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Evaluating and Managing Sleep Disorders in the Parkinson's Disease Clinic

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Abstract

Parkinson's disease is a multi-systems neurodegenerative disorder that is characterized by a combination of motor and non-motor symptoms. Non-motor symptoms of Parkinson's disease comprise a variety of cognitive, neuropsychiatric, autonomic, sensory, and sleep complaints. Although sleep disruption represents one of the most common non-motor symptom complaints among Parkinson's disease patients, recommendations regarding effective evaluation and management strategies for this specific population remain limited.

This review gives an evidence based summary of the available treatment options and management strategies for the sleep complaints commonly encountered by patients with Parkinson's disease.

Introduction

Parkinson's disease (PD) is a progressive disease in which motor symptoms are well known to cause significant disability. PD is now commonly approached as a global neurodegenerative process with increasing emphasis on the impact and treatment of not only the motor symptoms but the debilitating non-motor symptoms (NMS) such as sleep disruption, daytime sleepiness, fatigue, pain, impaired cognition, and depressive symptoms[1, 2]. Nearly two-thirds of the PD patients have sleep problems, making it one of the most common PD symptoms (motor or non-motor) after bradykinesia and rigidity, and likely more disabling. Bradykinesia and rigidity are readily treatable with dopaminergic medications, whereas sleep disorders are not. Despite the prevalent and debilitating impact of poor sleep in the PD population, published recommendations regarding the evaluation and management of sleep disorders specific to PD patients remain sparse. This article will review: (1) neurobiological link(s) between sleep and PD; (2) the common sleep complaints and disorders [excessive daytime sleepiness (EDS), insomnia, restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), rapid eye movement sleep behavior disorder

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(RBD)] frequently encountered in PD patients; and (3) the current evidence regarding optimal medical management.

Sleep Disorders: Overview of Prevalence and Impact in the Parkinson's Disease Population

There are more than 70 defined sleep disorders [3], most of which can be managed effectively. Interestingly, sleep disorders have been found to be unique predictors of poor quality of life in PD patients. In a large multicenter study, NMS were reported by 99% of 1072 PD patients[4, 5] with disturbed sleep (64.1% of respondents) representing the second most common NMS concern after psychiatric symptoms (66.8%). Another recent study[4] showed that comorbid sleep disorders predict the presence of additional NMS commonly encountered by patients with PD including symptoms of fatigue, depression, cognitive dysfunction and overall reduction in quality of life domains. Thus, identification and management of sleep disorders is crucial for overall care of PD patients. Despite extensive literature on the sleep problems faced by PD patients, an extensive literature search did not reveal any publications presenting evidence based treatment recommendations or guidelines geared to managing sleep complaints in the PD population specifically. There is no clear information on how best to manage sleep related complaints, thus in this review we have tried to address this gap. Using an electronic database, PubMed, an extensive search was conducted for literature (supplemental material) on PD and insomnia (n = 298), PD and RLS (n = 384), PD and RBD (n = 526), and PD and EDS (n = 370). A sub-categorized search was then performed for each treatment or medication option: PD and non-pharmacological treatment options for insomnia (n = 107), PD and pharmacological options for insomnia (n = 48), PD and pharmacological options for RLS (n = 236), PD and treatment options for RBD (n = 178), and PD and pharmacological options for EDS (n = 54). Only 9 randomized control studies were found on treatment options for sleep problems in the patients with PD.

The Neurobiological Link Between Parkinson's Disease and Sleep

The sleep state or more appropriately defined, sleep-wake state is regulated by several discrete regions (Figure 1) of the brain. The transition within the different stages of sleep [non-rapid eye movement (NREM) and rapid eye movement (REM)] also involve a complex interaction between multiple regions and central neurotransmitters[6].

Sleep disruption in PD is likely due to a multitude of factors including the neurodegenerative process of the disease itself[4]. The motor symptoms of PD have been largely linked to the dopamine dysfunction and degeneration of primarily nigrostriatal dopaminergic neurons. As noted in Table 1 and Figure 1, dopamine circuitry is also integral to sleep-wake homeostasis and it is thought to be implicated in several major sleep disorders common in PD such as insomnia and RLS. There are reports suggesting that patients with PD exhibit dopamine dysfunction in the hypothalamus (7), where they directly/indirectly regulate the orexinergic neurons. Hypothalamus is a key area in the regulation of the sleep-wake state that may contribute to symptoms of insomnia, circadian rhythm disruption, and daytime sleepiness [7].

Neurodegeneration in PD has also been shown in a variety of other cells/brainstem regions involving neurotransmitters such as serotonin, noradrenaline and acetylcholine[8, 9] (Table 1). Although, some evidence suggests, that these areas suffer degeneration prior to the dopamine rich striatal region, the etiology and time-line loss of these cells/regions is less understood. Regardless of the unresolved issues regarding the degenerative timing of these respective circuits, these circuits play key roles in sleep-wake regulation and are clearly affected in PD. Although studies have shown that the CSF orexin levels appear to be normal in PD patients, post-mortem studies have also shown degeneration in areas of the hypothalamus responsible for the production of orexin neurons[10, 11].

Rapid eye movement sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during rapid eye movement (REM) sleep with prominent motor activity and dreaming. The critical structures in the brainstem for REM sleep include the “REM-off” region [consisting of the ventrolateral part of the periaqueductal gray matter (vlPAG) and lateral pontine tegmentum (LPT)] and the “REM-on” region [consisting of the pre-coeruleus (PC) and sublaterodorsal nucleus (SLD)] [12]. Post-mortem studies of PD patients have shown a significant loss of cholinergic and noncholinergic neurons in several brainstem nuclei including those mentioned above[8, 12] These neurons extensively innervate rostral and caudal targets including hypothalamic sleep-wake regulating regions and spinal cord which are believed to control the REM state phenomenology (including motor atonia and REM specific cortical activity features). The dysfunctional brainstem circuitry in the PD patients could be responsible for the RBD symptoms and the degree of regional cholinergic neuron loss has also been associated with PD symptom severity[13]. RBD symptoms can often precede the motor deficits of PD by several years[14]. This clinical finding was first reported by Schenck et al. [15] who observed that in a group of patients diagnosed with the RBD, surprisingly 38% of patients were diagnosed as having a parkinsonian syndrome 12 years after RBD diagnosis. As a result of these findings, establishing links between RBD and PD sleep disturbances now represents as a major research focus aimed at identifying predictive markers of eventual PD manifestation.

With the exception of RBD, sleep disruption and disorders are more likely to occur in advanced PD [16]. A recent study [17] reported that PD patients with potential RBD have worse motor findings than those unlikely to have RBD. The PD population is also more likely to suffer from medical complaints commonly encountered in the advanced disease state to include motor symptoms, pain, and nocturia which can also serve as another source of sleep disruption [11, 12]. A study compared PD patients (sleep reported questionnaires) with and without sleep problems, nightmares, EDS along with other variables. A study compared PD patients with and without sleep concerns (based on sleep questionnaires only), nightmares, EDS along with other variables. They reported that patients with sleep concerns, nightmares and EDS had higher Unified Parkinson’s Disease Rating Scale (UPDRS) scores and were on higher relative doses of levodopa (~549mg/day) as compared with patients with no sleep related complaints (~352mg/day). Parkinson’s drug treatment itself may have either negative or positive impact on sleep quality. Lower doses of levodopa (150 mg) are able to improve sleep quality partly by reducing motor symptoms such as nighttime hypokinesia, dyskinesia or tremor which interfere with normal sleep [18] while, at the same time, minimizing adverse effects (nausea) which can contribute to improved sleep. Bliwise et al.,

[19] examined daytime sleepiness in medicated and unmedicated patients with polysomnography (PSG) measurements of nocturnal sleep and daytime alertness measures utilizing maintenance of wakefulness test MWT. They reported that the medicated patients were significantly less alert, independent of disease duration and severity, although a dose dependent relationship was seen among patients using levodopa and or/dopaminergic agonists (DA). Dopamine agonists (pergolide dose equivalents >2mg) had significantly less daytime alertness, by contrast, higher levodopa doses (~600mg) were associated with a greater degree of alertness [18, 19]. These dose dependent effects could partly be explained by the complex regulation of sleep and wake by dopamine and further on the complex dose dependent effects based on different receptor subtypes (D1, D2 and D3). For instance, dopamine agonists which act via D3 receptors leads to EDS, in contrast to agonists primarily acting via D1 receptors typically lower the arousal threshold and therefore increase sleep fragmentation and consolidation complaints. Therefore, PD medication dosage, duration of treatment and timing of administration is also a likely contributor to the sleep-wake process. [20].

Sleep Management Recommendations in Parkinson's Disease Patients

Hypersomnia

In the patients with EDS, despite adequate sleep opportunity, both behavioral and pharmacological interventions can be considered in the management. Behavioral strategies such as implementing good sleep practices including exercise, maintaining a consistent sleep wake pattern with a set bedtime and awakening time every day (including weekends and holidays), developing a bedtime routine, and unplugging from electronic devices 1 hour before bedtime have been noted to improve alertness in the general population.

Excessive daytime sleepiness (EDS) is uncommon in newly diagnosed, untreated PD patients [21]. EDS eventually affects up to 50% of PD patients and its incidence increases with the progression of the disease. The etiology of EDS in PD is multifactorial, including progression of the neurodegenerative process, potential interaction of a complex medication regimen, age-related sleep architectural changes, and presence of a primary sleep disorders including sleep related breathing and movement disorders, circadian rhythm sleep wake disorders. Thannickal et al., reported loss of the hypocretin (orexin), neurons in the brains of the PD patients [10]. This loss along with other brainstem, neurodegenerative changes may also contribute to EDS[8].

Treatment of EDS in PD is challenging. Patient education on healthy sleep hygiene is the first step in the management of EDS. Detailed review of the medication regimen is essential. The dose of dopaminergic medications may need to be reduced, and the class of dopaminergic agents may need to be substituted for a different one (specifically DA)[22, 23]. Patients who experience sudden onset(s) of sleepiness (sleep attacks) should be advised not to drive until the issue is resolved[24]. A suspicion of a co-existent primary sleep disorder should prompt a consultation with a sleep specialist.

If the aforementioned strategies do not improve EDS, then the use of stimulants and wake-promoting agents[25] should be considered, though none of them has been investigated in

the PD population. According to American Academy of Sleep Medicine (AASM), Modafinil is recommended as an effective treatment option for hypersomnia patients with PD[26], particularly when patients still complain of hypersomnia despite the use of PD medications without sedative properties[27, 28][29, 30]. Modafinil has been reported to be well tolerated by PD patients; however, patients should be advised that the most common side effects include depression, headaches, and insomnia. R-Modafinil (Nuvigil) is the long acting formulation of Modafinil but its efficacy has not been studied in this specific patient population. Stimulants, such as methylphenidate, sodium oxybate, anti-H3 drugs and amphetamine are used to treat hypersomnia in many other neurological diseases including neurodegenerative, demyelinating, and, vascular conditions. Emerging evidence suggests that sodium oxybate (FDA approved in 2002) may serve as another effective treatment option in the management of hypersomnia associated with PD. A study reported that the administration of sodium oxybate in PD patients improved the Epworth Sleepiness Score and increased slow-wave sleep time[31]. However, more research is required to validate the efficacy and potential side effects. No study has ever explored the effects of methylphenidate, a dopamine transporter inhibitor, on hypersomnia in PD, but it has been reported that it is effective in improving gait and motor dysfunctions in PD[32] [33].

Melatonin, a neurohormone produced by the pineal gland, has been shown to decrease sleep initiation difficulties and nighttime activity in older adults. A recent study found a blunted melatonin release “spike” circadian rhythm of melatonin secretion as compared with the controls[34]. Videnovic et al., [24] compared plasma melatonin concentration during 24 hours in PD patients vs controls and within the PD population a subset of patients with and without excessive daytime sleepiness. They reported that PD patients and further, PD patients with a daytime sleepiness (ESS>10) had significantly lower amplitude of the melatonin rhythm though no differences were observed in the timing of melatonin rhythm. It is worth noting however, that one of the potential confounders in these studies is levodopa administration itself which has been proposed to alter the endogenous melatonin secretion thus altering the melatonin phase. These changes in melatonin release which is a prominent biomarker of underlying circadian rhythmicity, may serve as a potential nonpharmacological (therapeutic) contributor to the EDS complaints noted by PD patients[35]. Decreased amplitude of melatonin rhythm in PD may result from suprachiasmatic nucleus (SCN) dysfunction although the SCN nuclei in and of itself appears to be preserved in the PD. The possible mechanisms could include impaired light transmission to the SCN due to dopaminergic retinal degeneration and /or the effect of altered sympathetic tone on the melatonin secretion[36]. In a recent study, PD patients with disturbed sleep were administered 5 mg or 50 mg of melatonin daily for two weeks. Melatonin resulted in improvements in subjective sleep disturbance, sleep quality and daytime sleepiness[37].

Deep brain stimulation (DBS) has become an important treatment option for PD patients with disabling motor complications and dyskinesias. Limited studies have reported an improvement in sleep architecture in PD with DBS. Reported symptom improvement include increase in total sleep time and decrease in the wakefulness after sleep onset. The authors suggested the role of reduced dopaminergic medications, a direct effect of subthalamic nucleus (STN) DBS on sleep, and improvements in motor symptoms as possible mechanisms[38].

Insomnia

Insomnia is characterized by chronic dissatisfaction with sleep quantity or quality that is associated with difficulty falling asleep, maintaining sleep (frequent nighttime awakenings with difficulty returning to sleep), and/or awakening earlier in the morning than desired[39].

Insomnia symptoms occur in approximately 33 to 50% of the adult population; and 10 to 15% of Americans fulfill the International classification of sleep disorders (ICSD-3) criteria for an insomnia diagnosis. Risk factors for insomnia include: increasing age, female sex, comorbid disorders (medical, psychiatric, sleep, and substance use), shift work, and possibly unemployment and lower socioeconomic status[40]. Insomnia is even more frequent in patients with PD compared to age matched controls. Studies have shown that up to 50% of PD patients complain about insomnia[41]. Patients report difficulty in falling and remaining asleep and early awakening. Coexisting mood disorders like depression may be responsible for insomnia but patients without depression experience similar difficulties which lead to the assumption that other factors such as the neurodegeneration itself and/or the influence of the PD drugs could play a role as well[41, 42].

Improved control of nighttime motor symptoms in PD may result in improved sleep quality. Possible approaches include medication regimen adjustments, for instance, consideration of the following: (1) the use of a long acting formulation of levodopa at bedtime; (2) the addition of a catechol-O-methyltransferase (COMT) inhibitor to the nighttime levodopa dose or; (3) night time administration of the new (FDA approved in January 2015) long acting enteral suspension DUOPA (carbidopa and levodopa). Introduction of one or more of these treatment strategies must also include monitoring for potential side effects of increased daytime somnolence. In patients with advanced PD, consideration of a middle of the night levodopa administration may also prove useful.

Cognitive behavioral treatment intervention for insomnia (CBT-I) is a brief and effective non-pharmacologic treatment based on a validated combination of both behavioral and psychological therapeutic approaches. A behavioral model of insomnia, put forth by Spielman et al, [43] identifies predisposing characteristics, precipitating events, and perpetuating attitudes and practices – three factors that together explain the development and course of insomnia[44]. CBT-I targets perpetuating “non-sleep-conducive” attitudes and practices then adopts interventions aimed at modifying these “non-sleep-conducive” cognitive views and behaviors. The interventions that constitute CBT-I are multipronged and include: sleep restriction, stimulus control, relaxation therapy, cognitive therapy, and sleep hygiene[45]. Direct comparisons of CBT-I with sleep medication in randomized control trials demonstrate that CBT-I has comparable efficacy with more durable and sustainable long-term maintenance effects even after treatment discontinuation.

The data demonstrating the efficacy of psychological and/or behavioral strategies in the treatment of insomnia within the PD population specifically are limited. One study explored the utility of CBT-I with bright light therapy for PD patients suffering with insomnia. While the CBT-I group displayed a considerable improvement in some categories of severity of insomnia, there was no improvement in other categories. For example, the Parkinson’s disease Questionnaire-39 (PDQ) demonstrated a decline in the CBT-I group when compared

to the placebo group[46]. There are many factors including motor dysfunction, nocturia, and medication side effect (fatigue, daytime sleepiness) which are unique in the PD population. Aside from the standard CBT-I treatment strategies, behavioral strategies aimed at addressing these PD specific sleep disruptors could prove worthwhile in developing an effective CBT-I treatment protocol for insomnia. Additional studies investigating the efficacy of each CBT-I approach as a monotherapy are also warranted.

Pharmacologic treatment alone or in combination with behavioral approaches is another treatment strategy for managing insomnia in the PD patient (Table 2). The AASM has provided the guidelines for the pharmacologic treatments of insomnia in the adult population. Levodopa has been a longstanding treatment of motor symptoms in PD, yet there is controversial data when it comes to its use in the treatment of insomnia[47, 48], thus calling for further investigation into the effects of levodopa on sleep symptomatology in PD. Due to its reported improvement in sleep quality and limited impact on motor function, melatonin may serve as a solid first line choice to treat insomnia in PD[49]. DBS of the STN may also have a role in treating insomnia in patients with PD[50–52]. However, it is not currently recommended as a viable treatment option because many questions regarding risk are yet to be answered. One study (6 week randomized trial of 30 patients) using Eszopiclone (2–3 mg) reported improved sleep quality in PD patients with no change in total sleep time[53]. Antidepressants (including trazodone, amitriptyline, and mirtazapine) could be beneficial for managing insomnia in patients with PD due to the prevalent comorbid presence of depression and anxiety[40]. Although no study has specifically looked at the efficacy of doxepin as an insomnia therapy in the PD patient population, the recent FDA approval of doxepin for the treatment of insomnia in the general population makes therapeutic consideration of doxepin worthwhile particularly in those suffering with both insomnia and depression.

Restless Legs Syndrome/Periodic Limb Movement Disorder

The International RLS Study Group developed the diagnostic criteria for idiopathic adult RLS, which includes the following core symptoms: (1) an unpleasant urge or need to move the legs; which is (2) worse at rest; (3) partially relieved by activity (i.e., movement/walking); (4) maximally present in the evening/night; and (5) not solely accounted for as symptoms primarily due to another medical or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping). Supportive features include the presence of periodic limb movements, a positive therapeutic response to dopaminergic agents, and a family history of the disorder. Iron deficiency, pregnancy, and renal failure with dialysis can predispose or worsen RLS symptoms.

Although several studies have found an increased prevalence of RLS in PD patients compared with controls, the prevalence rate reported has varied from 5.5 to 27%[54, 55]. No specific diagnostic criterion for RLS exist for PD patients and several conditions including sensory symptoms, pain, motor restlessness, akathisia and the wearing-off phenomenon should be differentiated from RLS. A study by Gjerstad et al. [56] showed that early unmedicated PD patients exhibit a 2-fold increased risk of leg restlessness compared to control subjects matched for age, gender, and ethnicity. However, this difference between

patients and controls was driven by a higher prevalence of leg motor restlessness (LMR) without diurnal fluctuation, thus potentially reflecting possible akathisia or other secondary causes for restlessness, rather than RLS. These findings argue against a strong etiologic link between PD and RLS, and highlight the need for a better characterization of the spectrum of motor restlessness in PD, particularly the distinction between RLS and LMR. Also the risk factors for RLS in PD patients vary and include insomnia, depressive symptoms, cognitive impairment, longer disease duration, a higher dose of dopaminergic treatment, younger-onset PD, older-onset RLS, and severe or mild severity of PD, depending on the study.

The precise pathophysiology of RLS is not known, but brain iron dysregulation seems to play an important role[57] and interestingly iron dysregulation has also been associated with PD pathology. However, the PD pathological features such as neuronal degeneration, Lewy Body deposition or alpha-synuclein pathology are not seen in patients with primary RLS[58] and the CNS iron abnormalities, also differ between the two entities. While abnormal accumulation of iron in the brain has been implicated in Parkinson's disease, significant iron deficiency has been found in the neurons of the substantia nigra in primary RLS patients[59].

Similarities between PD and RLS include a marked response to dopaminergic agents, aggravation by dopaminergic antagonists, and an association with periodic limb movements in sleep. Dopaminergic agents are the most extensively used therapies for the treatment of RLS. While these agents provide many benefits, there are some adverse effects. Similar to PD, RLS patients treated with dopamine agonist can develop dopamine dysregulation syndrome. This can manifest with addictive (dopamine replacement) drug seeking behavioral patterns or impulse control disorders such as pathological gambling, compulsive shopping, and, eating[60]. Prolonged dopaminergic therapy in RLS patients may also result in augmentation symptoms[61–63]. During augmentation, patients may experience an earlier onset of night time symptoms, more severe symptoms, and extension of symptoms to other body parts despite ongoing medication dose escalations. In a community sample, more than 30% of patients on levodopa develop augmentation of RLS. Respective rates for ropinirole and pramipexole were around 24 and 11%[62]. As the PD patients are on dopaminergic agents for the treatment of PD and RLS, the risk of augmentation is presumed to be even higher. As lower serum ferritin levels are associated with moderate/severe RLS symptoms in PD patients, serum ferritin may be assessed. When serum ferritin levels are less than 50 µg/L, iron supplementation should be considered though there is no clinical trial to evaluate the effectiveness of iron in PD population. *Rapid Eye Movement Sleep Behavioral Disorder (RBD)*

RBD is reported in up to 50% of the PD patients depending on the how it was diagnosed (i.e., objectively with evidence of REM sleep without atonia on PSG or based on sleep questionnaire only)[64][65] and may anticipate the diagnosis by several years[66]. The prevalence of PSG-confirmed RBD is generally higher than that of RBD diagnosed by questionnaire based study as patients are often amnesic of their dream enactment and therefore likely to under report the episodes. ICSD-3 defines RBD as 1) Repeated episodes of sleep related vocalization and/or complex motor behavior; 2) these behaviors are documented by polysomnography to occur during REM sleep or based on the clinical

history of dream enactment (presumed to occur during REM sleep); 3) polysomnography demonstrates REM sleep without atonia; 4) the sleep disturbance is not better explained by another sleep disorder, mental disorder, medication or substance use. The time interval between the onset of RBD and the Parkinsonian symptoms of resting tremor, bradykinesia, and cogwheel rigidity varies, but on average, 50% of patients presenting initially with RBD will convert to Parkinsonism within 10 years. Ultimately, 81 to 90% of otherwise idiopathic cases of RBD primarily develop into a alpha-synuclein neurodegenerative disorders including PD, dementia with Lewy Body and multiple system atrophy as compared to neurodegenerative taupathies including Alzheimer's disease and progressive Supranuclear palsy (PSP)[67]. A recent study also reported structural brain abnormalities in PD patients associated with RBD symptoms. They found a significant decrease of the thalamic volume in PD-RBD patients in comparison with PD patients using combined voxel-based morphometry and volumetric MRI techniques [68].

Protecting patient and bed partner by modifying the sleeping environment are the initial steps in RBD treatment. Bed partners should sleep separately until dream enactment is brought under control; the bed should be placed far from a window; and potentially injurious bedside objects, including a night table, lamp, and any firearms, should be removed[12]. Comorbid sleep disorders should be treated, and aggravating medications, if possible, should be eliminated. Most medication-induced RBD cases are self-limited following discontinuation of the offending agent, and dream enactment (due specifically to arousals from untreated sleep apnea [i.e. "PseudoRBD"]) typically resolves when any underlying sleep-disordered breathing is treated.

Pharmacotherapy is appropriate in the situations with a high probability of injury (Table 1). The most effective medications include clonazepam and/or melatonin[67]. Clonazepam, though very effective, patients can develop drug tolerance and subsequent treatment failure. Furthermore, clonazepam may be problematic among the elderly as its long duration of action may result in morning sedation and gait instability. In a double blind crossover trial of 12 patients, with idiopathic PD without dementia and with the RBD phenomenon refractory to melatonin (up to 5 mg/day) and clonazepam (up to 2 mg/day), rivastigmine (cholinesterase inhibitor) at the dose of 4.6 mg/24 hours was reported to decrease the frequency of RBD episodes [69].

More recent studies have suggested that melatonin is a safe and effective therapy for isolated cases of RBD and those associated with PD and related disorders. A recent study of melatonin and clonazepam reported equal efficacy; however, melatonin had a superior adverse effect profile, with fewer participants reporting falls and injuries[70].

Sleep Disordered Breathing

Obstructive sleep apnea (OSA) is the most common type of sleep disordered breathing (SDB). Apnea is defined as obstructive, if there is a cessation of air flow for at least 10 seconds accompanied by demonstration of respiratory effort while central sleep apnea (CSA) represents a cessation of airflow along with the absence of respiratory effort [3]. OSA is characterized by a repetitive collapse of the upper airway during sleep, often leading to blood oxygen desaturation and sleep fragmentation. OSA is commonly associated with

medical conditions that include diabetes, hypertension, A-fib, congestive heart failure and stroke. CSA is most commonly associated with heart failure, severe neurological conditions such as cortical or brainstem stroke and progressive neurodegenerative disorders like amyotrophic lateral sclerosis. Few studies have reported an increase prevalence of OSA in the PD patients[71, 72] though others have reported similar rates of OSA in PD as compared to the general population. There is no clear relationship between the prevalence of OSA in PD and disease duration, severity, or PD medication regimen [73] though hypokinesia and rigidity may be associated with airway obstruction. A study reported that the PD patients with OSA had a higher total arousal index (Arl) on PSG than the PD patients without OSA. The PD + OSA group also had a higher respiratory ArI than the PD – OSA group, although there was no significant difference in non-respiratory ArI between the two groups[74]. PD patients with poor sleep quality should be evaluated for sleep apnea especially if they or their bed partners report loud snoring, witnessed choking or gasping for air or waking up with headaches.

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA[75], but has not been systematically studied in the PD population. One study reported that in the patients with PD and OSA, therapeutic CPAP resulted in successful treatment of OSA as well as a deepening of sleep when compared to those receiving placebo CPAP [76]. CPAP use can be challenging in the advanced PD population. In advanced patients, limited mobility may create difficulties with adjusting the moving components of the CPAP apparatus like the mask and tubing that are often necessary for optimal comfort. Similar to the adherence issues in the general population, this therapy may be difficult to implement in a proportion of PD patients, due to comfort issues. Other factors that may interfere with CPAP use are nasal obstruction, sinus infection, chronic mouth breathing and lack of motivation. An additional consideration is the potential fall risk that a PD patient with both RBD and CPAP may encounter should they experience a dream enactment episode while their CPAP apparatus is in place. In cases where CPAP is difficult, conservative approaches (oro-mandibular devices, weight loss, and positional therapy) have also been successful [77].

Summary

Sleep disruption represents one of the most common NMS complaints among PD patients. Moreover, sleep disorders have been found to be unique predictors of poor quality of life in PD patients. Thus, identification and management of sleep disorders is crucial for overall care of PD patients. Further studies are warranted to establish evidence based guidelines to optimally manage sleep complaints within the PD population.

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Highlights

- Evidence based summary of the presence of different sleep disorders in patients with Parkinson's disease.
- Up to date summary of the recommended guidelines on the management of sleep disorders in this population.
- Guidelines for the use of non-pharmacological and behavioral therapies.

Figure 1.
Brain regions associated with Parkinson's disease and Sleep-wake

Table 1

Neurodegeneration of sleep wake associated regions in PD

Sleep-Wake regulating nuclei/regions	Neurotransmitter	Evidence of Neurodegeneration in PD (9)	Evidence of LN, LB, CB in PD (8)
Dorsal raphe nucleus	Serotonin	TH + cell loss (~25–60%) Serotonergic neuronal loss (~60%)	LN: ++ LB: ++ CB: ++
Locus coeruleus	Noradrenalin	Noradrenergic cell loss associated with LB presence (~64%)	LN: +++ LB: +++ CB: ++
Lateral hypothalamus	Hypocretin /orexin	Hcrt/orexin cell loss (23–62%)	
Ventral tegmental area	Dopamine	TH + cell loss (36–60%)	LN: +++ LB: ++ CB: ++
Basal forebrain/Nucleus basalis of Meynert (NBM)	Acetylcholine	ChAT +cell loss (30–77%)	
Parabrachial nucleus (lateral reticular formation)	Glutamate	+ LBs	LN: ++ LB: + CB: +
Median preoptic nucleus (MnPO)/ Ventrolateral preoptic nucleus (VLPO)	GABA	Not known	
Medullary parafacial zone (lower brainstem)	GABA	+ LBs	

- +LBs = Positive for Lewy bodies
- TH+ = Cells immunoreactive for Tyrosine hydroxylase
- ChAT+ = Cells immunoreactive for ChAT(Choline acetyltransferase)
- NBM = Nucleus Basalis of Meynert
- Hcrt/orexin = hypocretin
- LN = Lewy neurites
- CB = Coiled bodies
- + = Rare inclusions detection in approximately 3 minutes of microscopic examination
- ++ = well-developed inclusion pathology that is rapidly detectable by microscopic examination

Table 2

Treatment options for sleep disturbances in patients with PD

Sleep disturbance	Drug Category	Drug/Dose	PD population
Insomnia	GABA _A $\alpha 1\beta\gamma 2$ modulator	Zolpidem (5 – 12.5 mg)	Might be useful in PD (limited data)
	GABA _A modulator	Temazepam (7.5 – 30 mg)	Might be useful in PD (limited data)
	H1 receptor antagonist	Doxepin (10mg)	Might be useful in PD (limited data)
	Hormone/Neurotransmitter	Melatonin	Might be useful in PD (limited data)
	Cognitive-behavioral therapy for insomnia (CBT-I)		A high degree of clinical certainty
Hypersomnia	Unknown/possible dopamine modulator	Modafinil (100 – 200 mg)	Might be useful in PD (limited data)
RBD	Benzodiazepine	Clonazepam	First line therapy in PD
	Hormone/Neurotransmitter	Melatonin (3 – 12 mg)	Might be useful in PD (limited data)
	Dopamine agonist	Pramipexole	Might be useful in PD (limited data)