

Sleep disturbances in Parkinson's disease patients and management options

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Abstract: Sleep disturbances are among the most common nonmotor complaints of patients with Parkinson's disease (PD), and can have a great impact on quality of life. These disturbances manifest in a variety of ways; for instance, insomnia, sleep fragmentation, and excessive daytime sleepiness. Sleep-related movement disorders such as restless legs syndrome and periodic leg movements may share a common pathophysiology, and occurrence of rapid eye movement behavior disorder may predate the onset of PD or other synucleinopathies by several years. Medications for PD can have a significant impact on sleep, representing a great challenge to the treating physician. Awareness of the complex relationship between PD and sleep disorders, as well as the varied way in which sleep disturbances appear, is imperative for successful long-term management.

Keywords: sleep disorders, insomnia, restless legs syndrome, Parkinson disease, fatigue, REM behavior disorder

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized histologically by alphasynuclein accumulation in neurons, known as Lewy bodies.¹ While the disease is characterized by motor symptoms responsive to dopaminergic augmentation (bradykinesia, postural instability, resting tremor, and rigidity),² the neurodegenerative disease process extends beyond substantia nigral dopaminergic degeneration. PD involves the nervous system in its entirety – ranging from the enteric peripheral nervous system³ to the well-known region of the midbrain, to diffuse cortical regions of the central nervous system.⁴ Thus, for both the basic scientist and clinician, “non-motor symptoms” are increasingly recognized as symptoms important to recognize, understand, and treat. These symptoms can range from an impaired autonomic system such as postural lightheadedness, constipation, or urinary retention,⁵ psychiatric conditions such as psychosis, hallucinations, paranoia, or depression,⁶ cognitive changes related to mild cognitive impairment and progression to a dementia complex,⁷ and sleep dysfunction. Indeed, sleep-related concerns frequently arise when treating PD patients, and in fact may be associated with several non-motor (especially cognitive) findings in PD patients. Even in James Parkinson's initial description of “the shaking palsy,” sleep problems were recognized.⁸ This review will focus on the main clinical sleep concerns encountered in PD patients, beginning with subjective feelings of sleepiness and fatigue, and then focusing on sleep fragmentation and its causes, medication influences on sleep, and the important clinical finding known as rapid eye movement (REM) behavior disorder (RBD). An appendix is included at the

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end of this article to help guide the clinical assessment of sleep-related issues encountered in PD.

Excessive daytime sleepiness (EDS)

EDS is a very common clinical finding in PD^{9,10} and has been discussed in the context of PD and Parkinsonism-related disorders elsewhere.¹¹ The Epworth sleepiness scale (score greater than 10) is a useful questionnaire used to characterize a patient's subjective sleepiness,¹² although it has not been validated in PD patients. Typically, PD patients note chronic or episodic sleepiness throughout the day and find it difficult to distinguish a feeling of fatigue with sleepiness.¹³ There are certainly many factors that can cause both fatigue and sleepiness. These can include changes in the circadian cycle (patients sleep during the day, but not at night), depression and anxiety, cognitive impairment and dementia, the effects of PD-related and -unrelated medications, and concurrent medical illness. One of the most ubiquitous problems arising from this symptom complex is the issue of driving. Aside from sleep attacks, which are described below, EDS is a large contributor to driving accidents.¹⁴ Thus, the clinician must take a careful assessment and often recommend driving restrictions if there is clinical concern. Treatment of EDS is challenging, but modafinil, which appears to stimulate catecholamine production, has been used with variable results.^{15,16}

The emergence of the clinical phenomenon known as "sleep attacks" has generated much interest to the similarities and differences between PD patients and patients with narcolepsy. There appear to be important medication-associated side effects in PD that can produce sleep attacks, which are, by definition, the "sudden, irresistible and overwhelming sleepiness that occurs in situations where sleep normally does not occur and is not preceded by being sleepy."¹⁷ Patients typically note a compelling urge to sleep. Anecdotally, patients will often note such an urge to sleep, that they will instantaneously fall asleep while driving, at work, or even eating. This is a very dangerous problem to patients. Dopamine agonists are well described as contributing to this side effect.^{18,19} In addition, there are reports of levodopa, and catechol-O-methyl transferase inhibitors implicated in the evolution of sleep attacks,²⁰ but this side effect is very rare with these medications. When encountering this clinically, one should reduce or discontinue the offending medication – usually a dopamine agonist.

The role of dopamine in arousal, wakefulness, and sleep, appears to involve the ventral tegmental area (VTA). In this region, there is a preponderance of dopamine D2 receptors

that modulate dopaminergic activity. The VTA sends dopaminergic projections to mesocortical and mesolimbic regions, which include prefrontal regions associated with arousal. A recent dopamine D2 receptor knockout study showed that D2 receptors are needed for maintenance of wakefulness.²¹ Dopamine agonist administration at low doses purportedly inhibits VTA dopaminergic activity at the presynaptic autoreceptor,²² while in higher doses they stimulate arousal via postsynaptic receptors.²³ Interestingly, hypocretin/orexin, a neuropeptide that regulates sleep and wakefulness (described in more detail below), has been shown to communicate directly with the VTA. Hypocretin/orexin neurons both innervate the VTA and directly activate VTA dopaminergic neurons.²⁴ In fact, dopamine agonists appear to reduce hypocretin/orexin levels in rats.²⁵ This may explain why dopamine agonist use has a high association with sleep attacks, and why dopaminergic medications in general produce sleepiness.

Since there exist clinical similarities between PD-related sleep complaints and narcolepsy (excessive sleepiness, daytime sleep attacks, REM sleep behavior disorder, hallucinations, and depression), it is not surprising that laboratory similarities are also evident. The multiple sleep latency test (MSLT) (the objective measure of sleepiness) has been used in PD. About 20% of PD patients have a MSLT of less than 5 minutes.²⁶ In addition, sudden onset REM sleep has been found in roughly a third of PD patients who note the presence of EDS, and in almost three-quarters of patients with hallucinations.^{27,28} Several studies have suggested a hypocretin/orexin deficiency as is seen in narcolepsy, as a unifying feature to explain these symptoms. Measurement of hypocretin levels in cerebral spinal fluid of PD patients has produced inconsistent results, where a range from low to normal levels is found.^{29–32} Pathology studies suggest that a severe loss of hypocretin producing cells accompany the progression of PD.³³ This may partly explain the overlap of symptomatology between PD and narcolepsy.

Fatigue is one of the most disabling features in PD, and is often associated with other conditions such as depression, anxiety, sleepiness, and medications. There appear to be distinct types of fatigue, physical and cognitive, where physical fatigue relates to body weariness, while cognitive fatigue relates to difficulty with challenging mental tasks.³⁴ Often, a patient will complain of sleepiness, and in fact be referring to fatigue. EDS does not appear to account for fatigue in PD.³⁵ Clinical history is vital in attempting to distinguish between EDS and fatigue symptoms. There do exist questionnaires that try and provide an objective measurement of fatigue.¹³ Overall,

fatigue should result in difficulty in performing a continuous task due to the feeling of tiredness, weariness, or exhaustion,³⁶ thus one can consider myriad reasons for this finding. Fatigue that is attributable to psychiatric comorbidities (anxiety, apathy, and depression), medication, or other causes should be first considered in treatment. Then, medication adjustments should be considered (often fatigue is an off-symptom, or related to medication usage), or a coexisting cognitive process (for instance bradyphrenia or executive dysfunction). Methylphenidate has been used with marginal success, and there is a risk of tachyphylaxis and hallucinations.^{37,38} Other alerting medications such as modafinil may provide relief from fatigue symptoms, yet studies are mixed in their results.^{16,39}

Sleep fragmentation

As many as 80% of PD patients experience sleep fragmentation largely as a result of frequent and prolonged awakenings.⁴⁰ Fragmentation of sleep is defined as an interruption of sleep stage leading either to a stage of lighter sleep or wakefulness, and resulting in disruption of normal sleep architecture. Typically, such electroencephalography (EEG) changes must last for at least 3 seconds in order to be scored as an arousal on routine polysomnography.⁴¹ EEG changes in REM sleep must also be accompanied by an increase in chin electromyography (EMG) tone. Findings on polysomnogram indicative of sleep fragmentation include increased number of brief EEG arousals – or increased arousal index, increased number of stage shifts to stage 1 or wake, increased wake time after sleep onset (WASO), and increased percentage of stage 1 sleep. Sleep fragmentation in PD can result from a wide variety of factors including intrinsic sleep disorders such as sleep disordered breathing, parasomnias (RBD, periodic leg movements in sleep [PLMS]), and PD complaints reemerging during sleep, as well as general medical issues such as pain, discomfort from rigidity, and psychiatric comorbidities such as anxiety. In addition, increasing sleep fragmentation is a physiologic factor of aging, with the average number of hourly arousals roughly doubling between ages 30 and 50.⁴²

Studies of induced sleep fragmentation in normal sleepers suggest that increased sleep fragmentation is correlated with symptoms of EDS. In patients with obstructive sleep apnea, increased fragmentation of sleep is found to be a better predictor of daytime sleepiness than total sleep time, amount of slow wave sleep, or amount of REM sleep.⁴³ This correlation holds for both subjective measures of sleepiness, like the Stanford sleepiness scale and Epworth sleepiness scale, as well as on objective testing of sleepiness with the MSLT and the maintenance of wakefulness test. Even in

elderly populations, symptoms of daytime sleepiness are closely correlated with measures of sleep fragmentation.⁴⁴ Changes in psychomotor performance and cognitive function, as measured by tests such as vigilance testing, reaction time, and trailmaking, as well as changes in mood, have also been demonstrated as a result of increased arousals.^{45,46} Despite this, exact correlative ratios between sleep fragmentation and level of impairment have been difficult to establish, due to variations in definitions of arousals and the large number of confounding variables involved in such studies.

Sleep fragmentation is the most common nighttime sleep complaint of patients with PD,⁴⁷ and patients with PD complain of greater sleep fragmentation than healthy controls or age-matched subjects with chronic medical disorders such as diabetes.⁴⁸ The etiology of sleep fragmentation in PD is likely multifactorial. Increasing sleep fragmentation appears to be related to the severity of PD, as measured by both the unified Parkinson's disease rating scale and the Hoehn and Yahr score,^{49,50} as symptoms such as nocturnal akinesia and rigidity can lead to disrupted sleep. Autonomic dysfunction of the bladder leads to nocturia in PD patients, which can significantly contribute to sleep fragmentation.⁵¹ Several sleep disorders known to be associated with PD, including restless leg syndrome (RLS), PLMS, and altered dream phenomena, also contribute to increased arousals. Obstructive sleep apnea (OSA) is another cause for increased sleep fragmentation in PD. Although some have reported a greater frequency of sleep apnea in PD,⁵² others have demonstrated no difference in frequency between PD patients and age-matched controls.^{53,54} Interestingly, although the decreased muscle tone of REM is thought to contribute to an increased number of respiratory events during that time, the increased muscle tone of RBD appears to have no effect on the rate of apneas.⁵³ Despite this controversy, OSA should always be considered in PD patients presenting with fragmented sleep, especially if one or more risk factors is present, as it may be further contributing to poor sleep quality and EDS.

Medications to treat PD can have a varied effect on sleep fragmentation. Treatment of PD can improve nocturnal symptoms and thus decrease arousals. Dopaminergic “under-dosing” through nighttime hours can lead to wearing off, return of symptoms, and increased fragmentation.⁵⁵ Treatment with dopamine agonists may decrease fragmentation by improving PLMS and RLS.⁵⁵ However, higher doses of dopamine agonists such as pergolide have been shown to cause increased sleep fragmentation.⁵⁶ Treatment with levodopa has been shown to have similar effects on sleep to Bromocriptine.⁵⁷ Similarly, selegiline and amantadine are known to have an alerting effect.

Deep brain stimulation (DBS) of the subthalamic nucleus has been shown to improve subjective sleep quality as measured by the Pittsburgh sleep quality index, and subjective sleepiness as measured by both the Parkinson's disease sleep scale and the Epworth sleepiness scale.⁵⁸ There is evidence that treatment with DBS may improve sleep efficiency and decrease WASO.⁵⁹ These findings are thought to result in decreased sleep fragmentation and improved overall sleep architecture.^{60,61} In addition, DBS may improve symptoms of RLS in patients with PD by up to 50%.⁶² Although the paraventricular nucleus is not a common target in DBS treatment, there exist reports that total REM duration and percentage of sleep spent in REM improve in pedunculopontine nucleus-targeted patients.⁶³ It should be noted that regardless of stimulation site, DBS does not appear to improve symptoms of RBD.

RLS

RLS is characterized by an urge to move, typically associated with paresthesia, which is worsened during rest or inactivity and relieved by voluntary movement, with symptoms worsening during the evening and night. Symptoms of RLS are known to follow a circadian rhythm, with maximal severity typically occurring after midnight.⁶⁴ RLS can be differentiated from akathisia – the feeling of subjective restlessness commonly associated with PD and associated treatment – by its circadian pattern, as well as the patient's ability to voluntarily control the urge to move.⁶⁵

The relationship between RLS and PD is a current area of debate. It has been suggested that the two conditions share a common pathophysiologic process of central dopaminergic depletion. While this idea rests largely on the role of dopamine agonists in the treatment of RLS, this theory remains unproven, and the true pathophysiology of RLS is still unknown.⁶⁶ Studies to determine the frequency of RLS in the PD population have yielded conflicting results. While some studies demonstrate an increased prevalence of RLS in PD patients,^{67,68} others indicate a prevalence closer to that of the general population.⁶⁶ These conflicting data are the result of multiple confounding variables. The most important of these variables is the use of dopaminergic treatment, which may either be treating concurrent RLS and thus causing an underestimation of disease prevalence, or leading to feelings of restlessness during on or off times due to under- or over-dosage, and thus increasing its frequency.

The majority of patients with RLS experience difficulty falling asleep, increased nocturnal awakenings, and subsequent daytime sleepiness.⁶⁹ The dopamine agonists

pramipexole and ropinirole are approved for treatment of RLS, and are considered to be first-line therapy.⁷⁰ The dopamine agonist rotigotine, which is administered transdermally, has also shown efficacy for moderate to severe RLS, and may be advantageous in the PD population due to its method of administration and relatively slow release.^{71,72} While levodopa may also be effective in treatment of RLS, it is associated with increased frequency of side effects, including morning rebound and RLS augmentation.⁷³ Gabapentin may be an effective alternative, especially if pain is a prominent component of the patient's RLS symptoms.⁷⁴ Other RLS therapies like opiates and benzodiazepines may be considered, although the side-effect profiles of these classes of medications make them less advantageous in the PD population.

Insomnia

The subjective complaint of insomnia is often encountered in the treatment of PD patients. Of course, since a reversal of the sleep cycle is quite common in both the elderly population and PD patients, it has been found that a complaint of insomnia may amount to early morning awakening, and frequent naps during the day.³⁸ Sleep cycle reversal is noted in PD patients and may be attributed to the severity of PD, sedative effects of dopaminergic treatment, and motor fluctuations resulting in periods of akinesia.⁴⁷ Treating this latter phenomenon usually amounts to prescribing an evening dose of levodopa to prevent immobility at an early hour of the evening, counseling regarding advanced sleep-wake phase, review of evening medications that may be stimulating, and even phototherapy.³⁸

PD-related insomnia not related to sleep cycle or circadian rhythm alterations could be particularly sensitive to dopaminergic therapy (levodopa). Recent studies suggest that quetiapine or eszopiclone may be helpful, although larger patient series are needed.^{75,76} Medications are the most common culprit in the development of insomnia. Dopamine agonists may influence the subjective symptom of insomnia. Aside from increasing stage 1 sleep and awakenings, insomnia can be a side effect of low doses of dopaminergic medications.⁷⁷ Selegiline, can cause sleep-onset insomnia due to the metabolite of amphetamine.⁷⁸ Aside from dopaminergic agents, other stimulating antidepressants such as venlafaxine can cause this side effect, along with amantadine, which is used to reduce dyskinesia severity.^{79,80} Since increasing numbers of patients are now prescribed anticholinergic medications for dementia and mild cognitive impairment, it is worthwhile to remember that these can increase alertness by increasing REM latency and suppressing REM sleep.⁸¹

Trihexyphenidyl is occasionally used for tremor, and can increase wakefulness while decreasing REM sleep.⁸²

RBD

RBD is a parasomnia characterized by excessive motor activity during REM stage sleep and dream enactment.⁸³ Typically, patients will note fearful dreams, such as running from animals, or fighting people who are attacking them. A spouse or bed-partner will often note the patient “flings his arms violently” or “shouts out loud” during sleep. This behavior can be injurious to both the patient and bed partner. The entity of RBD has been nicely reviewed elsewhere,⁸⁴ but it is worth emphasizing that the presence of RBD in a patient usually points to the underlying existence of an alpha-synuclein-related disorder or a synucleinopathy.⁸⁵ Scattered reports of RBD in patients with multiple sclerosis and progressive supranuclear palsy suggest that there is a “localization”-related phenomenon in RBD, yet the vast number of autopsy patients reveal the presence of alpha-synuclein inclusions. This section will focus on the clinical benefit of recognizing this symptom in PD patients. In particular, it will argue that accurate identification of RBD in a patient with possible PD can be very helpful to the clinician – especially in clarifying the degenerative process (for instance, do the patient's symptoms represent a synucleinopathy, tau-related disorder, or an Alzheimer's-related disorder), guiding appropriate treatment, and ensuring the patient's wellbeing (protecting the patient and bed partner from injury), along with predicting and treating associated non-motor concerns.

In a case series presented by Schenck and colleagues, eight patients developed PD approximately 10 years after the onset of RBD symptoms.^{86,87} This series was the first to highlight the association between RBD and synucleinopathy. Additional longitudinal reports of patients who present with idiopathic RBD, and then develop a neurodegenerative disease phenotype (for instance multiple systems atrophy, dementia with Lewy bodies, or PD) have established the concept that RBD represents an early clinical finding that portends a neurodegenerative disease.⁸⁷ In one study, there was an estimated 5-year risk of neurodegenerative disease of 17.7%, the 10-year risk was 40.6%, and the 12-year risk was 52.4% after diagnosis of RBD.⁸⁸ In fact, one could go further and suggest that idiopathic RBD is in fact representative of an already evolving synucleinopathy. Not all PD patients present with RBD prior to developing PD. In fact, many patients develop RBD during the course of PD. Nonetheless, when evaluating a patient with Parkinsonism (motor features suggestive of PD), the clinician should carefully examine not

only for evidence of protean manifestations of motor-related symptomatology and improvement of symptoms following a dopaminergic trial, but also for the presence or RBD-related symptomatology.

Neuronal dysfunction that accounts for the symptoms of RBD localizes to the brainstem areas such as the sublaterodorsal nucleus and pedunculo-pontine nucleus/laterodorsal tegmental nuclei.^{89,90} Since some patients have an early clinical onset of RBD before the onset of PD, it appears that certain patients' clinical symptoms fit with the neuropathologic theory of caudal to rostral progression of neurodegeneration, where dysfunction begins in the medulla and ascends to more rostral structures.⁹¹ Furthermore, autopsy studies with RBD symptomatology show that RBD can be associated with brainstem Lewy bodies as well as both brainstem and a more extensive Lewy body dementia process.⁸⁵ Therefore, accurate recognition of RBD can assist in characterizing that indeed a patient has a synuclein disorder. Nowhere is this more evident than in the disease process diffuse Lewy body dementia, where RBD identification improves diagnosis.⁹²

Of course, a clinical history is of great importance when diagnosing RBD. The examiner should be persistent in the inquiry of the bed partner as to the patient “acting out dreams.” The RBD screening questionnaire is a useful aide to diagnosis, with a total score of 6 or higher indicating strong evidence of RBD.⁹³ A polysomnogram is necessary to diagnose RBD. Aside from providing objective evidence of abnormal suppression of submental motor EMG activity during REM sleep, and absence of atonia, it can sometimes clarify a confusing history. For instance, a patient who is apneic can sometimes suddenly arouse from sleep, which may be confused as an REM behavior. In addition, recent research has suggested that the level of atonia may in fact predict severity of dementia symptoms.⁹⁴ Since there is a high association of periodic limb movements of sleep with RBD, this too can be identified during a polysomnogram. This entity is characterized by stereotypical limb movements consisting of extension of the great toe and ankle, flexion at the knee, and sometimes hip. The association of PLMS and RBD is intriguing, and imaging studies suggest that the entity related to central dopamine dysfunction and decreased dopamine D2-receptor binding.⁹⁵ Treatment for PLMS includes an evening dose of a dopaminergic agent.

PD patients with RBD are more likely to have autonomic dysfunction like orthostatic hypotension than those without RBD.⁹⁶ This may be related to an increase in cardiac activation during sleep in patients with PD and RBD.⁹⁷ Once a diagnosis of RBD has been established, treatment options

include benzodiazepines or melatonin. Typically, clonazepam is prescribed, as it is long acting and lasts through the night. The mechanism of action of clonazepam is not clear, but it appears to act as a GABA-ergic medication (GABA, γ -aminobutyric acid), and may work by controlling phasic locomotor activity at the brainstem level and modify dream content in REM sleep.^{86,98} There are two important cautionary notes regarding clonazepam. First, in patients with gait instability, clonazepam can cause greater gait instability at night. Patients note this problem especially when they have to use the bathroom at night, and must ambulate from their bed to the toilet. Second, many patients complain of morning somnolence from a “hangover” effect of clonazepam. In patients with cognitive complaints, this is especially troublesome. For this, changing the medication to a shorter half-life benzodiazepine, or changing the dose schedule (earlier in the evening) can sometimes help. Emerging research suggests that melatonin may be a good alternative. The mechanism of action for treatment of RBD is not clear.⁹⁹

Finally, the presence of RBD is likely indicative of existing as well as an evolving cognitive deterioration. RBD is associated with not only early cognitive changes,^{88,100,101} but in PD represents an increased likelihood of progression to cognitive dysfunction.¹⁰² Since cholinergic neurons from the pedunculopontine and lateral dorsal tegmental nuclei in the pons inhibit the REM-off cells, the presence of RBD likely indicates a cholinergic deficit.⁹⁰ Cognitive symptoms are found in an overwhelming majority of PD patients. They may be especially amenable to acetylcholinergic enzyme inhibition (for example, donepezil, galantamine, or rivastigmine).

Conclusion

When caring for patients with PD, there becomes a realization that sleep-related disorders are ubiquitous in this population. In fact, the identification and treatment of sleep-related disorders are inherent to the clinical evaluation. Medications used for treatment of PD-related symptoms have led to better understanding of neurotransmitter influences on sleep. In the future, neuroprotective therapies, novel medications, and disease classification will rely on sleep-related subjective and objective findings. For instance, the presence and severity of RBD can prognosticate cognitive changes; idiopathic RBD may indeed predict the development of a neurodegenerative disorder related to a synucleinopathy, and early identification of this disorder may guide disease-modifying therapy; new medications for the treatment of EDS and fatigue may involve neuropeptides such as hypocretin/orexin. James Parkinson’s erudite commentary noted that “sleep becomes much disturbed,” and even though

our understanding of sleep-related issues has progressed, future work will follow James Parkinson’s call to find “appropriate modes of relief, or even of cure.”⁸

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Appendix

Appendix sleep disruption and PD

1. Sleep disturbance due to the disease itself:
 - a. Rigidity, tremor, early morning dystonia, etc
 - b. Urinary incontinence
 - c. Intrinsic drowsiness
 2. Sleep disturbance due to medications used to treat PD
 - a. Daytime drowsiness caused directly by medications, sleep attacks
 - b. Insomnia directly caused by medications
 - c. Secondary insomnia; daytime drowsiness, and naps leading to nighttime insomnia
 - d. Nighttime hallucinations and paranoia
 - e. Dyskinesias and dystonia
 3. Sleep disorders that may be more frequently associated with PD or occur commonly with PD
 - a. REM sleep behavior disorder
 - b. Restless legs and periodic limb movements in sleep
 - c. Sleep apnea
 - d. Increased prevalence of depression
-

Abbreviations: PD, Parkinson's disease; REM, rapid eye movement.

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