

# Parkinson's disease and obstructive sleep apnoea – establishing the link

**Dr Marta Kaminska** of the McGill University in Canada is investigating the putative role of breathing-related sleep disorders in exacerbating the common non-motor symptoms of Parkinson's disease. These symptoms can then lead to further pathologies, including dementia. Dr Kaminska's work represents a novel line of research, with great importance and potential for therapy development.

**P**arkinson's disease (PD) and obstructive sleep apnoea (OSA) are commonly occurring disorders worldwide. OSA is a sleep disorder, characterised by an upper airway restriction during sleep, resulting in a recurrent, partial or complete breathing obstruction. This causes disturbances in sleep architecture and intermittent intervals of low blood oxygen levels (hypoxemia) resulting in the core symptoms of OSA: day-time sleepiness and fatigue, and occasionally a decline in cognitive function.

OSA animal models show neuronal loss in areas associated with cognition, shown to result from both intermittent hypoxemia and sleep fragmentation – both of which are associated with neuroinflammatory processes in animals. In OSA patients, neuroimaging abnormalities suggest changes in the structure and function of the brain.

## THE NEURODEGENERATION OF PARKINSON'S DISEASE

PD is a neurodegenerative disorder which is primarily associated with progressive motor function impairment. However, sufferers also exhibit non-motor symptoms, which can be in the form of cognitive impairment (notably memory and executive defects and visuospatial problems) that can lead to dementia. Neuronal cell loss occurs throughout many areas of the PD brain but is particularly noted in the substantia nigra (linked to motor symptoms) and the locus coeruleus (LC) (associated with non-motor symptoms). This may occur via multiple

mechanisms related to various causes, for example genetic or environmental factors. It is documented that, regardless of the cause behind the initial insult, PD cell loss progresses through relatively common pathways, including oxidative stress and inflammation – this is also associated with the damaging effects of OSA.

## PARKINSON'S AND SLEEP APNOEA: THE PHYSIOLOGICAL CONNECTION

Several potential mechanisms might give PD patients an increased propensity to developing OSA.

Firstly, OSA risk is increased in neuromuscular disorders, such as PD. With this, the integrity of upper airway muscle function is reduced, increasing the probability of airway collapse during sleep. This airway restriction (apnoea or hypopnea) can potentially then cause a drop in oxygen levels and/or sleep arousal.

In addition to this, PD neurodegeneration in brain stem areas, central to the autonomic control of physical function, might affect the control of breathing – further promoting respiratory instability during sleep. Moreover, dilator muscles of the airways during sleep are controlled by levels of oxygen and carbon

dioxide in the blood, but sensitivity to this decreases during PD pathology. Problematic sleep patterns are a characteristic of PD and sleep disturbance itself results in irregular breathing patterns, further promoting this maladaptive cycle.

## PARKINSON'S AND SLEEP APNOEA: CONSEQUENCES

The PD brain, affected by a neurodegenerative process, is potentially more sensitive to the OSA effects, which can exacerbate the initial insult of PD. In such a situation, individuals with sub-clinical symptoms of PD, or those with a predisposition to the disease, are likely to have an increased susceptibility to OSA-related pathology. This consequently increases the likelihood and speed of full PD development, as well as the potential progression to dementia. This is also suggested by epidemiologic studies linking pre-existing OSA with increased risk of developing PD subsequently.

Additional evidence of the association between OSA and PD has come from imaging studies. These have highlighted changes in the structure and function of brain areas in both disorders but also, when associated with a decreased cognitive ability, have revealed the same patterns of degradation across OSA and PD.

These considerations have thus highlighted the unmet need to investigate OSA in PD and the roles in pathology it may have. Yet, so far, there has been little research into this connection. Prevalence studies of co-morbidity have shown mixed results – finding that 20–60% of PD patients have OSA, such that no consensus has emerged as to whether OSA is more frequent in PD than in the general population. However, Dr Kaminska's work has highlighted a correlation between OSA and PD symptom severity.

## PD NON-MOTOR SYMPTOMS

Non-motor symptoms are a leading cause of disability in PD patients, severely impacting sufferers' quality of life. Dementia is particularly relevant, affecting close to 85% of survivors after 20 years of follow-up. The onset

**Researchers are asking if PAP therapy can lead to improvement of PD patients' non-motor symptoms, including cognitive decline and quality of life**

of non-motor symptoms, and correlating cell loss in brain regions such as the locus coeruleus, may precede motor manifestations and PD diagnosis. Despite this, in comparison to the physical features of PD, there is limited research and intervention approaches focused on the problems experienced with sleep and their impact on cognition. In Dr Kaminska's most recent study, assessing PD and OSA co-morbidity and its implications, 85% of the PD participants exhibited non-motor symptoms – the most common being cognitive impairment, sleep difficulties and fatigue, highlighting the need for research addressing these symptoms.

### FINDING ASSOCIATIONS

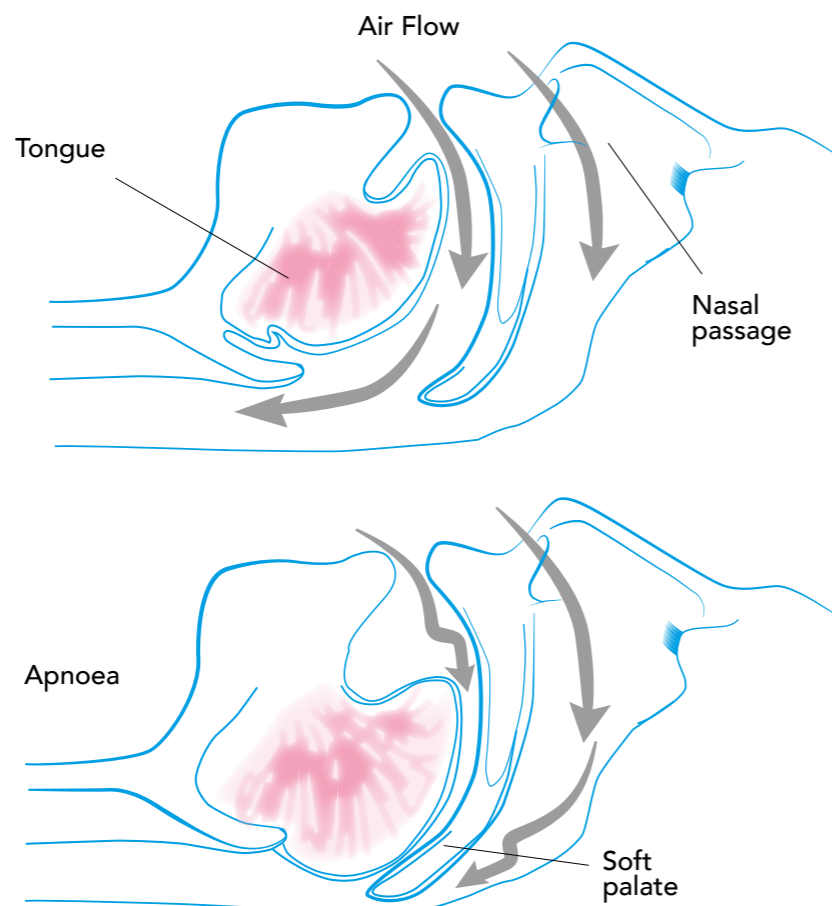
This year, Dr Kaminska published a paper on the co-morbidity of OSA and PD. In this study, the researchers found that individuals with OSA and PD showed higher degrees of global cognitive impairment and sleepiness than PD sufferers alone. Although this doesn't unequivocally demonstrate a causation effect, it can suggest a relevant relationship between the two disorders.

Cognitive impairment was primarily associated with OSA-related sleep fragmentation in Dr Kaminska's work, whereas sleepiness showed a more pronounced association with intermittent hypoxemia. No correlation between sleepiness and cognition was observed, and adjusting statistical analyses for sleepiness did not affect the relationship between OSA and cognition significantly. It was therefore concluded that OSA exacerbated PD cognitive dysfunction in these patients through specific neurological mechanisms rather than primarily via exacerbation of sleepiness.

In another study conducted earlier this year, Dr Kaminska found an association between blood markers of inflammation and OSA severity in PD patients. Worsening of inflammation in the blood and possibly the brain may be one mechanism explaining OSA effects on non-motor symptoms in these patients.

OSA contribution to PD pathology is a relatively new area of research, but Dr Kaminska's work presents a strong argument for an association of these disorders.

## Individuals with OSA and PD showed higher degrees of cognitive impairment and sleepiness than PD sufferers alone



### TREATMENT POTENTIAL

Although the specific neurological processes behind the cognitive decline in OSA have not yet been pinpointed, treatment via positive airway pressure (PAP) can be effective, in addition to improving sufferers' quality of life, quality of sleep and alleviating sleepiness. Dr Kaminska is considering the benefits of therapies for OSA in PD patients to improve their non-motor symptoms. This is particularly noteworthy as effective therapies for cognitive decline in PD do not exist. Could PAP therapy lead to an improvement of non-motor symptoms, including cognitive decline and PD patients' quality of life? In preliminary observations, Dr Kaminska's team has found that PD patients with OSA who used PAP therapy had an improvement in a number of non-motor symptoms including cognitive function over a 12-month follow-up period.

Following on from their novel findings, Dr Kaminska and her team currently hold a research grant to develop this work in a randomised, controlled clinical trial. Cognitive dysfunction is evidently important

to address, but no effective treatment is currently available in PD. OSA, on the other hand, is treatable using PAP therapy, but this therapy can be challenging, particularly for individuals with disabilities. For this reason, Dr Kaminska is investigating the plausibility of treating cognitive dysfunction and non-motor symptoms of PD patients by treating OSA. In addition to global cognitive function, the team is investigating which specific cognitive domains are most affected by OSA. Though adherence to PAP is problematic in PD, conductors of this study are highly experienced in this treatment, and may gain insight into how to increase use.

### ALTERNATIVE THERAPIES

Dr Kaminska's work is showing promise for novel approaches to OSA treatment. Her team has published a study that found that PD patients taking a certain type of PD medication (long-acting levodopa) at bedtime had less OSA. This may be due to the medication effect on the upper airway muscles in sleep and reinforces the notion of a bi-directional relationship between PD and OSA. The team is now conducting further work to study the effect of PD medication on OSA in PD. As well as providing valuable insight into the mechanisms of PD and OSA, this work has scope for valuable therapeutic development.

## Q&A

### Could PAP treatment benefit PD sufferers who may not exhibit OSA symptoms, and would it be beneficial to educate PD patients on their potential development of OSA?

Education of patients and their doctors regarding OSA in PD is key to allow more patients to potentially benefit from PAP treatment. OSA manifestations may not be typical in PD and classical symptoms of OSA may not be seen.

A sleep study is needed to determine if OSA is present. This is rarely a priority for PD patients or their neurologists. This is further complicated by the range of other sleep disorders occurring in PD, often difficult to treat. This may in turn give the impression that PAP therapy is not feasible in PD patients. Yet we have found that a significant proportion will be able to use it, with variable adherence, but often sufficiently to afford real clinical benefits.

We recommend sleep testing in PD patients with restless or fragmented sleep, daytime sleepiness or cognitive complaints. Though these symptoms are an integral part of PD, OSA may contribute and hence PAP therapy can be useful.

### Could any other sleep disorders related to PD contribute to worsening of PD non-motor symptoms?

PD is associated with a number of sleep disorders including insomnia and OSA but also sleep hallucinations, restless legs syndrome and notably REM sleep behaviour disorder (RBD). All of these may contribute to non-motor symptoms such as fatigue, depressive symptoms and reduced quality of life. The first step in addressing these issues is the identification and diagnosis of the sleep disorders. Only then can treatments be initiated, with the idea of improving the quality of life of patients with PD.

### Could OSA be linked to any motor symptoms of PD, which could thus potentially be aided with PAP?

OSA appears to predispose sufferers to developing PD later in life, based on large population studies. In patients with

PD, we have found that OSA severity was associated with more advanced motor dysfunction, but whether a causal link exists, and in which direction, is unknown.

The question also remains as to whether treatment of OSA could help modify the motor findings of PD, with immediate improvement or slowing of the rate of progression. This is the subject of our team's current work as well.

### Could OSA be detrimental in any other neurodegenerative disorders where treatments are not currently satisfactory, such as Alzheimer's?

Research is currently being conducted looking at these questions, particularly for Alzheimer's disease. OSA does appear to promote AD, especially in those with additional genetic predisposing factors. Some research work has found that patients with AD can benefit from PAP therapy for OSA, but as in PD, adherence to treatment is challenging. By consolidating patients' sleep, benefits can also extend to caregivers, which is an important aspect of care of patients with neurodegenerative disorders.

### If an improvement is seen in patients following PAP treatment, what do you hope to be able to do next with these findings?

I hope to be able to help PD patients by improving their quality of life in the immediate term, by addressing their non-motor symptoms with treatment of sleep disorders. Looking to the future, I plan further research to address whether OSA modifies the neurodegenerative disease process and whether OSA treatment can alter this.

Given the difficulty in using PAP therapy, I am also working on other treatments for OSA that could be better tailored to individuals suffering from PD. If our work shows positive results, pre-emptive OSA screening programmes in individuals at high-risk for PD could be developed to potentially delay onset of PD manifestations.

## Detail

### RESEARCH OBJECTIVES

Dr Kaminska's research focuses on respiratory issues in neurological diseases. Her latest research has focused on the effect of obstructive sleep apnoea, a sleep-related breathing disorder, on the progression of Parkinson's disease symptoms.

### FUNDING

- Canadian Institutes of Health Research (CIHR)
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- McGill University Health Centre

### COLLABORATORS

- Dr Anne-Louise Lafontaine, Movement Disorder Specialist, Director of the McGill Movement Disorder Clinic
- Dr John Kimoff, Pulmonary and Sleep Specialist, Director of the McGill Sleep Laboratory
- Dr Victoria Mery, Neurologist and Sleep Specialist, Clinica Alemana, Santiago, Chile
- Ann Robinson, Clinical Research Nurse

### BIO

Dr Kaminska completed Pulmonology training at McGill University and a Sleep Fellowship at the University of Montreal before obtaining an MSc in Epidemiology at McGill University between 2008 and 2011. Since then, she has continued as an Assistant Professor at McGill University, while also working as an Attending Physician at McGill University Health Centre.

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