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Review Article

Multifactorial sleep disturbance in Parkinson's disease

J. Andrew Albers [a, c, *], Pratap Chand [a, b], A. Michael Anch [c]

[a] Saint Louis University School of Medicine, 1402 South Grand Blvd, St Louis, MO 63104 United States
[b] Department of Neurology and Psychiatry, Saint Louis University School of Medicine, Monteleone Hall, 1438 South Grand Blvd, St Louis, MO 63104 United States
[c] Department of Psychology, Saint Louis University College of Arts and Sciences, Morrissey Hall, 3700 Lindell Blvd, St Louis, MO 63108 United States

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder, ranking only behind Alzheimer's disease and affecting 2% of the population over the age of 65. Pathophysiologically, PD is characterized by selective degeneration of the dopaminergic neurons of the substantia nigra pars compacta (SNpc) and striatal dopamine depletion. Patients may also exhibit mild-to-severe degeneration of other central and peripheral nervous tissues. The most dramatic symptoms of the disease are profound dopamine-responsive motor disturbances, including bradykinesia, akinesia, rigidity, resting tremor, and postural instability. PD patients commonly present with debilitating non-motor symptoms, including cognitive impairment, autonomic nervous system dysfunction, and sleep disturbance. Of these, sleep disturbance is the most consistently reported, and likely represents a disorder integrative of PD-related motor impairment, autonomic nervous system dysfunction, iatrogenic insult, and central neurodegeneration. The pathophysiology of PD may also indirectly disrupt sleep by increasing susceptibility to sleep disorders, including sleep disordered breathing, periodic limb movements, and REM behavior disorder. In this review, we will discuss these systems representing a multifactorial etiology in PD sleep disturbance.

1. Prevalence, types, and impact of sleep disorders in Parkinson's disease

Sleep disturbance is a major non-motor complaint of Parkinson's disease (PD) with extensive impact on patient quality of life. Despite the overwhelming prevalence of this symptom, the impact of PD-related sleep disturbance is often underappreciated in light of the profound motor disorder experienced by this population. Current estimates of PD-related sleep disturbance indicate that up to 98% of patients exhibit some symptoms of sleep disturbance, often with significant daytime impairment [1]. In fact, certain sleep disturbances, like rapid eye movement sleep behavior disorder (RBD), may be a prodromal symptom of PD, thus prompting a search for sleep-related "biomarkers" of the early, pre-motor stages of the disease [2,3].

Non-motor symptoms (NMS) of PD, including memory failure, autonomic dysfunction, affective disorders, and sleep disturbance, are the most significant determinant of patient quality of life (QoL) [4], with symptoms of insomnia ranking among the most profoundly detrimental to QoL [5]. Very poor nocturnal sleep may also contribute to excessive daytime sleepiness (EDS), which may precipitate falls [6], impulsive behavior [7], and poor automobile driving performance [8] in this population. Sleep disturbances (including RBD and sleep fragmentation) often worsen with disease progression [9,10], leading to potentially life-threatening synergies among nocturnal sleep disturbance, daytime sleepiness, disease-related motor impairment, and declines in executive functioning. Sleep disorders are common in PD, and in certain cases, may precede the classic motor manifestation of the disease. These disorders do not operate in isolation from the motor- and central degeneration-related sleep pathology. In fact, there may be significant overlap among the etiologies of seemingly idiopathic disease process-related sleep disturbance and diagnosed sleep disorders in PD. Sleep disorders that are common among PD patients include insomnia, REM behavior disorder (RBD), obstructive sleep apnea (OSA), periodic limb movement disorder (PLMD), restless legs syndrome (RLS), and nocturia [11]. In addition, it should be recognized that PD patients are certainly not excluded from

* Corresponding author. Saint Louis University School of Medicine, 1402 South Grand Blvd, St Louis, MO 63104 United States.
E-mail address: Albersj2@slu.edu (J.A. Albers).

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independent development of other common sleep disorders, such as narcolepsy, circadian disorders, shift work-related disorders, and others.

Whether or not PD patients are at greater risk for the development of OSA is a contentious issue in PD clinical research. Many prospective studies comparing PD patients to healthy age-matched controls have revealed no increased risk for diagnosis of OSA [12,13], while other studies contend increased risks of sleep disordered breathing – including OSA – in a PD population [14]. Berlin Questionnaire risk factors predict greater incidence of sleep disordered breathing in PD [15], but overall, the evidence for increased prevalence of OSA in PD populations is lacking. Notably, although PD patients with and without OSA obviously differ in respiratory arousal indices, OSA does not seem to contribute independently to daytime sleepiness within a PD population.

REM Behavior Disorder is characterized by vivid dreams and uninhibited, often violent, motor activation during rapid eye movement (REM) sleep. In addition to being highly disruptive of sleep for patients, bed partners, and caregivers, RBD is a putative prodromal sign of future PD diagnosis [16,17]. RBD may also emerge after the classic motor symptom manifestation of PD, but the presence of RBD at or before the onset of motor symptoms may predict a more rapid decline in motor symptoms relative to their non-RBD peers [10]. The often-prodromal nature of RBD is likely related to the Braak-modeled progression of synucleinopathy from hindbrain regions toward the neocortex, during which the REM- and motor output-controlling pontine neurons become dysfunctional prior to the midbrain and substantia nigra [18]. Predictions of the prodromal interval from RBD onset to motor manifestations of PD or other synucleinopathies range from 4.5 to 15 years [17,19], with up to 81% of RBD patients ultimately converting to a synucleinopathy [17]. It is notable/crucial to differentiate RBD symptoms from confusional arousals, which are also prevalent in Parkinson's disease and may be similarly described by the patient or bed partner [20].

Restless legs syndrome (RLS) is a disorder that causes an inappropriate urge to move the limbs prior to sleep onset, and most commonly manifests in the lower extremities. Indulging the urge to move the limbs typically allows brief respite from the unpleasant sensation, which returns shortly thereafter. Sleep onset can be dramatically delayed in those suffering from RLS, which is diagnosed at much higher rates in PD patients [21]. Treatment for RLS can include iron supplementation and dopamine agonists. Given that iron supplementation may exert its therapeutic effects through replenishment of iron cofactor for tyrosine hydroxylase or enhancement of D2 receptor binding [22], the combination of the prevalence of RLS in PD and the efficacy of dopamine agonists and iron supplementation may reflect a dopamine deficiency. For the treatment of idiopathic RLS, a primary goal of treatment should be the maintenance of ferritin levels above 50 ng/mL. However, the impact of restoring ferritin levels on RLS symptoms in the PD population is currently unknown.

2. Etiology of Parkinson's disease sleep disruption

2.1. Motor impairment

Nocturnal akinesia is a prime complaint of PD patients treated with short-acting levodopa/carbidopa or dopamine agonists. Patients revert to akinetic and rigid “off” states as dopaminergic medications are metabolized, and without middle-of-the-night redosing, may remain profoundly akinetic until the next morning's dose. Although many of the motor symptoms of PD, including resting tremor and rigidity, seem to be alleviated during sleep, they often do not completely remit. As a result, PD patients report significant motor-related sleep disturbances on the Parkinson's Disease Sleep Scale (PDSS), including increased frequency of muscle cramps, paresthesias, and painful or uncomfortable limb posture [23]. Minimizing nocturnal akinesia through optimization of dopaminergic therapies seems a viable option to restore sleep quality.

Early trials with sustained release levodopa taken before bed demonstrated a marked improvement in nighttime akinesia [24]. Later, the Randomized Evaluation of 24-Hour Coverage: Efficacy of Rotigotine trial (RECOVER) demonstrated both early-morning motor function improvement and subjective improvement in sleep quality using a once-daily transdermal rotigotine patch that provided dopamine agonist coverage [25]. Additionally, post-hoc analysis of RECOVER subjects revealed strong subjective reductions in wake-inducing nocturnal limb pain and immobility [26]. Recently, continuous intestinal infusion of levodopa/carbidopa has also been shown to improve motor symptoms, nocturnal sleep, and daytime functioning relative to prior treatment modality [27,28]. Taken together, evidence suggests that effective nocturnal dopamine coverage may improve nocturnal motor symptoms, and consequently sleep quality, in PD. Additionally, controlled release levodopa-carbidopa taken before bed seems to improve sleep disordered breathing in the latter half of the night [29].

Deep-brain stimulation (DBS) has become increasingly popular for treatment of parkinsonism. While DBS carries risks as an invasive neurosurgical procedure, patient outcomes are generally positive, and levodopa doses required to control motor symptoms are often reduced [30]. Improvements in sleep quality have been reported for both unilateral [31] and bilateral [32,33] subthalamic nucleus (STN) DBS, and some evidence suggests that pallidal stimulation may have similar sleep benefit [34].

Finally, PD patients are more susceptible to motoric disorders of sleep, including restless legs syndrome (RLS), periodic limb movement disorder (PLMD), and RBD [35–37]. It has been suggested that the etiology of some of these disorders may lie in midbrain dopamine depletion, as dopamine agonists are effective in treating RLS and PLMD [38], and in one isolated report, can reduce RBD symptoms [39]. However, there is currently insufficient evidence to recommend dopaminergic therapies for RBD in PD patients. Although deficits in nigrostriatal dopamine may explain the underlying pathophysiology of both RLS and PD [40], further research is necessary to determine whether dopamine replacement or agonist therapies are effective in treating the condition.

Although sleep quality improvements may parallel motor symptom improvement, it is likely that significant sleep quality improvement must be a product of a “functional mosaic” of corrected deficits. In the sleep functional mosaic, all factors underlying sleep regulation, including motor control, autonomic function, iatrogenic effects, and circadian control, contribute to an analogous composite image of patient sleep quality. As components of the mosaic are damaged, the composite image of sleep quality is gradually degraded. In PD, the damage to the components of the mosaic can be significant, requiring attention to a wide range of insults to sleep quality. While repairing individual components of the mosaic, such as the motor symptoms of PD, may partially ameliorate sleep disturbance, it is apparent that each independent sleep-regulatory component is only an individual piece of the profound sleep disturbance experienced by PD patients. Indeed, significant restoration of sleep quality in PD requires the alteration of multiple sleep-disrupting facets of the disease, including sleep disorders such as insomnia, RLS and RBD, motor and autonomic symptoms, iatrogenic insult, neurological damage, and circadian disorder.