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Obstructive Sleep Apnea in Parkinson's Disease—a Mini-Review

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Abstract

Purpose of Review Sleep disturbances in Parkinson's disease (PD) are very common and debilitating. In fact, obstructive sleep apnea (OSA) shares core symptomology with PD including cognitive disturbances and excessive daytime sleepiness. This narrative review aims to summarize the available research evaluating OSA in PD and provide treatment considerations based on available data.

Recent Findings Pathophysiological evidence suggests a possible increased risk for OSA in PD, yet rates of OSA in PD appear to be similar to that seen in the general older adult population. The relationship between OSA and cognitive disturbances as well as excessive daytime sleepiness in PD has been evaluated and there is some evidence improvement in sleep and sleepiness with OSA treatment.

Summary Discrepant results have led to a debate on the relevance of OSA in PD and there is little agreement in current research and firm clinical conclusions are hard to ascertain. Nonetheless, research suggests that treatment of OSA can be tolerated by patients with PD and treatment results in sleep improvements.

Keywords Parkinson's disease · Sleep · Obstructive sleep apnea · Sleepiness · Cognition

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder with increased prevalence in older age [1]. PD is classified as a movement disorder characterized by dopaminergic cell loss. Beyond typical movement dysfunction, there are significant non-motor symptoms associated with the disease and which do not respond to dopaminergic therapy. In fact, non-motor symptoms such as cognitive dysfunction and sleep disorders are reported to be most troubling to the patients, more disabling, and considered a major cause of morbidity and mortality [2–4].

Sleep disorders are common in every disease stage of PD and, in fact, REM sleep behavior disorder (RBD), a major sleep disorder and parasomnia, is considered a precursor for the development of neurodegenerative diseases with Lewy bodies [5–7]. Sleep disturbances are highly common and are reported by nearly all patients with PD [8–10]. In recent years, there has been increased empirical evidence to heighten the negative impact of sleep disturbance on patients with PD [11–14]. Comorbid sleep disorders in PD have been shown to increase likelihood for worse quality of life, increased depressive symptoms, poorer cognition, and increased fatigue all of which are significant concerns for this patient population [14]. Taken together, research has demonstrated that sleep dysfunction is highly disabling and concerning to patients and to their caregivers.

Obstructive sleep apnea (OSA) involves respiratory abnormalities of complete (apneas) or partial (hypopneas) obstructions of the airways during sleep which results in multiple arousals and significantly altered sleep architecture. The exact pathophysiology of OSA as it uniquely pertains to PD is uncertain. Possible mechanisms involved in the etiology of OSA in PD may include abnormal airway function and decreased effective muscle strength of the upper airway [15–19]. Studies have observed high prevalence of airway obstruction or restrictive pulmonary dysfunction in patients with PD including decrease in forced vital capacity, forced expiratory volume, and total airway resistance [20]. Ventilatory control and abnormal response to hypercapnia have also been observed in patients with mild PD [21]. Such respiratory abnormalities

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may increase risk for OSA. However, the majority of research evaluating relative risk of OSA development in PD compared to a general population have not observed increased risk [22, 23•]. This led researchers to conclude that the etiology for OSA in PD is likely similar to that of the general population [24••]. This assertion is further supported by OSA prevalence in PD which is similar to observed rates in non-PD older adults (20–70%) [24••, 25–28]. However, one study found 12.2 respiratory events per hour of sleep in mild-moderate PD compared to 5.7 events in age-matched controls. This study and others have observed a correlation between OSA and PD severity suggesting that the likelihood for OSA does increase with disease progression [26, 29].

Comorbid Symptomology of PD and OSA

In the general population, the sleep fragmentation and accompanying hypoxemia has been shown to lead to many negative consequences including excessive daytime sleepiness (EDS), cardiac arrhythmias, nocturnal hypertension, nighttime confusion, cognitive impairment, and overall increase utilization of healthcare services [30, 31]. Health consequences of OSA in PD have received only limited attention and studies report equivocal findings which challenge strong assertions or conclusions. For example, several studies failed to find any statistically significant increase in cardiac symptoms in PD patients with versus without OSA [29, 32•]. However, one of these studies, De Cock, 2010, observed a non-significant trend ($p < 0.07$) with 13% of controls reporting cardiovascular events (i.e., hypertension, coronary heart disease, and stroke) compared to 33% of patients who had an AHI≥5 [29]. Studies utilizing objective methodology (e.g., arterial pressure and autonomic variations) that is beyond cardiovascular events assessed by medical interview are necessary to better ascertain the impact of OSA on cardiovascular function in PD.

Some research suggests that PD patients may have less severe consequences of OSA compared to control populations. A study of heart rate variability as an indication of sympathetic response to apnea events suggested that the sympathetic response in PD is blunted compared to controls [33]. A different study found that PD patients with OSA had lower respiratory arousal index and less oxygen desaturation when compared to OSA patients with no PD, despite similar OSA severity levels [32•]. The clinical relevance of OSA in PD is a subject of debate [29], yet OSA and the non-motor symptoms of PD bare similarities in presentation. Symptoms of EDS and cognitive impairment are recognized in both disorders and are a major cause of distress, thus they have received more research attention. These symptoms are discussed in more detail.

OSA and Cognitive Dysfunction in PD

It has become increasingly apparent that patients with PD have impairment of certain cognitive functions and may develop dementia [4]. Cognitive decline and dementia have been reported in PD with rates up to 80% [34, 35]. Dementia is more common in later stages of the disease and observations suggest that dementia impacts most patients who reach later disease stages and do not die of other causes [4]. Cognitive dysfunction predicts caregiver stress, nursing home placement, and overall rate of decline [2].

The pathophysiology of cognitive decline in PD is not fully understood and highly debated. Nonetheless, it is thought to be related to a number of neurochemical and neuropathological changes resulting in the core PD pathology [36]. Loss of cholinergic, dopaminergic, and noradrenergic innervation is thought to be the neurochemical deficits that underlie cognitive impairment and dementia in PD [37, 38]. It also has been proposed that dopaminergic deficits may partly be responsible for the dysexecutive syndrome, cholinergic deficits may cause impairments in memory, attention, and frontal function, whereas noradrenergic deficits may contribute to the impaired attention. The underlying pathology of cognitive deficits and dementia associated with PD has been a matter of controversy, both in terms of site and type of pathology. Nigral cell loss and involvement of other subcortical structures (such as the locus coeruleus and nucleus basalis of Meynert), coincident Alzheimer-type pathology, and Lewy bodies and Lewy neurites in cortical and limbic structures have all been implicated [39, 40].

Sleep deprivation has been shown to have detrimental impact on cognition [41]. In non-PD populations, sleep disorders and primarily OSA have been linked with cognitive difficulties [42–45] and such OSA and cognitive dysfunction are more pronounced in older adults [46–48]. OSA has shown to impact several neurocognitive domains including executive dysfunction, attention/vigilance, verbal and visual delayed long-term memory, and visuospatial/constructional abilities [42]. Such domains are similar to those noted to be impacted in PD. More specifically, neurocognitive investigations of PD patients suggest that areas of attention, executive function, visuoconstructive skills, memory, and communication are impacted [49–51].

As impaired neurocognitive domains overlap in OSA and PD, researchers hypothesized a link between these disorders. There have been several studies that assessed the relationship between OSA and cognitive performance in PD with conflicting results. A small study of 14 PD patients, of which 7 had OSA and 7 did not, found significant differences between the groups in all memory measurements [52]. The Ancoli-Israel group conducted a significantly larger study evaluating treatment of OSA in PD ($N = 86$ with 55% showing an apnea/hypopnea index, AHI≥10). In this study, cognition was

assessed with the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), as well as with a large neurocognitive battery (only for patients receiving treatment for OSA) [53•]. This project suggested that PD patients with OSA compared to PD without OSA scored significantly lower on the MMSE and MoCA [14, 53•]. This is contradictory to an earlier study reporting no MMSE differences between PD patients with versus without OSA [29]. The MoCA score was also highly associated with OSA when controlling for theoretically relevant factors such as demographics, disease stages, and medications [14, 53•]. Interestingly, evaluating the MoCA-specific cognitive domains demonstrated lower scores for patients with OSA in visuospatial and executive functioning. These domain-specific findings were not replicated in the patients with OSA when evaluated with a more extensive neuropsychological battery [53•]. Importantly, studies evaluating the impact of OSA treatment on cognition in PD failed to observe any cognitive changes both short- and long-term with CPAP therapy [53•, 54•].

In summary, there are very few studies evaluating the relationship between cognitive deficits and OSA in patients with PD. The available data provides some, yet minimal evidence of a relationship between OSA and cognitive deficits in PD. This relationship appears small (OSA, RBD and restless legs syndrome, together, accounted for a total of 9% of the variability in the MoCA [14]) and this relationship is not consistently replicated. Brief assessment tools appear to show significant differences between PD patients with versus without OSA but more specific and comprehensive neuropsychological assessments are not able to note the impairments suggested by the brief assessments. It is important to note that there have been no large neuropsychological assessments that compared patients with versus without OSA. Finally, despite evidence showing that treating OSA results in improved cognition in other populations (including Alzheimer's disease) [55, 56], two independent studies failed to observe any cognitive improvement with OSA treatment in PD [53•, 54•].

OSA and EDS in PD

Symptoms of EDS in PD are common with estimates up to 60% [57] and about 66% higher than in healthy controls [58]. EDS has been shown to be associated with worse mood [59, 60], poorer quality of life [61], increased cognitive deficits [62], and increase the risk for sudden sleep attacks which are particularly serious if the patient is still driving [63, 64]. Because EDS is common and associated with poor outcomes in PD, there has been considerable interest in determining its etiology [65]. However, studies have yielded conflicting results and the etiology of EDS in PD remains elusive. There have been three main hypotheses explaining daytime sleepiness in PD, implicating dopaminergic therapy [64, 66–70], the neurodegenerative processes of the disease itself such as disease severity or duration [62, 71, 72], or as a result of a major sleep disorder such as OSA [73, 74]. However, research suggest that the etiology of daytime sleepiness is complex and may be multifactorial, with all factors—dopaminergic therapy, the neurodegenerative processes, and sleep disorders—potentially contributing to EDS.

EDS is a core symptom presentation of OSA. However, the relationship between OSA and EDS in PD is far from conclusive. Some studies demonstrated a relationship between AHI and sleepiness by objective (i.e., multiple sleep latency test, MSLT) or subjective (i.e., Epworth Sleepiness Scale, ESS) measures [27, 74]. Other studies did not observe a relationship between AHI and ESS [22, 29, 32•, 75, 76]. A recent systematic review of sleep disorders in PD concluded that based on the available data, OSA shows a consistent impact on objective measures of EDS but that the effects on EDS when assessed with subjective measures are not determined [24••]. Researchers commonly observe poor agreement between subjective and objective measures of EDS in PD as exemplified by one study that reported that only 14% of patients ($N = 134$) showed significant EDS on MSLT while 46% reported EDS on subjective measures [75, 77]. There has been research suggesting that EDS and obesity are associated in PD but that this association is independent of OSA [75].

Differences between objective and subjective EDS assessment methods can be also be observed in reported findings from CPAP trials in PD. CPAP treatment of OSA in PD has shown to improve objective sleepiness as measured by MSLT [78••]. In this study, the patients fell asleep at baseline in 8.7 min on average indicating increased sleepiness since this is below the clinical cutoff for sleepiness (10 min). After 3 weeks of CPAP therapy, patients improved to a mean sleep latency of 12.3 min (normal sleepiness). Additionally, after 3 weeks of treatment, patients fell asleep on fewer naps in less than 10 min (2.5 at baseline to 1.9 at 3 weeks) [78••]. A different study of CPAP in PD that assessed EDS using the ESS found no improvement on the subjective assessment [54•]. Importantly, in this study, only 2/9 patients exhibited abnormal ESS scores at baseline and thus improvements would be difficult to show in such small sample.

To summarize, there is no debate that EDS is a major factor in PD that causes significant impairment, yet the involvement of OSA in EDS in PD is unclear. Some evidence suggests that the relationship between OSA and EDS in PD is better elucidated when utilizing objective measures. The stark lack of agreement between objective and subjective measures of EDS in PD calls into question the utility of subjective questionnaires in this patient population. Future research and development of PD-specific sleepiness questionnaires is necessary to improve the utility of subjective assessment in PD. Involvement of partners or caregivers in assessment may also improve the utility and validity of measures.

Consideration of OSA Treatment in PD

As mentioned above, there have been only two studies evaluating continuous positive airway pressure (CPAP) treatment in PD. The Ancoli-Israel group conducted a randomized placebo-controlled, crossover design of 38 PD patients that were assigned to either therapeutic CPAP or sham CPAP for 3 weeks [78••]. After 3 weeks, patients who received the sham CPAP were switched to therapeutic CPAP for an additional 3 weeks (those who started on therapeutic CPAP remained on therapeutic CPAP for an additional 3 weeks). Polysomnography evaluation was conducted at baseline, at 3 weeks, and at 6 weeks. The findings showed that therapeutic CPAP significantly improved AHI, sleep architecture, and nighttime oxygenation. More specifically, there was a significant decrease in stage 2 sleep (N2) and a significant increase in stage 3 sleep (N3, i.e., slow-wave sleep). As indicated previously, this study also observed significant improvement in EDS as measured by MSLT but not with ESS.

Terzaghi et al. [54•] conducted a longitudinal trial providing therapeutic CPAP to 36 PD patients with OSA and evaluated them at baseline and after 3 months with polysomnography. However, only nine patients completed the evaluation after 3 months. Despite the small sample size at follow-up, this study did manage to see a trend ($p = 0.06$) for increased N3 sleep which confirms the Neikrug et al. findings. This study did not report on oxygenation levels and found no change in EDS as evaluated with a subjective questionnaire (ESS).

The study by Terzaghi et al. [54•] highlights a significant treatment challenge in this patient population. In their study, 34/70 (49%) patients who were diagnosed with OSA refused CPAP treatment altogether and 27/36 (75%) were lost to follow-up. This is compared to only 5/43 (12%) that refused CPAP a priori and 7/38 (18%) who dropped during the 6 weeks in the Ancoli-Israel project [78••]. Terzaghi et al. suggested several possibilities for this difference including lower social-economic status of their sample or lower MMSE. However, it is more likely that the increased patient contact as well as active involvement of the caregiver in the Ancoli-Israel study resulted in less attrition. In that study, patients were contacted weekly and were evaluated in person at 3 and 6 weeks and the majority of patients came with their caregivers/partners as assessment of caregivers was included in the protocol and the caregivers were actively involved in the diagnostic and treatment process. This increased contact and caregiver support resulted in very high compliance rates as illustrated by an average of 5.2 h of CPAP use per night for 88% of the nights during the entire 6-week period.

Based on these studies, it appears that when CPAP is used by PD patients, sleep improves in ways of reduced arousals, decrease in AHI to within normal levels, and improved sleep architecture (increase in deep sleep and decrease in N2 sleep). Achieving adequate compliance may be challenging in this population. Motor deficits may prevent the patients to appropriately place the CPAP as appropriate fit may require dexterity which is significantly challenged in a movement disorder such as PD. This is especially difficult in the middle of the night where confusional states are more common. Multiple awakenings due to nocturia are common in this population, thus patients should be advised, unhook the hose from the machine, and place the hose over their shoulder while keeping the mask on when going to the bathroom. Reducing the need to manage the mask fit in the middle of the night can improve with compliance. Partner or caregiver involvement is highly important to achieve adequate compliance, especially in the presence of cognitive dysfunction and nighttime confusion. More frequent follow-up with this population can provide necessary support, problem solving, and improve the ability to troubleshoot any difficulties while reiterating educational components. Such supportive intervention is known to improve adherence in other populations and is highly recommended for this patient population.

Conclusion

Sleep disorders are a significant concern for PD patients. There are some etiological indications that may suggest increased risk of OSA in PD, but it appears that OSA is as common in PD as it is in the general older adult population. OSA and PD overlap in symptomology and some research suggests that PD patients may have less severe consequences of OSA in some measures compared to control populations. Nonetheless, overlapping symptoms such as EDS and cognitive disturbances are highly debilitating in this patient population. Research suggests some association between OSA and cognitive disturbances in PD, but this association appears to be small and cognition does not appear to improve with either short- or long-term CPAP treatment. The relationship between OSA and EDS in PD is heavily debated and findings appear to be measurement dependent. Research suggests that CPAP can be tolerated by PD patients especially when sufficient support is provided with increase in therapeutic and supportive contact. Treating OSA in PD appears to have a significant impact on nighttime sleep, providing for a deeper and less fragmented sleep as well as improved nighttime oxygenation. Some improvement to EDS may be achieved with CPAP treatment when objective measures are utilized. There is a significant gap in current research which prevents drawing firm conclusions in regard to the impact of OSA on PD symptomology. Specifically, there is need for longitudinal studies to evaluate the impact of OSA on clinical factors beyond EDS and cognitive dysfunction. Unfortunately, there have been some who call into question the clinical relevance of OSA in patients with PD. Studies that test the effect of CPAP on quality of

life, caregiver burden, cardiovascular parameters, stroke rates, and overall survival in patients with PD who also have OSA are critical before calling into question the clinical utility of CPAP in this population or the relevance of OSA. Disturbed sleep can be so significantly distressing in this population and any improvement, even minimal, can provide relief to the patients and their caregiver.

Take home points

- OSA is common in PD and these disorders may share etiological pathways in addition to overlapping debilitating symptoms including sleepiness and cognitive disturbances.
- OSA has been shown to be associated with cognitive disturbances in PD but this association appears to be small and cognition does not appear to improve with either short- or long-term CPAP treatment.
- Excessive sleepiness is a highly disturbing and debilitating symptom common in PD. The relationship between OSA and excessive daytime sleepiness in PD is debated and findings appear to be measurement dependent.
- Current data suggest that PD patients can tolerate OSA treatment using continuous positive airway pressure (CPAP) and that CPAP treatment in PD may result in positive impact on nighttime sleep and excessive daytime sleepiness.

Compliance with Ethical Standards

Conflict of Interest Ariel B. Neikrug declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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