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Review/ Praca poglądowa

# Sleep disorders in Parkinson's disease

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ABSTRACT

The clinical presentation of Parkinson's Disease (PD) encompasses a wide spectrum of non-motor symptoms, among which sleep disruption is one of the most common and occurs in virtually all patients with PD. Sleep disorders are complex including insomnia, restless legs syndrome, periodic limb movements of sleep, rapid eye movement sleep behavior disorder (RBD), sleep fragmentation and excessive daytime sleepiness. Sleep disturbances are independent and important determinant of poor quality of life, influence daily living and can be an important factor contributing to earlier institutionalization. Sleep disorders (RBD) are markers of prodromal PD, additionally they may influence the process of neurodegeneration. Sleep problems frequently remain undeclared by patients and under-recognized by healthcare professionals, leaving many patients without adequate treatment. In this work we review the current knowledge on sleep disorders in PD with the emphasis on therapeutic options including pharmacological and surgical procedures.



## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, with its prevalence being estimated at 0.3% of the entire population in the developed countries [1].

The clinical presentation of PD encompasses cardinal motor signs (bradykinesia, rigidity, resting tremor, and postural instability), and a wide spectrum of non-motor symptoms (NMS). The most common non-motor manifestations include behavioral and mood disorders (apathy, anhedonia, anxiety, depression, dopamine dysregulation syndrome, impulse control disorders, fatigue), cognitive dysfunction (from mild cognitive impairment to dementia), sensory abnormalities (anosmia, pain, paresthesias, impaired visual acuity, contrast and color sensitivity), dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, sialorrhea, sweating, weight loss) and disorders of sleep and wakefulness. Sleep disorders (SD) are complex

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and include insomnia, sleep fragmentation, rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), vivid dreaming and hallucinations, sleep disordered breathing, excessive daytime sleepiness and sleep attacks [2, 3].

Moreover, according to many studies NMS are more disabling than motor symptoms and are a key determinant of quality-of-life impairment [2–4]. Depression, clinical fluctuations and the advanced stage of the disease were found to be the major contributors to quality-of-life impairment [4].

Sleep disruption is one of the most common non-motor symptoms occurring in virtually all patients with PD [5–7]. SD as RBD may appear early in the disease course, hence they can be used as markers of the prodromal phase of PD [3, 8]. Preceding clinical diagnosis, sleep disturbances are regarded as a potential factor contributing to the process of neurodegeneration [9].

Studies show that SD are independent and important determinants of poor quality of life, of both patient and caregiver [5, 6]. Sleep disruption influences daily living and can be an important factor in the development of depression and cognitive decline as well as contributing to earlier institutionalization [5, 10].

Sleep problems as well as other NMS frequently remain undeclared by patients and under-recognized by healthcare professionals, leaving many patients without adequate treatment [3].

The aim of this work is to review the current knowledge on sleep disorders in PD with the emphasis on therapeutic options including the role of pharmacological and surgical procedures.

## Insomnia

Insufficient sleep and sleep fragmentation are, overall, the most common night complaints reported by up to 80% of patients with PD [11]. Patients complain of difficulty in falling asleep (sleep initiation, sleep onset insomnia), staying asleep once sleep is achieved (sleep maintenance insomnia) and premature awakening in the morning [6, 11]. Sleep maintenance insomnia is the most common of these three problems and occurs in up to 88% of patients with PD [6]. Furthermore, difficulty in staying asleep is listed among the top five most troublesome symptoms of advanced PD [10]. The underlying etiology is multifactorial, including motor problems, mood disturbances, a degenerative process of the sleep regulating systems and adverse effects of antiparkinson drugs [12]. The major motor symptoms of PD (bradykinesia, rigidity and tremor) are reduced during sleep; however, they can still be troublesome to patients [13]. Tremor can contribute to light sleep and once a patient is awakened it may prevent returning to sleep [13]. Rigidity can be a major cause of nocturnal pain and complaints of stiffness [13]. Bradykinesia impedes mobility and makes it difficult to assume a comfortable position in bed [13]. Dystonic spasms and postures usually occur in the morning and can be very painful (so called early-morning dystonia, usually within the foot) [13]. Abnormal absorption and accumulation of levodopa during the day can result in severe dyskinesia in the evening (“time bomb effect”) and delay sleep onset [13, 14]. Depressed patients with advanced PD complain of insomnia more often than others and nocturnal motor symptoms in this group of patients are more pronounced [12]. Autonomic dysfunction symptoms (dysautonomia), like nocturia, can also have an impact on sleep [10]. Bladder hyperactivity in PD leads to urgency, frequency and the need to get up at night many times [15, 16]. Nocturia is the most common urinary symptom, which is reported by over 60% of patients [16].

To our knowledge, there has been only one autopsy study primarily comparing PD and PD/dementia patients with versus without sleep disturbances [17, 18]. This study demonstrated a significant association between disturbed sleep in PD and pathological changes in specific brain structures relating to sleep physiology [18]. In this study the authors found α-synuclein (αSyn) pathology in the locus coeruleus, raphe nuclei, paramammillary nuclei, posterior nucleus, amygdala, thalamus and entorhinal cortex; additionally, they observed a statistically significant increase in tau pathology in the amygdala, CA2 sector of hippocampus and entorhinal cortex in PD patients with disturbed sleep [18]. The pedunculopontine tegmental nucleus (PPN) may play an important role in the sleep cycling control and REM sleep in PD [17]. Deep brain stimulation (DBS) of this area has been observed to improve subjective sleep and increase REM sleep [17].

## REM sleep behavior disorder

RBD is a parasomnia characterized by loss of muscle atonia during REM sleep [13, 19]. The absence of muscle atonia, which occurs during physiological REM sleep, results in dream enactment behaviors and excessive motor activity [6, 13, 19, 20]. The severity varies from subliclinical RBD (RWA – REM without atonia), when there is only polysomnographic evidence of pathology, to vigorous movements and vocalization while experiencing fighting or being chased, that may lead to serious injuries to patients and their bed partners [6, 11, 19]. Dreams are usually unpleasant and violent [19]. The most typical motor and vocal behaviors include kicking, hitting, punching, jumping, screaming, talking, crying, laughing and singing [19, 21]. Intriguingly, a striking disappearance of parkinsonian features during RBD dream enactment behaviors is observed [10, 12]. The frequency and intensity of symptoms varies, with temporary remissions of weeks or months [19]. Generally, as the disease progresses the symptoms of RBD diminish [19].

Epidemiological studies show that RBD occurs in 15–58% of PD patients, depending on the methods of patient selection and the use of polysomnography (PSG) [19, 20]. RBD is more common in males and in the akinetic-rigid subtype than the tremor dominant subtype [11, 13, 20]. RBD can be seen in other synucleinopathies like multiple system atrophy (MSA), dementia with Lewy bodies (DLB) and less frequently in tauopaties like progressive supranuclear palsy (PSP), Alzheimer's disease, and corticobasal degeneration [19]. Increased autonomic dysfunction has been associated with RBD symptoms [17]. Patients with RBD are at a high