IPS and reduced iron stores in many cases of IPS (with or without concomitant PD) [80].

Furthermore, four criteria are needed to diagnose PIS: (1) the need to move the limbs due to discomfort or severe pain (some patients may also have symptoms in the arms or back); (2) appetite occurs or worsens during periods of rest; (3) appetite may be present during the day, but worsens at night; (4) cravings are weakened or relieved by movement. A fifth criterion was added, stating that the above characteristics should not be explained solely by another medical or behavioral disorder, such as muscle pain or leg cramps. This is particularly important in PD, as patients may experience symptoms of restlessness or

tremors at night that can mimic SPI. Movement often does not relieve these symptoms, which can help to distinguish between nocturnal motor symptoms in PD and in PIS [81].

Finally, the treatment of PIS in PD is behavioral and pharmacological. Conservative measures, such as avoiding alcohol or caffeine and light or moderate exercise, can be used at the start of treatment [82]. Reducing or discontinuing offending medications (e.g., serotonergic antidepressants) should be approached with caution due to the high prevalence of concomitant depression and anxiety but can also help reduce symptoms [83]. If the ferritin level was < 75 ng/ml and/or the transferrin saturation index was < 20%, oral ferrous sulphate with 325 mg of vitamin C was recommended [84]. In cases where oral supplementation is not tolerated or a rapid response is required, 1 g of iron dextran or iron carboxymaltose in two separate doses 1 week apart may be useful. Clinical improvement can be expected in 50-60% of patients and, interestingly, is often delayed by 3-5 weeks [81]. However, iron supplementation has not been studied in the PD population and it is not yet known whether oral or intravenous supplementation is beneficial [85].

3.5 Behavioral REM sleep disorder and other parasomnias

REM sleep has been a specific topic of studies on sleep disorders in PD. Lack of REM sleep is often associated with ailments including shorter REM sleep [86] and longer latency to reach the REM stage [87], although there is still a conversation around the extent of these changes [88]. Additionally, the EEG of REM sleep is often characterized by a continuous increase in high theta/alpha frequencies (7.8-10.5 Hz) at the onset of sleep in individuals with Parkinson's [89], although the usefulness of these changes is questioned [90]. Diederich and his collaborators concluded that sleep "disorganization," which is characterized by longer sleep duration, less time in deep sleep, and reduced sleep efficiency, is related to the progression of PD, independently of other relevant disease factors such as medication [88].

Disruptions in the REM sleep stage are responsible for one of the most frequent sleep disorders related to PD, REM sleep behavior disorder (RBD), which is characterized by complex motor behaviors and loss of muscle atonia during REM sleep. In the general population, the incidence of RBD is approximately 0.04-0.05% [91]. In contrast, RBD manifests in up to 47% of PD cases [92]. However, the cumulative risk of neurodegenerative disease 14 years after the onset of RBD exceeds 90% [93]. As such, RBD is considered a prodromal marker of neurodegeneration, most strongly linked to synucleinopathies [94]. RBD has the highest predictive capacity and specificity of any prodromal indicator of PD [95]. In addition, it is an indicator of cognitive decline and increased motor symptoms [96].

The locus coeruleus is crucially involved in the PD prodrome [97]. It has been proposed that the LC is a relevant area to be studied in experimental animal models to better characterize the PD prodrome [98]. In addition, restless legs syndrome (RLS), a comorbid sleep-wake disorder characterized by an uncontrollable compulsion for limb movement, often accompanied by an unpleasant sensation in the limbs, is reported in up to 20% of Parkinson's patients [99] and is observed in 3.9-14.3% of the general population [100]. Furthermore, it has been suggested that dopaminergic pharmacological therapy, as opposed to the disease, is the most relevant factor for SPI [101]. Although recent studies have highlighted a connection between the two disorders [77]. It has been suggested that PD is a risk factor for motor restlessness in the legs, often mistakenly identified as PIS [102].

3.6 Assessment and treatment of sleep disorders in Parkinson's disease

Based on the various clinical manifestations and pathophysiological mechanisms of sleep disorders described in PD patients, it is clear that treatment should be individualized according to the predominant clinical symptom and the specific sleep-related diagnosis. However, a major problem is the scarcity of randomized clinical trials on sleep disorders in PD [103]. Sleeping pills are sometimes recommended to treat insomnia in PD

patients, but caution should be exercised about the possible worsening of daytime sleepiness or sleep-related breathing. Quetiapine is sometimes used clinically, and clozapine has been used with standard therapies for very severe insomnia. Melatonin therapy is not specifically indicated for insomnia in PD, but is often used for RBD. Rotigotine has been reported to improve sleep quality and consistency in PD patients, promoting sleep stability and increasing REM sleep [104].

In general, however, there is insufficient evidence of drugs to treat insomnia in PD patients, although eszoplicon and melatonin are considered "potentially beneficial." Some authors suggest that cognitive-behavioral treatment of insomnia, such as in PD patients, may be beneficial [105]. To treat daytime sleepiness in PD, caffeine [106] and modafinil can be used [103].

In addition, there is some controversy regarding the treatment of sleep-related breathing disorders. If sleep apnea is moderate or severe, PD patients may be prescribed positive airway pressure therapy [107]. However, the response to this treatment in terms of improved sleep patterns or daytime sleepiness is less clear than in PD patients [108]. Due to motor impairments, PD patients often have difficulty operating a CPAP machine. Intraoral devices as an alternative therapy in certain patients with obstructive sleep apnea may also be limited in patients with abnormal salivation or orofacial dyskinesia [103].

In the treatment of circadian disorders, phototherapy has shown promising results on sleep and arousal in PD, with beneficial effects on sleep, mood, and other non-motor symptoms of PD [109]. As there have been no treatment trials for SPI concomitant with PD, the most commonly used drugs in the PD population are the same as in the general population with SPI, i.e., dopamine agonists, alpha-2, delta calcium channel agonists, clonazepam, and opioids [110]. As dopamine agonists and levodopa are already used to treat the motor symptoms of PD, adjusting the dose according to the time of onset of the symptoms of SPI may be beneficial. If ferritin levels are low, iron supplementation should be considered [79].

Furthermore, the treatment of REM sleep behavior disorder should include safety measures to ensure maximum safety in the sleep environment. Such measures may include removing objects near the bed that could cause injury during dream imagery, or adjustments by moving furniture or using pillows to cover furniture, walls, and floors. Bed partners should be instructed to sleep separately. Medications that can worsen RBD (e.g., antidepressants) should be avoided if possible [111]. In preliminary studies, bed alarms have been shown to be beneficial for RBD [112]. In addition, rotigotine has been shown to improve RBD in one study [113]. A reduction in the frequency of RBD episodes (according to bed partner diaries) was observed with rivastigmine in a double-blind crossover study in 12 patients [114]. Based on case reports and series, effective drug therapy includes clonazepam and melatonin, but there are no double-blind, placebo-controlled studies [110].

4. Conclusion

PD is associated with various sleep disorders, which are common and significantly affect quality of life. Routine analysis of sleep problems by healthcare professionals can enhance their detection and clinical treatment. The analysis of sleep disorders has been reviewed in this article. Future research should focus on improving selection and diagnostic techniques for individuals with PD. Additionally, patient-centered therapeutic plans and mechanisms should be further developed. Managing sleep disorders in Parkinson's disease patients is a time-consuming task that requires constant review. The priority is to find the most appropriate treatment, aiming to minimize side effects and ensure lasting and consistent improvement.

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