Obstructive Sleep Apnea in Parkinson's Disease: Motor Subtypes and Effects of Long-acting Levodopa

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June 2023

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science.

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Abstract

Introduction: Parkinson's disease (PD) is characterized by an array of motor and non-motor symptoms, including sleep disruption. PD can be classified into subtypes based on prominent motor symptoms such as tremor dominant (TD) and postural instability/gait difficulty (PIGD) subtypes. Obstructive sleep apnea (OSA) is frequent in PD and contributes to daytime sleepiness and cognitive dysfunction, however, its pathogenesis in PD is unclear. Our previous work suggests that long-acting levodopa (LALD) taken at bedtime may lead to a reduction in respiratory disturbances during sleep in PD patients. The objectives were to explore the differences in sleep structure and OSA within PD motor subtypes and to assess the magnitude of the effect of LALD taken at bedtime on OSA severity (Effect of Long-acting Levodopa on OSA in PD (ELO-PD) trial).

Methods: To assess sleep and OSA within the PD motor subtypes, data was used from PD patients with or without OSA (defined as apnea-hypopnea index (AHI) ≥ 15 events/hour on overnight polysomnography) recruited for two of our group's clinical trials, including the ELO-PD trial. Patients were separated into two groups: PIGD and non-PIGD. Multivariable logistic regression models were used to determine if the prevalence of OSA differed across groups. Multivariable linear regression models were used to explore differences in AHI and other respiratory parameters between groups. Sensitivity analyses with three subsets excluding patients on psychoactive medication, levodopa and/or dopaminergic agonists, or both, were performed. The ELO-PD trial was a randomized, crossover placebo-controlled pilot trial. Patients were randomized and allocated to either: group A – LALD followed by placebo or group B – placebo followed by LALD. Treatment was administered daily at bedtime for two weeks, separated by a two-week washout period. The AHI was determined by polysomnography at screening, at the end of each treatment

period and at the end of the washout period (baseline 2). The effect of LALD on AHI was assessed using a linear mixed model. A paired t-test was performed as a sensitivity analysis to compare the change in AHI from baseline on placebo and on LALD.

Results: 146 participants were analyzed to assess sleep in PD motor subtypes. Fewer patients had OSA in the PIGD versus non-PIGD subtypes [adjusted OR 0.5, 95%CI (0.2, 1.1), p=0.09 in the full sample; adjusted OR 0.2, 95%CI (0.06, 0.9), p=0.04) in subset 3 (n=60)]. The AHI was lower in the PIGD group (p=0.047 in the full sample; p<0.05 in all subsets). In the ELO-PD trial, 36 patients were randomized. From the mixed model, the unadjusted difference in the change in AHI from baseline to LALD versus from the other baseline to placebo was 3.2 events/hour (95%CI: -2.5; 8.9, p-value: 0.28). The mean difference in AHI on placebo versus on LALD was 2.1 (p-value = 0.65) for the total sample by t-test.

Conclusions: Our results suggest that OSA is more frequent and more severe in non-PIGD motor subtypes when assessing subsets free of psychoactive medication, and of levodopa and dopaminergic agonists at nighttime, possibly relating to specific neurodegenerative patterns or motor complications. Analyses suggest LALD taken at bedtime may not reduce OSA severity overall in PD. However, certain individuals might respond to LALD, but further research will be needed to define predictors of response.

Résumé

Introduction : La maladie de Parkinson (MP) se caractérise par un ensemble de symptômes moteurs et non moteurs, y compris la perturbation du sommeil. La MP peut être classée en sous-types en fonction des symptômes moteurs dominants, tels que les sous-types tremblements dominant (TD) et instabilité posturale/difficultés de marche (PIGD). L'apnée obstructive du sommeil (AOS) est fréquente dans la MP, mais sa pathogenèse dans la MP n'est pas claire. Nos travaux antérieurs suggèrent que la lévodopa à longue durée d'action (LALD) prise au coucher peut entraîner une réduction des troubles respiratoires pendant le sommeil chez les patients atteints de la MP. Les objectifs étaient d'explorer les différences dans le sommeil et de l'AOS dans les sous-types moteurs de la MP et d'évaluer l'ampleur de l'effet de la LALD prise au coucher sur la sévérité de l'AOS (essai Effect of Long-acting Levodopa on OSA in PD (essai ELO-PD)).

Méthodes : Pour évaluer le sommeil et l'AOS dans les sous-types de la MP, nous avons utilisé les données de patients atteints de MP avec ou sans AOS (défini par un indice d'apnée-hypopnée (IAH) ≥ 15 événements/heure lors d'une polysomnographie nocturne) recrutés pour deux essais cliniques de notre groupe, y compris l'essai ELO-PD. Les patients ont été répartis en deux groupes : PIGD et non-PIGD. Des modèles de régression logistique multivariables ont été utilisés pour déterminer si la prévalence de l'AOS différait d'un groupe à l'autre. Des modèles de régression linéaire multivariable ont été utilisés pour explorer les différences d'IAH et d'autres paramètres respiratoires entre les groupes. Des analyses de sensibilité ont été réalisées avec trois sous-ensembles excluant les patients sous médicaments psychoactifs, sous lévodopa et/ou agonistes dopaminergiques au coucher, et excluant les deux à la fois. L'essai ELO-PD était un essai pilote randomisé, croisé et contrôlé par placebo. Les patients ont été randomisés et répartis entre le groupe A - LALD suivi d'un placebo - et le groupe B - placebo suivi d'un LALD. L'IAH a été

déterminé par polysomnographie lors de la sélection, à la fin de chaque période de traitement et à la fin de la période d'élimination (base de référence 2). L'effet du LALD sur l'IAH a été évalué à l'aide d'un modèle linéaire mixte. Un test t apparié a été réalisé en tant qu'analyse de sensibilité pour comparer la variation de l'IAH par rapport à la ligne de base dans le cas du placebo et dans le cas de la LALD.

Résultats : 146 participants ont été analysés pour évaluer le sommeil dans les sous-types moteurs de la MP. Moins de patients présentaient de l'AOS dans les sous-types PIGD par rapport aux sous-types non-PIGD [RC ajusté 0,5, IC 95 % (0,2, 1,1), p=0,09 dans la population totale ; RC ajusté 0,2, IC 95 % (0,06, 0,9), p=0,04) dans le sous-ensemble 3 (n=60)]. L'IAH était plus bas dans le groupe PIGD (p=0,047 dans la population totale ; p<0,05 dans les sous-ensembles). Dans l'essai ELO-PD, 36 patients ont été randomisés. D'après le modèle mixte, la différence non ajustée dans le changement de l'IAH entre la ligne de base et la LALD par rapport à l'autre ligne de base et le placebo était de 3,2 événements/heure (IC 95 % : -2,5 ; 8,9, p=0,28). La différence moyenne d'IAH entre le placebo et la LALD était de 2,1 (p=0,65) pour l'ensemble de l'échantillon, d'après le test t.

Conclusions : Nos résultats suggèrent que l'AOS est plus fréquent et plus sévère dans les sous-types moteurs non-PIGD lorsqu'on évalue les sous-ensembles exempts de médicaments psychoactifs, de lévodopa et d'agonistes dopaminergiques pendant la nuit, ce qui pourrait être lié à des schémas neurodégénératifs spécifiques ou à des complications motrices. Les analyses suggèrent que la prise de LALD au coucher ne pourrait pas réduire la sévérité de l'AOS dans son ensemble. Cependant, certains individus pourraient répondre au LALD, mais des recherches supplémentaires seront nécessaires pour définir les prédicteurs de la réponse.

Acknowledgements

I would first like to thank my supervisor, Dr. Marta Kaminska, for her constant guidance and support throughout my graduate studies. Her advice and mentorship were invaluable to my success. Her research team has also continually provided support and assistance throughout my time as a student. Specifically, I thank Marianne Gingras, Ann Robinson and Teresa Gomes for all the knowledge and expertise they have contributed to my research and my personal growth.

I'd also like to thank the members of my thesis committee, Dr. Andrea Benedetti and Dr. John R. Kimoff, who have continued to guide me and encourage me to perform to the best of my abilities. I am grateful to the Weston Brain Institute, the Canadian Institutes of Health Research, and the American Thoracic Society who have financially supported the projects that brought this thesis to fruition.

Thank you to all the patients who contributed their time and energy to move science forward, allowing us to make meaningful contributions to medicine.

To my parents, sister, family, and best friends – thank you for constantly reminding me of what I am capable of and for unconditionally supporting my dreams and endeavours.

Last, but most certainly not least, I would like to thank my inspiration – my grandmothers – both of whom were burdened by respiratory illnesses but never let their strength and resilience falter. I will embody those qualities in all that I do, in honour of them.

Contribution of Authors

This is a traditional thesis according to McGill University guidelines. I, the student, authored all thesis components, including the introduction, literature review, methods, results, and discussion. Dr. Marta Kaminska, Dr. Andrea Benedetti, Dr. R John Kimoff and I jointly discussed the methods for data analyses included in this thesis.

Dr. Marta Kaminska, Dr. Anne-Louise Lafontaine, Dr. Andrea Benedetti, and Dr. R John Kimoff planned both the studies discussed in this thesis (COPE-PAP and ELO-PD). Data collection for COPE-PAP was executed by Dr. Annie Lajoie, Ann Robinson, and Dr. Joelle Crane. Data collection for ELO-PD was executed by Marianne Gingras, Melissa Gomez, and me. Dr. Marta Kaminska, Dr. Andrea Benedetti, Dr. R John Kimoff and I jointly discussed the data analyses for both studies (Chapters 2 and 3). Dr. Marta Kaminska was involved in organizing all statistical analyses, interpretation of the analyses, and critical review of the thesis draft.

Abbreviations

AASM: American Academy of Sleep Medicine

AHI: Apnea-hypopnea index

APAP: Automatic positive airway pressure

BMI: Body mass index

CI: Confidence interval

CPAP: Continuous Positive Airway Pressure

DA: Dopaminergic agonist

EDS: Excessive daytime sleepiness

ESS: Epworth Sleepiness Scale

LALD: Long-acting levodopa

LED: Levodopa equivalent dose

MDS-UPDRS: Movement Disorders Society – Unified Parkinson's Disease Rating Scale

MoCA: Montreal Cognitive Assessment

NMS: Non-motor symptoms

OSA: Obstructive sleep apnea

PD: Parkinson's disease

PDSS-R: Parkinson's Disease Sleep Scale

PIGD: Postural instability/gait difficulty

PSG: Polysomnography

RBD: Rapid-eye movement sleep behaviour disorder

RDI: Respiratory disturbance index

REM: Rapid-eye movement

RLS: Restless legs syndrome

SD: Standard deviation

SDB: Sleep-disordered breathing

SNpc: Substantia nigra pars compacta

TD: Tremor-dominant

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Chapter 1. Introduction and Literature Review

1.1. Introduction

People living with Parkinson's disease (PD) can spend numerous years managing symptoms that impair daily activities and negatively affect quality of life, including disturbed sleep. Sleep issues can manifest as trouble initiating and maintaining sleep and as specific sleep disorders that can contribute to other comorbid clinical conditions, such as obstructive sleep apnea (OSA).

Dr. Marta Kaminska and her research team have provided evidence that treating OSA by administering long-acting levodopa (LALD) at nighttime can reduce the number of respiratory events that occur during sleep, effectively reducing OSA severity[1]. Moreover, she and her team have shown that OSA may be caused motor dysfunction occurring due to the natural course of neurodegenerative progression in PD and that treating OSA in PD can improve comorbid symptoms of sleepiness and reduced cognition[2,3].

The principal objectives of this thesis are to explore whether specific motor profiles in PD are associated with changes in sleep structure, and with OSA and OSA severity, and to estimate the magnitude of the effect of LALD at bedtime on the severity of OSA in a population of patients with PD.

This thesis will begin with an extensive literature review of PD and OSA (Chapter 1), including an excerpt from our literature review titled "An Overview of the Effects of Levodopa and Dopaminergic Agonists on Sleep Disorders in Parkinson's Disease". Chapter 2 includes the objectives (2.1.), methodology (2.2.) and results (2.3.) of the first study exploring the differences in sleep architecture and OSA within PD motor subtypes. Chapter 3 will outline the objectives (Chapter 3.1.), methodology (Chapter 3.2.), and results (Chapter 3.3.) of the clinical trial assessing the effects of LALD on OSA in PD (ELO-PD trial). Chapter 4 includes a scholarly discussion of

the implications of the findings of both studies, including their strengths and limitations (Chapter 4.5.). Finally, a brief conclusion and future directions are presented in Chapter 5.

1.2. Parkinson's Disease

1.2.1. Overview

PD is the second most common neurodegenerative disorder worldwide. Its incidence and prevalence have rapidly increased in the past two decades, affecting approximately 6.1 million people in 2016[4]. PD is diagnosed clinically by taking into consideration a patient's medical history and neurological examination. Standardized clinical diagnostic criteria have been established to guide diagnoses[5]. The major pathological factor in PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the depletion of dopamine in the nigrostriatal pathway[6]. An additional hallmark of PD is the presence of intraneuronal inclusions known as Lewy bodies in surviving neurons of the SNpc, caused by insoluble aggregates of the misfolded alpha-synuclein protein[6]. These neuropathological changes lead to the hallmark motor symptoms observed in PD, including bradykinesia, muscular rigidity, and tremor[7]. Neurodegeneration also occurs in noradrenergic, cholinergic, serotonergic, and orexinergic systems, contributing to the non-motor symptoms (NMS) caused by PD. In their seminal model, Braak and colleagues proposed that PD neurodegeneration frequently occurs temporally and spatially in distinct stages, beginning in the lower brainstem structures and following an ascending pathway[8]. However, it is likely that the Braak hypothesis does not pertain to all cases of PD[9].

PD is also characterized by non-motor features that can aid in the diagnostic process because of the prodromal nature of certain NMS. Indeed, constipation, depression, hyposmia and certain sleep issues, including excessive daytime sleepiness (EDS) and rapid-eye movement sleep behaviour disorder (RBD), generally precede the occurrence of motor symptoms, making them important clinical biomarkers[7]. Other NMS include hallucinations, pain, anxiety, cognitive

dysfunction, dementia and nocturia[10]. Santos Garcia and colleagues[11] have shown increased NMS burden to be a significant contributor to health-related quality of life impairment in PD patients. Moreover, the authors report that the progression of NMS can cause significant worsening of quality of life, making the frequent assessment of NMS in PD imperative to proper disease management. This is especially crucial because treating PD primarily involves symptom management given there is currently no cure[11].

1.2.2. Sleep and sleep disorders in PD

Sleep issues are among the most reported NMS in PD, affecting nearly 66% of all PD patients[12] and are associated with worse quality of life and greater overall NMS burden[12]. Moreover, poor sleep was shown to be associated with more severe motor symptoms and NMS in PD[13], suggesting sleep issues may exert an impact on disease burden. However, it is possible that sleep issues and worse quality of life are associated due to more severe disease, or that worse motor impairment leads to more disturbed sleep. Sleep structure itself is altered in PD through changes in sleep efficiency, total sleep time, sleep fragmentation, prolonged sleep latency and a reduced percentage of rapid-eye movement (REM) sleep[14–16]. Alterations in sleep architecture advance progressively as disease duration increases[14], suggesting that the neuropathological process of PD may be inherent to sleep issues in this disorder.

Specific sleep disturbances and disorders can occur in PD including insomnia, EDS, and circadian rhythm disorders, as well as sleep disordered breathing (SDB), RBD and restless legs syndrome (RLS)[17]. Insomnia is the most common sleep disorder affecting between 27 and 80% of PD patients[18]. RBD and SDB, specifically OSA, are also common and can affect up to 30%[19] and 63%[20] of patients, respectively.

The intrinsic pathophysiology of PD causing the disturbance of motor and sleep-wake regulating structures, as well as their related neurotransmitters[21], plays a key role in the generation

of sleep disorders. Pathological changes in the brainstem[8] and hypothalamus[22] are greater in PD patients with sleep disturbances than in PD patients without sleep disturbances[23]. Insomnia[24] may be due to neurodegeneration in hypothalamic regions such as the ventrolateral preoptic[25,26] and median preoptic areas[27]. Moreover, SDB in PD may be in part caused by the degeneration of neurons in distinct brainstem regions involved in ventilatory control[28].

The degeneration of nondopaminergic pathways – serotonergic[29], noradrenergic[30] and cholinergic[31] – can also result in sleep disturbances and disorders in PD. EDS may, in part, be attributed to a deficiency in hypocretin-containing neurons[32], which are involved in hypersomnolence and the pathogenesis of narcolepsy[33]. The noradrenergic locus coeruleus and subcoeruleus complex, involved in regulating sleep-wake states[34], are also affected in PD[30] and may be involved in the pathogenesis of RBD, as shown through neuroimaging which exhibited a more marked decrease in signal intensity on magnetic resonance imaging in these regions in PD patients with RBD than in those without, implying structural damage in patients with PD and RBD[35].

There are numerous alternative factors that may also contribute to sleep disturbances in PD including nocturnal motor symptoms, nocturnal akinesia, and NMS such as mood disorders, nocturia, pain and hallucinations[21]. Other potential factors affecting sleep in PD include adverse and/or side effects of medication, genetic susceptibilities[17], age-related sleep changes, since PD is a disorder that primarily affects the aging population, and other comorbidities[21].

1.2.3. Levodopa and dopaminergic agonists in PD

The following section is a short summary of the literature review: "An Overview of the Effects of Levodopa and Dopaminergic Agonists on Sleep Disorders in Parkinson's Disease," published in the *Journal of Clinical Sleep Medicine* in June 2023, of which I am the first author[36]

(Appendix 1). This review provides an overview of the effects of levodopa and dopaminergic agonists (DAs) on sleep structure, insomnia and subjective sleep, EDS, OSA, RBD, and RLS.

Levodopa is the gold standard for managing PD symptoms. Levodopa is decarboxylated in the striatum to form dopamine which then acts on dopaminergic receptors[37]. Adverse drug reactions include motor fluctuations and the recurrence of symptoms due to the drug effect wearing off, leading to more severe motor symptoms in some cases[38]. Levodopa-induced dyskinesia is a frequent and biologically intricate complication in PD[39] and can affect up to 94% of patients with PD[40]. Levodopa-induced dyskinesia occurs when dopamine concentrations are at their maximum in the brain and occurs dose-dependently[39,41]. This form of dyskinesia also depends on the method of drug administration[39]. LALD has a longer half-life than regular levodopa, maintaining a greater plasma concentration over a longer period[42]. LALD exhibits the same safety and tolerability as immediate-release levodopa but also has similar rates of motor complications. Its role as an alternative for immediate-release levodopa remains unclear due to less predictable absorption and effect[43]. DAs are another pharmacological treatment in PD[44]. DAs act directly to continuously stimulate the central dopamine receptors[45]. Pramipexole, ropinirole, apomorphine, and rotigotine are most frequently prescribed[45]. In contrast to levodopa, DAs are appreciated for their longer half-life and can be used to reduce motor fluctuations caused by levodopa[46].

There is conflicting evidence regarding the effects of these drugs on sleep and sleep disorders in PD. In their study, Diederich and colleagues found that abnormal sleep architecture in PD was independent of the dosage of levodopa or dopaminergic medication[14]. Moreover, other results show that sleep efficiency may increase, and sleep latency and wake-time after sleep onset may decrease in drug-naïve patients started on levodopa[47]. These sleep improvements were attributed to an improvement in motor symptoms, however. In their meta-analysis, Zhang et al.

found that the levodopa equivalent dose (LED) contributed significantly to sleep alterations on polysomnography (PSG) in patients with PD, and that a higher LED was associated with less total sleep time, and a greater wake-time after sleep onset and REM latency[48]. The overall effects of these drugs on sleep structure seem to be variable and can depend on disease duration and medication dosage.

The effects of these drugs in specific sleep disturbances and disorders are also variable. Levodopa and DAs are treatment options for some sleep-related movement disorders, such as RLS[49,50], but they can also exacerbate sleep issues like EDS[51,52], and may contribute to insomnia severity[53] and the presence of insomnia[54]. EDS and insomnia are affected by these medications in diverse ways. First, DAs may have a biphasic effect on specific dopaminergic receptors where lower doses may promote sleepiness and higher doses can lead to insomnia in certain patients[53,55,56]. Second, both these sleep disturbances can be caused secondarily due to other sleep disorders such as OSA or RBD. Third, different neurodegenerative patterns may invoke insomnia in some patients and EDS in others[57]. Thus, EDS and insomnia may affect patients differently depending on patterns of neurodegeneration and the type of medication, as well as the dosage. Levodopa and the LED have also been found to be associated with symptomatic RBD severity[58], although this may be confounded by disease duration, while DAs may be beneficial for RBD symptoms[59,60]. However, studies assessing DAs and RBD are observational and have small sample sizes, and some assess idiopathic RBD as opposed to RBD in PD, which may change response to treatment. Thus, other randomized controlled trials in PD would be beneficial to confirm these observations.

Levodopa and DAs may be beneficial for SDB in PD. Several studies have shown a decrease in upper airway obstruction following treatment with levodopa using spirometry[61,62].

Herer et al. showed that approximately 23% of patients had upper airway obstruction upon withdrawal of levodopa[62]. Moreover, the DA apomorphine may also improve dysfunction of the upper airway musculature potentially resulting in OSA[63]. These findings suggest that OSA in PD may indeed be caused by motor dysfunction, which may be alleviated by these drugs, but the extent by which the patient may benefit is dependent on the severity of motor dysfunction[62]. Nonetheless, the effects of levodopa and dopaminergic drugs on OSA in PD remain ambiguous and require further investigation.

1.2.4. Motor subtypes

PD is a heterogeneous disorder – its symptomatic manifestations differ from patient to patient owing to different clinicopathologic phenotypes. Clinical observations and analyses of cohort studies have been used to identify PD subtypes, with a focus on data sets that identify clinical traits that cluster together[64]. In 1990, the DATATOP cohort was used to explore clinical heterogeneity among 800 drug-naïve patients with early PD. This study was the first to describe distinct clinical subtypes based on prominent motor features: postural instability and gait difficulty (PIGD) and tremor-dominant (TD). The authors used specific items of the Unified Parkinson's Disease Rating Scale (UPDRS) to calculate a mean tremor score and a mean PIGD score. The ratio of the mean tremor score over the mean PIGD score determined the subtype[65]. Stebbins et al. validated this method using the new Movement Disorders Society sponsored UPDRS (MDS-UPDRS) in 877 PD patients[66]. This subtyping method has been used in many subsequent studies aiming to understand the pathophysiology of PD and to identify relationships with NMS.

The PIGD subtype is characterized by a late disease onset with a poor prognosis, rapid progression[64], and worse NMS in general[67,68], including worse cognitive impairment[69], more autonomic features[67,70], and worse sleep and fatigue[71,72]. The TD subtype is associated with an earlier onset of disease with a better prognosis, slower progression, as well as fewer and less severe

NMS[64]. However, different subtyping classification systems were used in some of these studies[70,72]. Rather than the PIGD subtype, some studies use the akinetic-rigid subtype[73]. The inconsistent definition of motor subtypes limits the generalizability of findings regarding NMS and the motor subtypes. Moreover, these studies use different questionnaires to evaluate NMS in general, such as the Non-Motor Symptom Scale and the Non-Motor Symptom Questionnaire, as well as different assessments for specific NMS such as cognition and sleep issues. Finally, only some studies included a control group[68,72], while others were cross-sectional, examining associations in PD patients only[67,71].

The TD and PIGD motor subtypes also differ in terms of neural circuitry involvement. Using functional magnetic resonance imaging, one study compared the activation of striatothalamocortical and cerebellothalamocortical circuits in motor subtypes and showed that in patients with TD PD, there was significantly more activity in cerebellothalamocortical circuits contralateral to the brain region activated by finger tapping than in the non-TD subtype[74]. Differential impairment and degrees of dysfunction of these circuits may explain the clinical heterogeneity of motor symptoms in PD. Patients with non-TD PD may have reduced brain activity in the prefrontal cortex and globus pallidus according to one study[75], and smaller gray matter volume in cortical areas involving motor, cognitive, limbic, and associative functions in another study[76]. Patients with PD and rest tremor had decreased grey matter volume in the cerebellum compared to those without rest tremor[77]. Finally, the PIGD and TD motor subtypes may also differ in terms of neurotransmitter deficiencies. Doder et al. analyzed midbrain raphe 5-HT(1A) binding as a functional measure of the integrity of the serotonergic system in PD patients and found that UPDRS tremor scores correlated with serotonergic binding and not bradykinesia or rigidity scores[78]. Bohnen et al. found a significantly slower gait speed in a subgroup of PD patients with

low cholinergic activity visualized using PET imaging[79]. Thus, cholinergic denervation may be a marker of slowing of gait, associated with the PIGD motor subtype. These neuropathological differences in the motor subtypes may affect the variations in NMS experienced by the different subgroups of PD patients.

1.3. Obstructive Sleep Apnea

1.3.1. Overview

OSA is a sleep-related breathing disorder characterized by recurrent upper airway obstruction caused by pharyngeal collapse during sleep, resulting in repeated episodes of partial (hypopnea) or complete (apnea) cessation of airflow lasting a minimum of 10 seconds. These episodes are frequently associated with arousal from sleep and a decline in blood oxygen saturation, leading to sleep fragmentation[80]. The apnea-hypopnea index (AHI) – the number of apneas plus hypopneas per hour of sleep – is the gold standard in diagnosing this sleep disorder[80]. An AHI of 5 obstructive breathing events per hour is the threshold for diagnosing OSA, if combined with symptoms. An AHI of 15-30 obstructive breathing events per hour is considered moderate, and an AHI above 30 is considered severe OSA, as per the American Academy of Sleep Medicine (AASM) criteria[81]. There are several definitions of hypopnea, which can result in different AHI values. Patients may be impacted by these definitional variations (for example, the stated severity may impact eligibility for government-funded therapy), and the interpretation of research studies may be affected as well[80]. OSA is highly prevalent, affecting an estimated 1 billion people globally between the ages of 30 and 69, with an estimated 425 million people affected by moderate or severe OSA, rendering this disorder a global health issue[82]. The prevalence of OSA in population-based studies, using PSG, is as high as 49.7% to 59% in men and 23.4% to 33% in women[83,84].

The most reported symptoms include snoring, apneas witnessed by a bed partner, arousal from sleep with a sensation of choking, and EDS. Fatigue is also a common symptom, as well as symptoms of insomnia including difficulty with sleep initiation and maintenance[85]. Most patients, however, are asymptomatic[86]. Since EDS is the most reported symptom, the Epworth Sleepiness Scale (ESS) can be used to determine sleepiness severity[87]. The STOP-BANG questionnaire is a screening tool that has good sensitivity and specificity to establish whether a patient is at an elevated risk of having moderate or severe OSA[88]. To definitively diagnose OSA, an overnight PSG is performed where several signals are monitored, namely EEG, EMG, EOG, ECG, pulse oximetry, oral and nasal flow using pressure sensors and a thermistor, and respiratory effort, typically with respiratory inductance plethysmography[85].

The pathogenesis of OSA is complex and multifactorial, incorporating anatomical and non-anatomical factors which vary from patient to patient. The pharynx is a collapsible tube, and its narrowing can occur due to a narrow pharyngeal airway, airway length and particular pharyngeal lumen shape, as shown in different imaging studies[89,90] using drug-induced sleep endoscopy[89], magnetic resonance imaging, and acoustic reflection[90]. Furthermore, characteristics of the craniofacial structure such as the mandible and maxilla influence the cross-sectional area of the pharynx[91]. Although anatomical abnormalities were considered the primary cause of OSA historically, research suggests OSA is phenotypically and endotypically heterogeneous[92–94]. Upper airway patency is maintained by activation of upper airway dilator muscles such as the genioglossus and tensor palatini, thus dysfunction of the dilator muscles can also lead to pharyngeal collapse. Oliven and colleagues speculate that upper airway muscle activation may be dyssynchronized during sleep which can delineate the mechanism of destabilization of airway patency during sleep in patients with OSA[95]. In addition to compromised craniofacial anatomy and

pharyngeal dilator muscle dysfunction, unstable ventilatory control, or loop gain, and a low arousal threshold can contribute to SDB in certain cases. Elevated loop gain is the instability of a system under perturbation, as opposed to low loop gain, which is intrinsically stable[96,97]. In respiratory physiology, loop gain is the ventilatory response to ventilatory disturbance ratio[98,99]. Patients with high loop gain have rapid, large negative inspiratory pressures in response to minimal changes in CO_2 levels, which "sucks" the pharyngeal airway closed. High loop gain can also contribute to fluctuations in respiratory drive due to excessive ventilatory response causing subsequent low ventilatory drive, associated with a decrease in pharyngeal dilator muscle activity[98,100]. High loop gain contributes to OSA[96,99]. A low respiratory arousal threshold refers to an awakening from sleep that is triggered by a minor respiratory disturbance. An arousal is accompanied by an increase in ventilatory drive that relates to wakefulness, as compared to sleep[101–103]. While this results in restoration of upper airway patency, it may lead to unstable breathing patterns[104]. Respiratory instability is likely facilitated by an interaction between a low arousal threshold and elevated chemosensitivity[105]. Studies show that hypnotic agents such as eszopiclone[103] may improve OSA severity by increasing the respiratory arousal threshold. This drug led to a significant reduction in AHI[103] in all patients, and this reduction was most pronounced in those with a low arousal threshold[103]. The recognition of different pathophysiologic traits contributing to OSA may provide benefit by contributing to advancements in personalized therapies[80].

Male sex, obesity and older age are some of the major risk factors associated with the development of OSA. Obesity may contribute to the propensity for airway collapse due to increased muscle deposition around the neck and within the tongue[106] which can lead to crowding of the airway and consequently decreased cross-sectional area of the pharynx[100]. Moreover, the accumulation of fat around the abdomen contributes to a reduction in lung volume and an increase

in intraabdominal pressure, which can increase upper airway collapsibility via reduced caudal traction exerted on the upper airway, also affecting the stability of ventilatory control[107]. Indeed, Schwartz et al. have found that weight loss leads to a significant decrease in upper airway collapsibility[108]. Fat accumulation in men tends to occur centrally, potentially predisposing to OSA. Additionally, men tend to have a greater proportion of neck fat in certain regions, specifically inside the mandible, than women[109]. It has also been shown that men have a higher passive pharyngeal airway collapsing pressure[80], predisposing the male sex to pharyngeal collapse.

OSA can lead to various comorbidities including cardiovascular complications such as hypertension, and diabetes. OSA and hypertension are bidirectionally related; up to 50% of patients with OSA may have hypertension, and 30% of hypertensive patients may have OSA[110,111]. Over 86% of obese patients with type 2 diabetes were shown to have OSA in a study by Foster et al.[112], however, this may simply be an association because obesity is considered a risk factor for both disorders[80]. Other comorbidities include metabolic syndrome, renal disease, chronic obstructive pulmonary disease, asthma, and cancer[113].

Management of OSA includes treating symptoms and managing comorbidities. Continuous positive airway pressure (CPAP) is mainstay treatment for OSA. A flow generator produces a pre-specified pressure through a mask worn by the patient, which maintains patency of the upper airway, preventing respiratory events during sleep. A systematic review assessing CPAP for OSA in adults showed that compared to control, objective and subjective sleepiness, and several quality of life, cognitive, and depression measures were significantly improved in patients on CPAP[114]. However, CPAP adherence is a major issue, given this device can be cumbersome and inconvenient for certain patients. The CPAP non-adherence rate over a span of 20 years was 34.1%, with no improvement over that time frame[115]. Oral appliances can also be used to treat

OSA, however, compared to CPAP, they are not as effective at reducing AHI, improving sleep efficiency, and improving oxygen saturation[114]. Doff et al. reported no significant differences in the proportions of successful treatments between oral appliance therapy and CPAP in treating mild to severe OSA over 2 years, although CPAP remained more effective in lowering AHI and reducing oxygen desaturation[116]. Oral appliances are the preferred treatment among patients, but studies have shown that withdrawal from treatment was more likely in patients using oral appliances than in patients using CPAP therapy[114,116].

1.3.2. OSA in PD

OSA is common in PD, affecting up to 63% of patients[20]. The prevalence of OSA in PD spans a wide range, with some studies finding a prevalence as low as 20%[117], likely due to differences in patient populations, small sample sizes, and differences in respiratory event scoring across laboratories[118]. OSA may be less prevalent in patients with advanced PD compared to the general population due to a lower body mass index (BMI) in this subpopulation[119]. However, BMI is not correlated with severity of OSA in PD, hence OSA may be pathologically different in PD[120]. A correlation between OSA severity and PD severity has been found in several studies[121–123], however, causation has yet to be established.

Although some research has shown that OSA is not more common in PD than in the general population[121], it is evident that the two conditions frequently coexist. This may be due to the wide prevalence of OSA in society in general which thus coincides with PD, or because PD-related changes predispose to OSA, or both. Moreover, older age is associated with both OSA and PD. Four mechanisms have been proposed whereby it is biologically plausible that PD is involved in the pathogenesis of OSA in certain patients[118]. First, upper airway dilator muscles may be affected in PD leading to abnormalities in spirometry that are consistent with upper airway obstruction, which may be exacerbated during sleep[61,118]. Autonomic dysfunction in PD may also impair

control of breathing, specifically during non-REM sleep. Altered control of breathing in PD, specifically reduced chemosensitivity to hypoxia and reduced respiratory drive in response to hypercapnia, may contribute to OSA as well. Finally, sleep fragmentation itself can lead to respiratory instability leading to OSA[118].

OSA can be characterized by different pathophysiologic endotypes, including compromised craniofacial anatomy, dysfunction of pharyngeal dilator muscles, unstable ventilatory control, or elevated loop gain, and a low arousal threshold[124]. Distinct clinical phenotypes of OSA have also been outlined including OSA associated with sleepiness with higher cardiovascular risk, OSA with disrupted sleep and insomnia, and asymptomatic OSA[92]. It is unknown, however, if and how these OSA subtypes manifest in PD. Exploring the variable expression of OSA in PD may allow for a better understanding of disease complications occurring in these patients due to OSA, further guiding how this sleep disorder can be managed clinically in this population.

In some of the earliest studies, abnormal flow-volume loops were found in 89% of patients, with 37% manifesting physiological evidence of upper airway obstruction[125], corroborating the idea that the upper airway musculature may be involved in OSA. Research has shown that levodopa can reverse upper airway obstruction in PD[62,126]. In a case report, Vincken and colleagues show that inspiratory and expiratory flow rates improved 90 minutes post-intake of levodopa in one patient, and inspiratory and expiratory plateaus disappeared, shown using a flow-volume loop after spirometry. Before the intake of levodopa and at the peak of PD and respiratory symptoms, the flow-volume loop showed signs of severe airflow limitation and a contour consistent with fixed upper airway obstruction, allowing the authors to attribute airflow limitation to the upper airway[126]. Herer et al. report similar findings in their double-blind, placebo-controlled, crossover study of 22

patients with PD. Upper airway obstruction was defined as meeting 4 of 6 spirometric criteria. Of the 5 patients with upper airway obstruction, 3 no longer qualified for upper airway obstruction after treatment with levodopa, whereas only 1 patient qualified for this in the placebo group. Spirometry showed an improvement in the saw-tooth pattern and an important increase in inspiratory and expiratory flow rates with levodopa. However, some of the parameters used to assess upper airway obstruction, namely peak expiratory flow, may have been caused by an amelioration of motor impairment, i.e., respiratory muscle strength, and not necessarily a reduction in airway obstruction[62]. Contrastingly, Obenour and colleagues reported no difference in expiratory flow or lung volume in patients with PD after treatment of levodopa. The authors concluded that airway obstruction thus occurs due to airway resistance and lung elastic recoil and not necessarily due to impairment in upper airway musculature[127]. While informative, these studies were conducted with small sample sizes, and differences may result from different patient selection.

Upper airway obstruction during sleep in PD has not been well-defined. However, given the reported effect of levodopa on airway obstruction during wakefulness, Gros et al. sought to assess the effects of levodopa on OSA. Here, patients with PD were separated into groups taking Sinemet CR (LALD) and those not taking Sinemet CR. After adjusting for confounders, PD patients receiving Sinemet CR at bedtime had a significantly lower AHI, and fewer respiratory-related arousals, specifically in the second half of the night, where residual effects of any other levodopa or dopaminergic medication taken prior is likely nullified. These results justify further investigation of the effects of Sinemet CR on OSA in PD, despite its inability to correct OSA completely[1].

OSA leads to daytime sleepiness and cognitive dysfunction. Harmell et al. showed that patients with PD and OSA scored significantly lower on cognitive screening measures, indicating worse cognitive functioning, compared to PD patients without OSA[128]. Moreover, Mery et al.[129] established an association between Montreal Cognitive Assessment (MoCA) scores and respiratory indices related to OSA, including the AHI. MoCA scores were negatively associated with respiratory arousals. OSA and compromised quality of sleep, measured by PSG, was found to be associated with cognitive impairment in PD, and global cognitive performance was decreased in patients with OSA in PD[130].

Neikrug and colleagues were among the first to establish that CPAP is effective for OSA in PD. Their clinical trial included 38 patients who were randomized to receive either therapeutic CPAP or placebo CPAP treatment. Therapeutic CPAP resulted in a significant decrease in AHI and in oxygen desaturation compared to placebo, as well as deeper sleep. Moreover, objective sleepiness was significantly reduced overall after 3 weeks of therapeutic CPAP. Although the sample size of this study was small, they had a high rate of CPAP adherence – 88% of days for an average of 5.2 hours per night[131].

The effect of CPAP on cognition in PD has led to variable findings. Harmell and colleagues found no improvement in overall cognition after 3 or 6 weeks of CPAP. However, this was a relatively small follow-up time. The work of Kaminska et al. showed that, after 12 months, the MoCA score improved significantly in PD patients with OSA on CPAP showing a possible need for longer CPAP treatment to see differences in global cognition. Parkinson's Disease Sleep Scale (PDSS) scores also improved from baseline, indicating better subjective sleep quality overall[2].

Despite the clear effectiveness of CPAP treatment for OSA in PD, CPAP adherence is a challenge for some. Terzaghi et al. showed a lack of feasibility in their study where 75% of subjects

dropped out due to CPAP intolerance, most of those subjects stopping CPAP treatment within the first 3 weeks. Most demographic and disease-related variables were not significantly different between subjects who completed the study and those who did not. However, a trend towards a lower UPDRS part 3 score (less motor impairment) was found in those who completed the study, though this difference was insignificant[132]. Nonetheless, this finding suggests that motor impairment may play a role in CPAP intolerance in PD. Other treatment options are vital for intolerant PD patients.

Overall, OSA is frequently present in patients with PD, and may exacerbate NMS such as daytime sleepiness and cognition, reducing health-related quality of life. Thus, it is important to continue to investigate how the pathophysiology of PD may contribute to OSA to alleviate the burden of OSA in this population. Moreover, it is equally important to further investigate the possible beneficial effect of LALD, a potential non-CPAP treatment option, on OSA, considering that it may constitute a lesser burden in patients with PD.

Chapter 2. Sleep Architecture and Obstructive Sleep Apnea in Parkinson's Disease Motor Subtypes

The objectives, methods, results, figures, and tables were adapted from a to-be submitted manuscript, where the student is the first author.

2.1. Objectives

There is still much that is unclear and unknown about the pathogenesis of OSA in patients with PD. Although this sleep disorder is common in the general population, there is meaningful evidence suggesting that upper airway obstruction caused by motor dysfunction itself may be a contributor to the development of OSA, as discussed above. We thus explored whether OSA is more prevalent and more severe among patients with a particular motor subtype of PD as means to understand which motor profiles are associated with more severe OSA, if any. Given that our group had two ongoing clinical trials involving PD patients with OSA, we used this patient data to analyze various respiratory indices related to OSA, as well as other sleep variables obtained by PSG.

The objectives were to:

1. explore whether sleep structure differs among different PD motor subtypes.
2. explore the frequency and severity of OSA among the different PD motor subtypes.

2.2. Methodology

2.2.1. Study subjects

This was a secondary study using patient data from two randomized controlled trials: Cognition and OSA in PD, Effect of Positive Airway Pressure Therapy (COPE-PAP) (NCT02209363), and the Effect of Long-acting Levodopa on OSA in PD (ELO-PD), both conducted at the McGill University Health Centre, Montreal, Canada. Details of the ELO-PD trial will be discussed in detail in **Chapter 3** of this thesis.

The COPE-PAP trial is a single-blind, parallel group, randomized controlled trial involving patients with OSA and PD[133]. Patients were randomized to a 1:1 ratio to treatment (auto-positive airway pressure (APAP) or control (nasal dilator strip) interventions. The primary outcome of the COPE-PAP study was the change in global cognition following six months of APAP or nasal dilator strip in PD patients with OSA and reduced cognition assessed using the MoCA. Subjects were recruited from April 2015 to September 2022 from the McGill Movement Disorders clinic, and other affiliated neurological centres.

Inclusion criteria for the COPE-PAP study were[133]:

- A diagnosis of PD based on the movement disorder society (MDS) criteria
- evidence of cognitive dysfunction (clinical impression of mild cognitive impairment and MOCA <=27)
- presence of OSA (respiratory disturbance index (RDI) ≥ 15/h) on screening diagnostic PSG
- stable regimen of anti-PD medication for 1 month prior
- adequate knowledge of English or French for completion of study assessment.

Exclusion criteria for the COPE-PAP study were[133]:

- oxygen saturation <75% for >10% of the diagnostic PSG
- other major neurological and medical disorders
- active treatment of OSA
- significant vision or hearing impairment that could affect performance on neurocognitive assessment tasks
- latex allergy

For the present secondary study, data from the participants' screening/baseline visits from COPE-PAP and ELO-PD only were used. A patient was excluded from our analyses if they did not complete the MDS-UPDRS at their screening visit.

2.2.2. Procedures

At the study visits, several assessments were completed for the COPE-PAP and ELO-PD trials, including the ESS[134], MoCA[135], PDSS or the revised version (PDSS-R)[136], the MDS-UPDRS[137], and questionnaire assessment of RBD[138]. PSG scoring for RBD was performed according to Frausher et al.[139]. Patients were considered as having probable RBD (pRBD) if they did not meet the criteria for RBD or had no REM sleep on PSG but reported symptoms of RBD in the questionnaire. The current medication regimen was obtained from the patient's medical chart and the exact medication schedule was verified with the patient.

2.2.3. Polysomnography

Patients underwent standard overnight PSG. A commercial recording system was used with 6-channel EEG (C3, C4, F3, F4, O1, O2), bilateral tibialis anterior electromyography (EMG), and digital video were used. Respiratory inductance plethysomography was used for thoracoabdominal motion, and nasal pressure cannula measured airflow. Oxygen saturation was continuously monitored with a finger oximeter. Manual scoring of the data was done by one certified registered PSG technician using standard AASM clinical criteria[140]. Total sleep duration of minimum 2 hours during PSG was required.

2.2.4. Statistical analyses

We compared subjects with different PD motor subtypes. Subjects were assigned a clinical motor subtype based on the method of Stebbins and colleagues[66]. Specific elements of the MDS-UPDRS parts II and III to obtain a ratio of the mean MDS-UPDRS tremor scores to the mean MDS-UPDRS PIGD scores. Subjects were separated into the PIGD subtype if the resulting ratio

was ≤0.9; or non-PIGD subtype if the resulting ratios were >0.9, combining TD and indeterminate[66]. The following formula was used to calculate the LED: regular levodopa dose + Sinemet CR × 0.75 + pramipexole dose × 100 + rasagiline dose × 100 + rotigotine dose × 30 + amantadine dose × 1 + selegiline dose (oral) × 10 + selegiline (sublingual) × 80 + entacapone (LED × 0.33)[141]. Patients on Stalevo or Comtan were considered as having an equivalent dose of entacapone. Missing questionnaire data was replaced using values from other study timepoints (last observation carried backward) when available[142]. Missing PDSS or PDSS-R data was replaced using other study timepoints, and if that was not feasible, the average of the other individual values was used (person-mean imputation)[143]. Any total scores missing for the MDS-UPDRS were calculated according to a validated technique outlined by Goetz et al., when possible[144].

Baseline demographic data was presented as means and standard deviations (SD) unless specified otherwise. Simple univariable analyses were performed for outcomes of interest using linear regression or logistic regression where appropriate, and χ^2 for categorical variables. Multivariable regression was performed adjusted for confounders determined a priori by the investigators based on the literature. Regression models for the sleep parameters were adjusted for age, sex, and BMI, whereas the regression models for the respiratory parameters were adjusted for age, sex, BMI, and additionally for total sleep time in stage N3, in stage REM, and in the supine position. Total sleep time in stage N3 was included as a covariate because it showed differences with p-values <0.02 between our study groups. Total sleep time in stage REM and total sleep time in the supine position were then included because they are known to impact the AHI.

Sensitivity analyses were done on three subsets to explore the effects of certain medications: subset 1 excluding patients on psychoactive medication (antidepressants,

anticonvulsants, benzodiazepines, opioids, etc.), subset 2 excluding patients taking levodopa or DAs at nighttime, and subset 3 excluding patients on psychoactive medication and/or patients taking levodopa or DAs at nighttime. Psychoactive drugs are known to affect sleep and sleep-disordered breathing[145,146], as are levodopa and DAs; the two latter drugs exerting beneficial and adverse effects on the different sleep disorders[36]. Due to the smaller sample sizes in the subsets, when looking at respiratory variables, model 2 was adjusted for demographic variables only as for the full sample, but model 3 was adjusted for total sleep time in stage N3, in stage REM and in the supine position only.

Linear regression was also performed to determine whether there was an association between AHI and MDS UPDRS IV scores in the full sample and in all subsets, adjusted for confounders including age, sex and BMI, because there was a trend for higher MDS UPDRS IV scores in the non-PIGD group.

A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using R version 2023.03.0+386[147].

2.3. Results

2.3.1. Patient characteristics

Of the 168 participants that were considered for our analyses, 20 were excluded due to missing MDS-UPDRS data and two due to insufficient sleep on PSG. The remaining 146 subjects were then categorized into two groups: PIGD (n=55) and non-PIGD (n=91). The demographic characteristics of this population are shown in Table 1. About 50% of patients were on psychoactive medication and 30.8% were on levodopa or DAs at nighttime.

2.3.2. Sleep architecture and PD motor subtypes

Sleep architecture was similar between groups, except for greater sleep time in stage N3 in the PIGD group, though not statistically significantly so. Differences in sleep architecture between

the groups are shown in Figure 1 and in detail in Appendix Table A1. In subset 1 (n=73), the PIGD group had significantly greater proportion of sleep time in stage N3 by 6.7% (p=0.03) after adjusting for confounders. In subset 2 (n=101), the trend for total sleep time in stage N3 was consistent with the full sample analyses, but not reaching statistical significance in neither unadjusted nor adjusted models. Subset 3 (n=60) showed that total sleep time in stage N1 was less in the PIGD group (p=0.018, adjusted) and total sleep time in stage N3 was significantly greater, as shown in Figure 1.

2.3.3. Respiratory parameters, OSA, and PD motor subtypes

In the fully adjusted model of the full sample, the AHI was significantly lower in the PIGD group (β = -6.6 events/hour, p = 0.047). Although insignificant, similar trends were observed for the RDI and oxygen desaturation index. In subset 1, there were significantly fewer respiratory arousals and the RDI was significantly lower in the adjusted model. The AHI was significantly lower in the PIGD group in subset 2 (-10.4 events/hour, p=0.006) in the model adjusted for age, sex, and BMI, and remained significantly lower in the model adjusted for total sleep time in stage N3, REM and in the supine position. The RDI and RDI NREM were also significantly lower in the PIGD group across all models of adjustment in this subset. In subset 3, the total arousals index and respiratory arousals index were significantly lower in the PIGD group across all models of adjustment. The AHI remained significantly lower in the PIGD group in this subset after adjusting for confounders (-12.3 events/hour, p=0.003). RDI, RDI NREM (unadjusted and adjusted for age, sex and BMI only) and RDI in the supine position were also significantly lower in the PIGD group. Detailed results from the linear regression models are included in Appendix Table A2.

The PIGD group had fewer subjects with OSA in the full sample (OR = 0.5, 95%CI = 0.2; 1.1, p=0.09) after adjusting for confounders (Table 2), but this was not statistically significant. In subset 1, there were fewer subjects with OSA in the PIGD group, reaching significance in the

model adjusted for age, sex and BMI, whereas in subset 2, the prevalence of OSA was not significantly different between groups (OR=0.4, p=0.06). Finally, as in subset 1, the prevalence of OSA in subset 3 was significantly lower in the PIGD group in the model adjusted for demographic variables (OR=0.2, p=0.04) but not when adjusting for the different sleep parameters (OR = 0.3, p=0.1).

2.3.4. Exploratory analyses

There was no significant association between AHI and UPDRS IV scores in the full sample nor in the subsets (Appendix Table A3).

2.4. Figures and tables

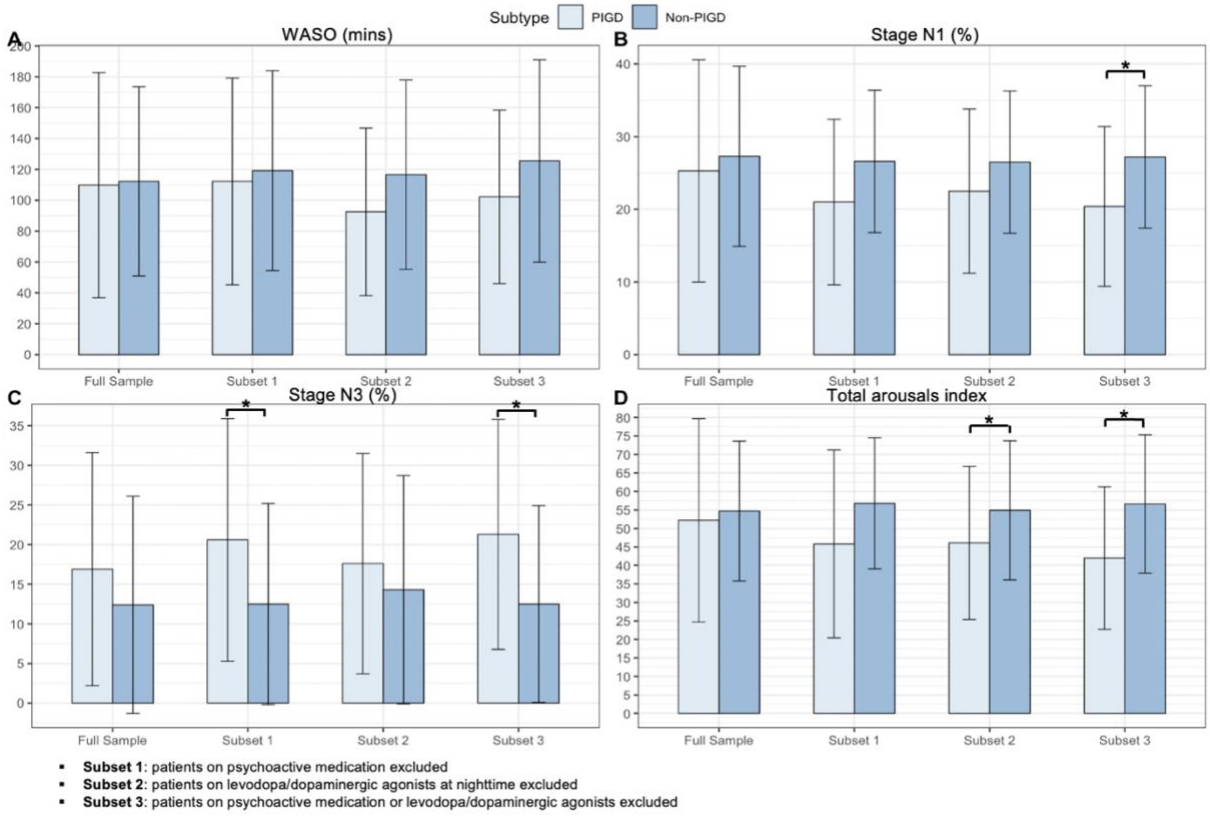
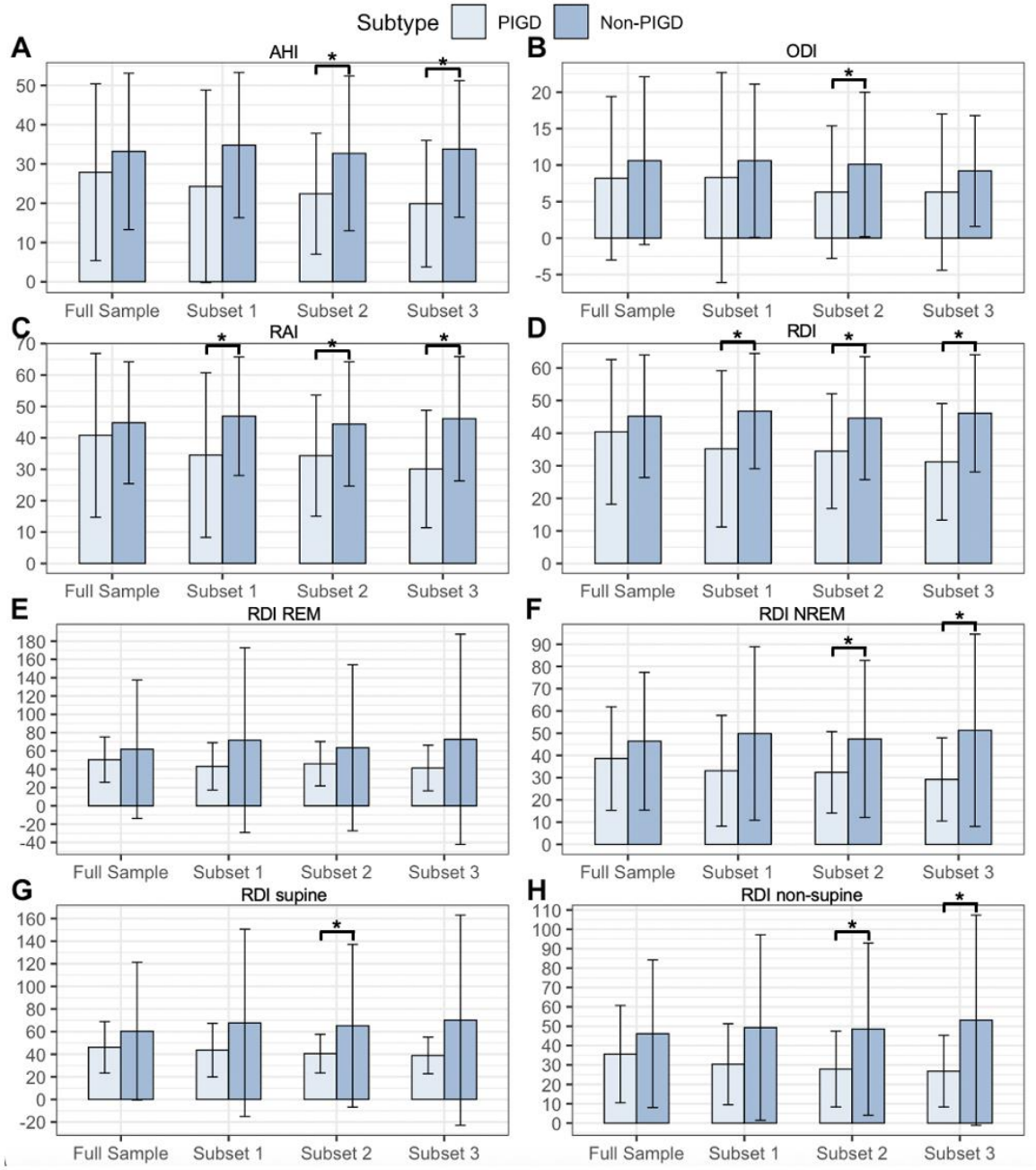


Figure 1. Means and standard deviations of sleep parameters including wake-time after sleep onset (WASO) (A), total sleep time in stage N1 (B), total sleep time in stage N3 (C) and the total arousals index (D) in the full sample and in patient subsets (cf. methods).
Statistically significant differences between the PIGD and non-PIGD group were determined using linear regression.
* = $p<0.05$ adjusted for age, sex, body mass index

Figure 2. Means and standard deviations of respiratory indices including the apnea-hypopnea index (A), the oxygen desaturation index (ODI) (B), and the respiratory arousals index (RAI) (C), the respiratory disturbance index (RDI) (D), the RDI during REM sleep (E), NREM sleep (F), in the supine position (G), and in the non-supine position (H) in the full sample and patient subsets.



Statistically significant differences between the PIGD and non-PIGD group were determined using linear regression.

* = $p<0.05$ adjusted for age, sex, body mass index

Table 1. Patient baseline characteristics.

Clinical Data	Full sample (n=146)	PIGD (n=55)	Non-PIGD (n=91)
Age, years	65.2 (9.9)	66.7 (9.8)	64.3 (9.9)
Male sex, n(%)	100 (68.5)	35 (63.6)	65 (71.4)
Body mass index (kg/m^2)	27.8 (4.7)	28.3 (4.9)	27.5 (4.6)
Currently smoking, n(%)	10 (6.8)	3 (5.5)	7 (7.7)
Alcohol consumption, drinks per week	3.6 (5.5)	3 (4.1)	3.9 (6.1)
Medication			
Levodopa equivalent dose, mg/day	648.2 (368.7)	636.7 (389)	655.2 (357.9)
Nighttime levodopa/DA, n(%)	45 (30.8)	15 (27.3)	30 (32.9)
Psychoactive medication, n(%)	73 (50)	27 (49.1)	46 (50.5)
MoCA	24.3 (3.6)	24.1 (3.6)	24.4 (3.6)
ESS	9.3 (4.5)	9.6 (4.7)	9.1 (4.4)
PDSS (n=101)	57.3 (15.2)	55.8 (13.6)	58.2 (16.1)
PDSS-Revised (n=45)	72.5 (13.2)	70 (14.4)	74.5 (12.1)
Disease duration from diagnosis, years	5.8 (4.9)	6.4 (6.2)	5.5 (4.1)
Total MDS-UPDRS score	55.7 (21.7)	59.2 (25.9)	53.6 (18.5)
Motor MDS-UPDRS score	28.1 (12.5)	29 (14.6)	27.5 (11)
MDS-UPDRS part IV score	4.1 (3.6)	3.5 (3.7)	4.5 (3.4)
RBD, n(%)			
Definite RBD (n=136)	25 (18.4)	11 (22.4)	14 (16.1)
Probable RBD	58 (39.7)	26 (17.8)	36 (24.7)
Hypertension, n(%)	25 (17.1)	8 (14.5)	17 (18.7)
Heart disease, n(%)	14 (9.6)	6 (10.9)	8 (8.8)
Diabetes, n(%)	13 (9.2)	7 (13.2)	6 (6.7)
Asthma, n(%)	3 (2.1)	2 (3.6)	1 (1.1)
Total sleep time (minutes)	305.5 (69.2)	297.7 (70.2)	310.2 (68.5)
Sleep efficiency (%)	69.8 (15.1)	70.4 (15.9)	69.4 (14.7)
Wake-time after sleep onset (minutes)	111.3 (65.6)	109.8 (72.9)	112.2 (61.3)
Stage N1 (%TST)	26.5 (13.6)	25.3 (15.3)	27.3 (12.4)
Stage N2 (%TST)	49.9 (13.9)	48.9 (13.3)	50.5 (14.3)
Stage N3 (%TST)	14.1 (14.2)	16.9 (14.7)	12.4 (13.7)
Stage REM (%TST)	10 (7.6)	8.9 (7.2)	10.7 (7.7)
%TST in supine	60.8 (34.7)	65.9 (34.5)	57.7 (34.7)
Total arousals index (events/hours)	53.8 (22.4)	52.2 (27.5)	54.7 (18.9)
Respiratory arousals index (events/hour)	43.3 (22.2)	40.8 (26.1)	44.8 (19.4)
PLM index (events/hour)	12.3 (22.9)	15.4 (27.3)	10.4 (19.7)
PLM arousals index (events/hour)	1.9 (4.8)	2.1 (4.1)	1.9 (5.2)
OSA (AHI $\geq$ 15 events/hr) n(%)	116 (79.5)	40 (72.7)	76 (83.5)

AHI (events/hour)	31.2 (20.9)	27.9 (22.5)	33.2 (19.9)
ODI (events/hour)	9.7 (11.4)	8.2 (11.2)	10.6 (11.5)
%TST under 90% SpO_2	0.9 (2.5)	0.7 (2.3)	0.9 (2.7)
RDI (events/hour)	43.4 (20.3)	40.4 (22.2)	45.2 (18.8)
RDI REM index (events/hour) (n=133)[a]	57.6 (62.1)	50.5 (24.8)	61.9 (75.7)
RDI NREM index (events/hour)	43.4 (28.5)	38.6 (23.3)	46.4 (31)
RDI supine index (events/hour) (n=137)[b]	55.3 (51)	46.1 (22.8)	60.4 (60.9)
RDI non-supine index (events/hour) (n=116)[c]	42.3 (34.2)	35.6 (25.1)	46.1 (38.1)

Values are means (SD) unless stated otherwise. Bold values are statistically significant.
PDSS: PIGD n=35, Non-PIGD n=66
PDSS-Revised : PIGD n=20, Non-PIGD n=35
RBD: PIGD n=47, Non-PIGD n=84
[a]PIGD : n=49, Non-PIGD: n=84
[b]PIGD n=49, Non-PIGD: n=88
[c]PIGD : n=42, Non-PIGD: n=74
Abbreviations: PIGD postural instability and gait difficulty, MoCA Montreal Cognitive Assessment, ESS Epworth Sleepiness Scale, PDSS Parkinson's Disease Sleep Scale, MDS-UPDRS Movement Disorders Society-Unified Parkinson's Disease Rating Scale, RBD REM sleep behaviour disorder, AHI apnea-hypopnea index, TST total sleep time, PLM periodic limb movement, ODI oxygen desaturation index, RDI respiratory disturbance index, REM rapid-eye movement, NREM non-rapid eye movement, SpO_2 blood oxygen saturation

Table 2. Odds ratios for the association between Parkinson subtype and OSA in the full sample and in various subsets[a]

	Model of adjustment	**PIGD vs. Non-PIGD**							
		Full sample (n=146)		**Subset 1* (n=73)**		**Subset 2* (n=101)**		**Subset 3* (n=60)**	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
OSA	Model 1	0.5	0.2; 1.2	0.3	0.09; 0.8	0.4	0.2; 1	0.3	0.08; 0.8
	Model 2	0.5	0.2; 1.2	0.2	0.07; 0.8	0.4	0.2; 1.1	0.2	0.06; 0.9
	Model 3	0.5	0.2; 1.1	0.2	0.08; 1.2	0.4	0.1; 1.1	0.3	0.07; 1.3

[a]estimated via logistic regression
Subset 1: Excluding patients on psychoactive medication (n=73), Subset 2: Excluding patients on levodopa medication at nighttime (n=101), Subset 3: Excluding patients on psychoactive medication and patients on levodopa and dopaminergic agonists at nighttime (n=60).
All patients: Model 1: Unadjusted; Model 2: Adjusted for age, sex, and body mass index; Model 3: Adjusted for age, sex, body mass index, total sleep time in stage N3, total sleep time in stage REM, total sleep time in the supine position.
*All subsets: Model 1: Unadjusted; Model 2: Adjusted for age, sex, and body mass index; Model 3: Adjusted for percent sleep time in stage N3, percent sleep time in stage REM and percent sleep time in the supine position.
Bold values are statistically significant.
Abbreviations: PIGD postural instability and gait difficulty, OSA obstructive sleep apnea

Chapter 3. Effect of Long-Acting Levodopa on Obstructive Sleep Apnea in Parkinson's Disease (ELO-PD trial)

3.1. Objectives and hypotheses

Given the findings of this group's previous observational study[1], we hypothesized that, in patients with PD and OSA, LALD taken at bedtime may reduce the severity of OSA. The ELO-PD trial is a prospective, randomized, placebo-controlled, two-period, crossover pilot trial that assessed the effect of LALD at bedtime on the AHI in patients with PD and OSA.

The principal objectives were:

1. to obtain an estimate of the magnitude of the effect of LALD on AHI in PD
2. to obtain feasibility and tolerability data, and obtain preliminary data on which subgroups of PD patients are more prone to adverse effects, if any
3. to obtain preliminary data on which subgroups of PD patients are more likely to respond with respect to AHI.

Secondary objectives were:

4. to obtain preliminary data regarding effect of LALD on measures of oxygenation and objective sleep quality from PSG studies
5. to obtain preliminary estimates of effects on subjective sleep quality, daytime sleepiness, cognitive function, and non-motor symptoms.

3.2. Methodology

3.2.1 Study subjects

The following are the inclusion and exclusion criteria for patients enrolled in this study:

Inclusion criteria:

- Diagnosis of clinical PD consistent with the Movement Disorder Society criteria[5];

- Presence of OSA on screening PSG, as defined by an AHI ≥ 15/h (moderate to severe OSA);
- Stable regimen of anti-PD medication for 4 weeks prior to entry into the study, and no planned change during the study

Exclusion criteria:

- Other major neurological disorder;
- Already taking LALD (at any time of day);
- Taking short-acting levodopa at bedtime or during the night;
- Any contraindication to LALD;
- Severe levodopa-induced dyskinesias;
- Already on or requiring treatment for restless legs syndrome;
- Body mass index >35 kg/m^2;
- Intercurrent upper respiratory tract infection;
- Other known cause of OSA (such as craniofacial malformation);
- Active treatment of OSA (CPAP, dental appliance or other), unless treatment ceased two weeks prior to the start and throughout the duration of the study.

3.2.2. Procedures

Recruitment for the ELO-PD trial occurred from April 2017 to November 2022. Patients with PD were recruited in Montreal, Quebec, from the Movement Disorders Clinic of the McGill University Health Centre, other affiliated neurological centres, and through the Quebec Parkinson Network. Patients were pre-screened by phone call to assess preliminary eligibility. If the patient was interested, an overnight PSG appointment was booked. Patients who were found to have OSA

(AHI ≥ 15/h) and who met the eligibility criteria were randomized via a computer-generated randomization code using the online database system Dacima Software Inc.

Participants were randomized to one of two treatment sequences: group A – LALD followed by placebo; group B – placebo followed by LALD. Treatment was administered daily at bedtime for two weeks followed by a two-week washout period. The dosage of LALD was 200mg/50mg (200 mg levodopa and 50 mg carbidopa). On the last day of each two-week treatment period, and of the two-week washout period, participants underwent PSG. On the evening of each PSG, including after the washout period, participants also answered questionnaires regarding blinding and OSA-related outcomes such as sleep quality using the PDSS – Revised (PDSS-R)[136], daytime sleepiness using the ESS[87], and cognition using the MoCA[135]. We used different available versions of the MoCA at each visit to avoid a learning effect. PD motor and nonmotor symptoms, as well as side effects of treatment including motor complications, were assessed using the MDS-UPDRS[137]. RBD was also diagnosed by PSG scoring according to a procedure established by Frauscher and colleagues[139]. Patients were considered as having probable RBD (pRBD) if they did not meet the criteria for RBD on PSG but were symptomatic for RBD according to an RBD screening questionnaire[138,148]. Patients remained on their usual PD treatment regimen throughout the study, however, they were asked not to take any levodopa at least four hours prior to any PSG to minimize any potential residual effects.

3.2.3. Polysomnography

Standard full overnight PSG was performed at the sleep laboratory of the Centre for Innovative Medicine of the Research Institute of the McGill University Health Centre (Polysmith, Nihon Kohden, Irvine, CA). Subjects were instructed to take their study treatment – either LALD or placebo – 15 minutes before 'lights out', mimicking a typical bedtime dosing. The signals recorded include 6 EEG channels (C3, C4, F3, F4, O1, O2), submental EMG, EOG, bilateral tibialis anterior

EMG and digital video. Respiratory inductance plethysomography was used for thoracoabdominal motion, and nasal pressure and oronasal thermistor for airflow. Data was scored manually using standard AASM[149] criteria by a certified PSG technologist. Subjects with a total sleep time of less than 2 hours[150] on their baseline PSG were asked to undergo a second study to improve diagnostic accuracy of OSA.

3.2.4. Statistical analyses

Standard summary statistics were calculated for demographic variables, the AHI and other PSG sleep variables, recruitment, dropout rates and questionnaire results. Missing data for the ESS or MoCA was replaced using values from the next study timepoint (last observation carried backward)[142]. Missing PDSS-R data was replaced using the value at the closest study timepoint with available data, and if that was not possible, we used the average of the other individual values for the questionnaire on that date (person-mean imputation)[143]. When possible, missing MDS-UPDRS scores were calculated according to a validated technique by Goetz et al.[144], otherwise, values from the next study timepoint were used (last observation carried forward)[142].

Objective 1: The primary outcome for this pilot trial was the change in AHI from baseline to treatment. The screening PSG and the PSG after the washout period were considered baseline sleep studies. Patients were on LALD at PSG two or four only, depending on the study sequence they were assigned at randomization. The primary analysis was done via a mixed model with AHI as the dependent variable. A term for time and an interaction term for treatment and time were included in the model to assess the difference in the change in AHI from baseline to LALD versus from baseline to placebo. A random effect for subject was included in the model. The primary analysis was intention-to-treat; thus, all randomized patients were included in the model regardless of whether they completed the study protocol. A sensitivity analysis was performed including terms for period and carryover effects of active treatment on subsequent study procedures. Other

sensitivity analyses included a paired t-test to assess the change in AHI from baseline to treatment in each period (on LALD or on placebo). Per-protocol analyses where done for patients who changed PD medication throughout the study and those who had missing AHI data points were excluded.

Objective 2: Acceptable feasibility was defined as more than 80% compliance to the protocol treatment regimen. Descriptive statistics are provided for feasibility of this treatment and for all reported adverse events.

Objective 3: The characteristics of patients who responded to the treatment and those who did not were compared to assess whether certain characteristics are inherent to patients who are more likely to benefit from LALD. Two definitions of responders were used: first, responders were considered as patients in which the AHI on LALD was reduced by any amount, and second, as patients whose AHI on LALD was reduced by at least 10 events/hr or was reduced by at least 50% of the baseline AHI. One patient was excluded from these analyses (n=35) due to missing AHI data points.

Objective 4: We used the mixed model described above to observe secondary outcomes including sleep variables, oxygenation, and other respiratory indices.

Objective 5: The same mixed models as above were also used to assess any potential changes in subjective sleepiness, daytime sleepiness, cognition, and PD motor and non-motor symptoms.

The data were analyzed using R statistical computing software version 2023.03.0+386[147]. Statistical significance was set at $p<0.05$ and 95% confidence intervals (95% CI) were calculated for all statistical models.

3.2.5 Sample size

According to our calculations using the formula suggested by Jones and Kenward[151], we determined that 42 subjects were required to detect a difference in AHI of 10 with power 80%, considering a potential 15% drop-out rate.

3.3. Results

3.3.1. Patient characteristics

242 patients were contacted to assess preliminary eligibility. Of those patients, 55 were eligible and interested in taking part in the study and were thus screened for OSA. 16 patients did not meet the criteria for a diagnosis of OSA and 3 patients were screen failures for other reasons, leaving a total of 36 patients randomized to the study (Figure 3). The median period for study completion was 96 days; the minimum was 50 days, and the maximum was 195 days. Baseline demographic characteristics are outlined in Table 3. Baseline sleep parameters are outlined in Table 4. The average AHI was 30.7±13.9 events/hr and the average respiratory disturbance index (RDI) was 40.9±15.1 events/hr.

3.3.2. The magnitude of the effect of LALD on OSA in PD

The mean change in AHI from baseline to on LALD was 0.9 events/hr. The mean change in AHI from baseline to on placebo was -4.7 events/hr. Using a mixed model, the AHI increased by 3.2 events/hr (95% CI: -2.5; 8.9, p=0.28, unadjusted) during the LALD treatment compared to placebo (Figure 4). The inclusion of period and carryover effects in the model did not lead to any substantial changes in the estimate. Moreover, adjusting for different demographic variables such as age, sex, BMI, and UPDRS part III (motor) score did not lead to any notable changes in the estimate (Table 5). Adjusting for different sleep parameters including total sleep time in the supine position, proportion of sleep time in stage N3, and proportion of sleep time in stage REM led to a reduction in the estimate of the change in AHI (1.2 events/hr, 95%CI: -4.3; 6.8, p=0.66). However,

the results remain statistically insignificant. By t-test, the mean difference in the change in AHI from baseline to treatment between periods was 2.1 events/hr (p=0.65).

Per-protocol analyses included all patients who adhered to the study protocol (n=34). In the unadjusted model, the change in AHI was 2.8 events/hr (95%CI = -2.9; 8.5, p-value=0.34) when comparing the difference from baseline to on treatment versus baseline to on placebo. The results remained almost identical when adjusting for confounder such as age, sex, BMI, UPDRS motor score, and LED. The model adjusted for total sleep time in the supine position, total sleep time in stage N3, and total sleep time in stage REM resulted in a change in AHI of 0.6 events/hr (p=0.83) for LALD vs. placebo. These results are detailed in Table 6.

3.3.3. Feasibility and tolerability

Feasibility of this pharmacologic treatment approach was assessed by determining how compliant patients were to the treatment regimen (% out of 14 nights where subjects took the study drug). The data was available for 35 patients due to missing data from one patient who discontinued the study early. In the treatment period with LALD, 28 patients (80%) were compliant for the entirety of the treatment period (100%) and 7 were (20%) compliant more than 90% to <100% of the time. In the placebo period, 32 patients (91%) were 100% compliant, 2 patients were 90% to <100% compliant, and only 1 patient had <80% compliance to the treatment regimen.

3 adverse events were reported. 1 patient experienced an adverse event while on LALD (ear infection). 2 patients reported adverse events during the placebo period: one reported dyskinesia, dyspnea, and dizziness, and the other experienced a nosebleed.

3.3.4. Responders and non-responders

Table 7 outlines the demographic characteristics at baseline of patients whose AHI on LALD was reduced by any number of events (responders, first definition) versus patients whose AHI did

not change on LALD or increased (non-responders). 62.9% of patients were responders (Figure 5) Demographically, responders and non-responders were not significantly different, including in their disease duration (5.2±5.6 years versus 4±4.7 years, respectively). There were significantly more patients with hypertension among non-responders – 46.2%, than among responders – 13.6% (p=0.043). Sleep parameters were similar between responders and non-responders, except for sleep efficiency which was better among non-responders (77.8±1.8% versus 70.5±10.5%, p=0.018), and wake-time after sleep onset which was shorter among non-responders (versus 84.1±50.6 minutes 121±52.1 minutes, p=0.049) (Table 8).

Table 9 outlines the baseline characteristics of patients whose AHI was reduced by at least 10 events/hr or was reduced by 50% of the baseline AHI on LALD (responders, second definition) versus patients whose AHI did not change or increased on LALD (non-responders). Here, 25.7% of patients were responders (Figure 5). On average, responders were younger by approximately 7 years (p=0.045), the percentage of male patients was lower (p=0.046), and the average BMI was lower (25.5±4.7 kg/m^2 versus 28.9±3.7 kg/m^2, p=0.034). Responders also had a significantly lower UPDRS motor score (less disability) compared to non-responders (18.4±7.7 and 30.3±12.6, respectively, p=0.012). There were no patients that responded to the treatment that had hypertension (0% versus 34.6% in the group of non-responders, p=0.04). Sleep parameters were similar between the groups, except for the oxygen desaturation index, which was lower among responders – 4.3 events/hr versus 12.8 events/hr for non-responders, p=0.0092 (Table 10). The change in AHI on placebo from baseline and on LALD from baseline for both groups of responders and non-responders is shown in Figure 6.

3.3.5. LALD, sleep and non-motor symptoms

Table 11 outlines changes in PSG sleep parameters. None of the sleep parameters were significantly altered by treatment with LALD in these unadjusted models. Secondary outcomes

including the total ESS score (daytime sleepiness), the MoCA score (cognition), the PDSS-R score (subjective sleep quality), and PD motor and non-motor symptoms (MDS-UPDRS scores) showed no significant changes after treatment with LALD versus treatment with placebo (Table 12) when assessed using the same abovementioned mixed model (unadjusted).

3.4. Figures and tables

Figure 3. CONSORT diagram

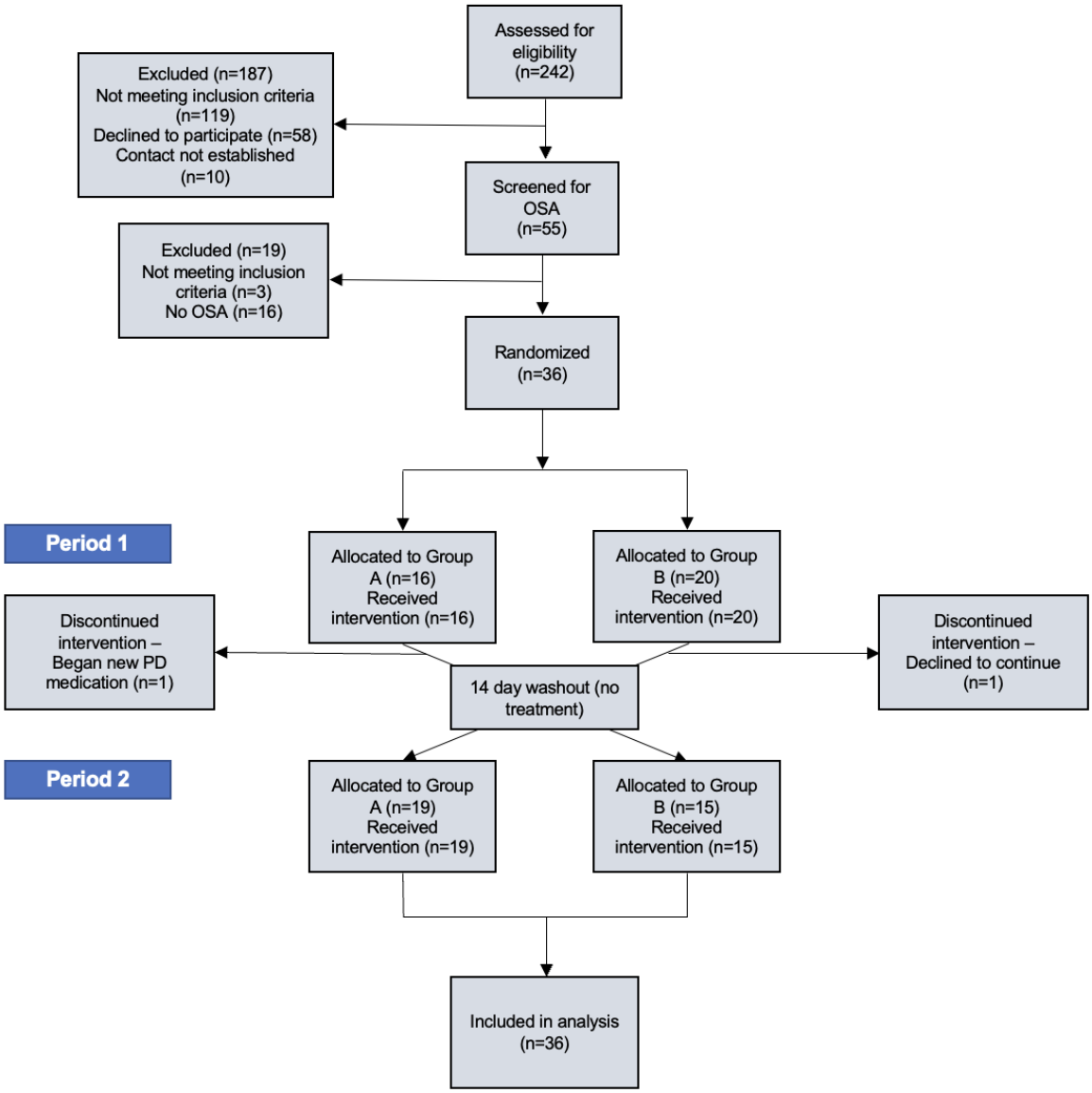


Figure 4. The difference in the change in the apnea-hypopnea index (AHI) from baseline to each intervention (n=36).

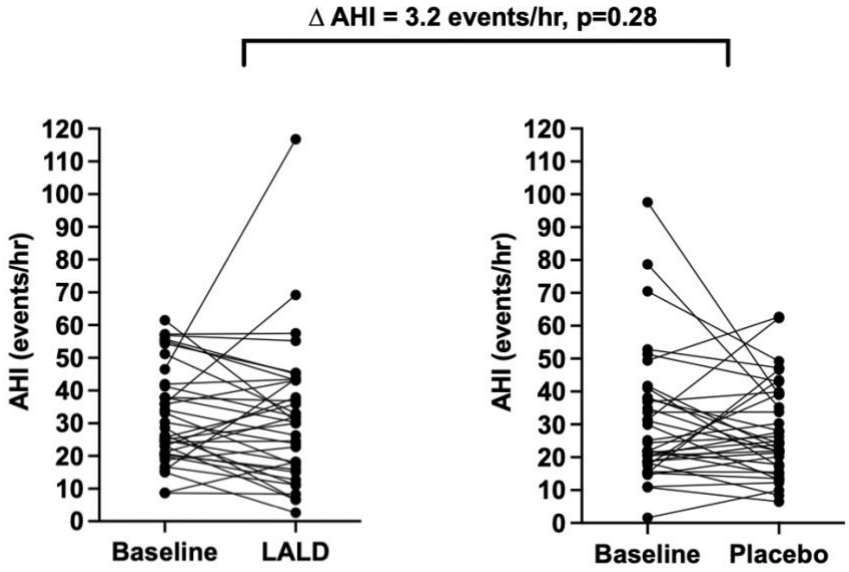
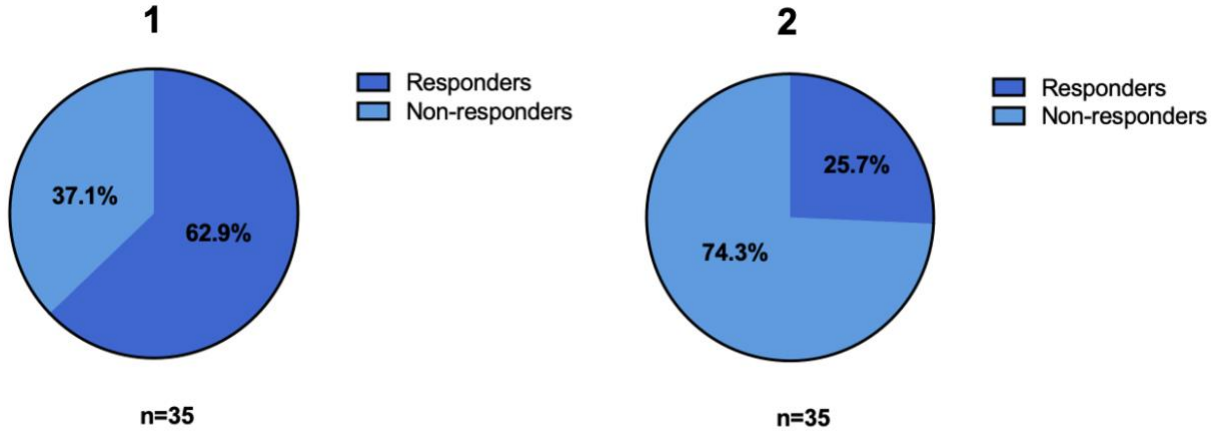
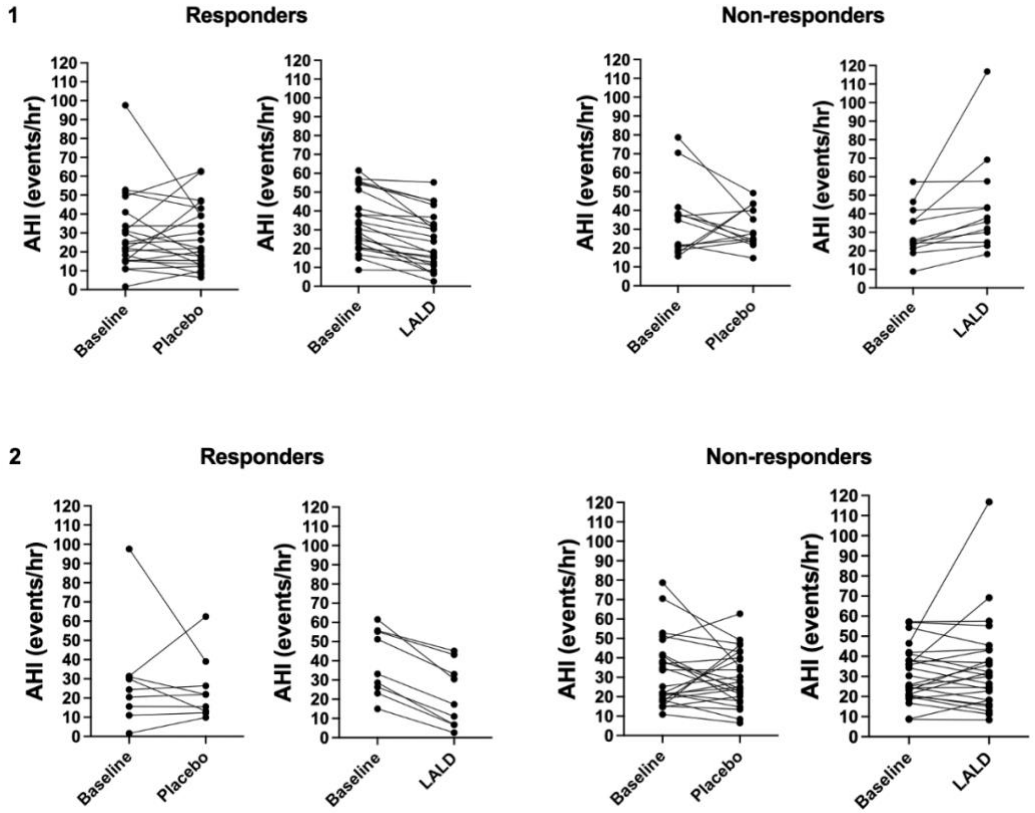


Figure 5. The proportion of patients who responded to treatment with long-acting levodopa and those who did not.



1: responders defined as patients who had a reduction in AHI of any amount.
2: responders defined as patients who had a reduction in AHI of at least 10 events/hour or at least 50% of baseline.

Figure 6. The difference in the change in the apnea-hypopnea index (AHI) from baseline to each intervention stratified by responders and non-responders (n=35).



1: responders defined as patients who had a reduction in AHI of any amount.
2: responders defined as patients who had a reduction in AHI of at least 10 events/hour or at least 50% of baseline.

Table 3. Baseline clinical data.

Clinical Data	All patients (n=36)	Group A (n=16)	Group B (n=20)	p-value
Age, years	65.6 (9.5)	66.3 (9.9)	64.9 (9.3)	0.68
Male sex, n(%)	29 (80.5)	13 (81.3)	16 (80)	0.93
Body mass index (kg/m^2)	27.9 (4.2)	28.1 (4.5)	27.9 (4)	0.89
Currently smoking, n(%)	1 (2.8)	1 (6.3)	0 (0)	0.99
Alcohol consumption, drinks per week	4.5 (4.7)	4.4 (5)	4.6 (4.6)	0.91
Disease duration, years	4.7 (5.2)	4.6 (6.1)	4.8 (4.5)	0.92
Levodopa equivalent dose, mg/day	523.7 (243.5)	481.2 (161.5)	557.7 (293.1)	0.36
Medication				
On levodopa alone, n(%)	17 (47.2)	7 (43.8)	10 (50)	0.71
On dopaminergic agonists, n(%)	8 (22.2)	2 (12.5)	6 (30)	0.22
On Stalevo, n(%)	4 (11.1)	2 (12.5)	2 (10)	0.81
On Comtan, n(%)	3 (8.3)	1 (6.3)	2 (10)	0.69
On levodopa and dopaminergic agonists, Stalevo or Comtan, n(%)	2 (5.6)	1 (6.3)	1 (5)	0.87
On dopaminergic agonists, Stalevo or Comtan, n(%)	13 (36.1)	4 (25)	6 (30)	0.22
Motor subtypes				1
PIGD, n(%)	12 (33.3)	5 (31.3)	7 (35)	
Non-PIGD, n(%)	24 (66.7)	11 (68.8)	13 (65)	
Tremor dominant, n(%)	17 (47.2)	8 (50)	9 (45)	
Indeterminate, n(%)	7 (19.4)	3 (18.8)	4 (20)	
Montreal Cognitive Assessment	25.7 (2.7)	25.5 (2.9)	25.9 (2.5)	0.7
Epworth Sleepiness Scale	8.5 (4.5)	7.7 (3.6)	9.1 (4.9)	0.35
PDSS-Revised	68.7 (12.7)	70 (13)	68 (13)	0.59
Motor MDS-UPDRS	27.3 (12.4)	27.3 (10.1)	27.3 (14.2)	1
MDS-UPDRS part IV	3.4 (2.8)	2.9 (2.5)	3.7 (3.1)	0.43
Total MDS-UPDRS score	51 (19.6)	49.8 (18.5)	52 (20.9)	0.75
REM sleep behaviour disorder (RBD)				0.39
Definite RBD, n(%)	9 (25)	4 (25)	5 (25)	
Probable RBD, n(%)	6 (16.7)	1 (6.3)	5 (25)	
No RBD, n(%)	21 (58.3)	11 (68.8)	10 (50)	
Comorbidities				
Hypertension, n(%)	10 (27.8)	4 (25)	6 (30)	0.74
Heart disease, n(%)	5 (13.9)	3 (18.8)	2 (10)	0.46
Diabetes, n(%)	3 (8.3)	2 (12.5)	1 (5)	0.43
Prostate issues*, n(%)	8 (22.2)	3 (18.8)	5 (25)	0.65
Depression, n(%)	4 (11.1)	0 (0)	4 (20)	0.99
Anxiety, n(%)	4 (11.1)	0 (0)	4 (20)	0.99

Abbreviations: PIGD Postural instability/gait difficulty PDSS-Revised Parkinson's Disease Sleep Scale – Revised, MDS-UPDRS Movement Disorder Society-Unified Parkinson's Disease Rating Scale. *Prostate issues include benign prostatic hyperplasia and prostate cancer

Table 4. Baseline polysomnographic data.

Polysomnographic da	All patients (n=36)	Group A (n=16)	Group B (n=20)	p-value
AHI, events/hour	30.7 (13.9)	30.6 (13.5)	30.9 (14.6)	0.95
ODI, events/hour	10.4 (8.6)	8.8 (6.4)	11.8 (10)	0.3
RDI, events/hour	40.9 (15.1)	41.2 (16.1)	40.8 (14.6)	0.94
RDI REM index, events/hour (n=35)	49.9 (19.4)	54 (19.1)	46.5 (19.6)	0.26
RDI NREM index, events/hour	39.6 (16.4)	39.6 (17.9)	39.5 (15.5)	0.99
RDI supine, events/hour (n=35)	52.6 (22.6)	53.9 (28)	51.5 (17.6)	0.76
RDI non-supine, events/hour (n=29)	38.8 (19.8)	42.7 (22.9)	35.2 (16.3)	0.32
%TST under 90% SpO_2	0.6 (1.5)	0.2 (0.4)	0.9 (1.9)	0.13
Total sleep time, minutes	297.9 (77.2)	296.1 (85.6)	299.5 (71.9)	0.89
Sleep efficiency, %	73.6 (9.3)	73.9 (9.3)	73.5 (9.6)	0.89
Wake-time after sleep onset, minutes	105.5 (54.3)	104.9 (61.5)	105.9 (49.4)	0.96
Stage N1, %TST	25.8 (12.7)	23 (10.3)	27.9 (14.2)	0.25
Stage N2, %TST	44.1 (12.6)	46.7 (11.3)	41.9 (13.5)	0.26
Stage N3, %TST	20.2 (14.4)	20.3 (14.5)	20.1 (14.7)	0.96
Stage REM, %TST	10.3 (7.9)	9.9 (6.7)	10.6 (8.9)	0.81
%TST in supine	55 (34.4)	58.1 (35.2)	52.5 (34.4)	0.63
Total arousals index, events/hours	51.6 (18.2)	49.9 (17.8)	52.9 (18.8)	0.62
Respiratory arousals index, events/hour	37.8 (16.8)	39.4 (17.4)	36.4 (16.7)	0.61
PLM arousals index, events/hour	5 (9.1)	2.9 (3.6)	6.7 (11.7)	0.22

Abbreviations: AHI apnea-hypopnea index, ODI oxygen desaturation index, RDI respiratory disturbance index, REM rapid-eye movement, NREM non-rapid eye movement, TST total sleep time, SpO_2 blood oxygen saturation, PLM periodic limb movement

Table 5. Primary mixed model assessing the change in the apnea-hypopnea index at baseline to after treatment with long-acting levodopa versus at baseline to after placebo (intention-to-treat) (n=36).

	ΔApnea-hypopnea index	95% CI	p-value
Unadjusted	3.2	-2.5; 8.9	0.28
Model 1	2.4	-5; 9.8	0.53
Model 2	3.2	-2.5; 8.8	0.28
Model 3	1.2	-4.3; 6.8	0.66
Model 4	2.9	-2.7; 8.6	0.31

Model 1: Adjusted for period and carryover effects
Model 2: Adjusted for age, sex, and body mass index
Model 3: Adjusted for total sleep time in the supine position, sleep time in stage N3 and sleep time in stage REM
Model 4: Adjusted for sex, body mass index, and Movement Disorders Society – Unified Parkinson's Disease Rating Scale part 3 (motor) score

Table 6. Mixed models assessing the change in the apnea-hypopnea index at baseline to after treatment with long-acting levodopa versus at baseline to after placebo in patients who completed the study protocol as intended (per-protocol) (n=34).

	ΔApnea-hypopnea index	95% CI	p-value
Unadjusted	2.8	-2.9; 8.5	0.34
Model 1	2.8	-2.9; 8.5	0.34
Model 2	2.8	-2.9; 8.5	0.34
Model 3	0.6	-4.9; 6.2	0.83
Model 4	2.5	-3.1; 8.2	0.38

Model 1: Adjusted for age, sex and body mass index
Model 2: Adjusted for levodopa equivalent dose
Model 3: Adjusted for total sleep time in the supine position, total sleep time in stage N3 and total sleep time in stage REM
Model 4: Adjusted for sex, body mass index, and Movement Disorders Society – Unified Parkinson's Disease Rating Scale part 3 (motor) score

Table 7. Comparison of baseline demographic data of responders (defined as patients who had a reduction in AHI of any amount) and non-responders.

Clinical Data	Responder (n=22)	Non-responder (n=13)	p-value
Age, years	66.7 (9.5)	64.2 (9.8)	0.45
Male sex n(%)	17 (77.3)	11 (84.6)	0.6
Body mass index (kg/m^2)	27.3 (4.3)	29.4 (3.8)	0.16
Currently smoking n(%)	0 (0)	1 (7.7)	0.99
Alcohol consumption, drinks per week	5.2 (4.9)	3.5 (4.4)	0.29
Disease duration, years	5.2 (5.6)	4 (4.7)	0.51
Motor subtypes			0.74
PIGD, n(%)	8 (36.4)	4 (30.8)	
Non-PIGD, n(%)	14 (63.6)	9 (69.2)	
Tremor dominant, n(%)	9 (40.9)	7 (53.8)	
Indeterminate, n(%)	5 (22.7)	2 (15.4)	
Levodopa equivalent dose, mg/day	549.4 (253.8)	520.5 (190.2)	0.72
Medication			
On levodopa alone n(%)	10 (45.5)	7 (53.8)	0.63
On dopaminergic agonists n(%)	4 (18.2)	4 (30.8)	0.39
On Stalevo n(%)	1 (4.5)	3 (23.1)	0.13
On Comtan n(%)	3 (13.6)	0 (0)	0.99
On levodopa and dopaminergic agonists, Stalevo or Comtan, n(%)	1 (4.5)	1 (7.7)	0.7
On dopaminergic agonists, Stalevo or Comtan n(%)	8 (36.4)	5 (38.5)	0.9
Montreal Cognitive Assessment	26.2 (2.3)	24.7 (3.1)	0.12
Epworth Sleepiness Scale	7.8 (3.9)	9.5 (5.4)	0.28
PDSS-Revised	69.8 (13.7)	67.1 (11.7)	0.56
Motor MDS-UPDRS	27.9 (12.4)	26.2 (13.2)	0.69
MDS-UPDRS part IV	3.2 (2.4)	3.3 (3.3)	0.89
Total MDS-UPDRS score	51.8 (18.2)	48.8 (22.9)	0.67
REM sleep behaviour disorder (RBD)			0.91
Definite RBD, n(%)*	7 (33.3)	5 (38.5)	
Probable RBD, n(%)	5 (22.7)	3 (23.1)	
No RBD, n(%)	12 (54.5)	5 (38.5)	
Comorbidities			
Hypertension n(%)	3 (13.6)	6 (46.2)	**0.043**
Heart disease n(%)	5 (22.7)	0 (0)	0.99
Diabetes n(%)	1 (4.5)	2 (15.4)	0.29
Prostate issues* n(%)	5 (22.7)	3 (23.1)	0.98
Depression n(%)	3 (13.6)	1 (7.7)	0.59
Anxiety n(%)	3 (13.6)	0 (0)	0.99

*Prostate issues include benign prostatic hyperplasia and prostate cancer
Abbreviations: PIGD Postural instability/gait difficulty PDSS-Revised Parkinson's Disease Sleep Scale – Revised, MDS-UPDRS Movement Disorder Society-Unified Parkinson's Disease Rating Scale. P values by t-test or chi squared as appropriate

Table 8. Comparison of baseline polysomnographic data of responders (defined as patients who had a reduction in AHI of any amount) and non-responders (n=35).

Polysomnographic data	Responder (n=22)	Non-responder (n=13)	p-value
AHI (events/hour)	30.7 (13.7)	31.7 (14.9)	0.85
ODI (events/hour)	8.5 (7.9)	14.2 (8.9)	0.06
RDI (events/hour)	42.5 (16.5)	39.9 (12.4)	0.63
RDI REM index (events/hour) (n=35)	47.5 (19.2)	55.6 (19.3)	0.24
RDI NREM index (events/hour)	41.1 (18)	38.3 (13.4)	0.63
RDI supine (events/hour) (n=35)	46.9 (16.9)	60.2 (27.9)	0.091
RDI non-supine (events/hour) (n=29)	39.7 (19.3)	39.2 (21.3)	0.96
%TST under 90% SaO_2	0.6 (1.5)	0.8 (1.6)	0.73
Total sleep time (minutes)	284.1 (68.5)	312.2 (85.9)	0.29
Sleep efficiency (%)	70.5 (10.5)	77.8 (1.8)	**0.018**
Wake-time after sleep onset (minutes)	121 (52.1)	84.1 (50.6)	**0.049**
Stage N1 (%TST)	27.4 (13.6)	24.2 (11)	0.47
Stage N2 (%TST)	43.1 (11.4)	43.6 (13.1)	0.91
Stage N3 (%TST)	19.2 (14.5)	22.2 (15)	0.56
Stage REM (%TST)	10.8 (8.3)	10 (7.6)	0.78
%TST in supine	62.1 (29.2)	47.1 (39.7)	0.21
Total arousals index (events/hours)	56.2 (19.7)	44.9 (13.6)	0.079
Respiratory arousals index (events/hour)	40.1 (17.9)	35.1 (14.7)	0.4
PLM arousals index (events/hour)	6.9 (11.2)	1.9 (2.9)	0.13

Abbreviations: AHI apnea-hypopnea index, ODI oxygen desaturation index, RDI respiratory disturbance index, REM rapid-eye movement, NREM non-rapid eye movement, TST total sleep time, SpO2 blood oxygen saturation, PLM periodic limb movement

Table 9. Comparison of baseline demographic data of responders (defined as patients who had a reduction in AHI of at least 10 events/hour or at least 50% of baseline) and non-responders (n=35).

Clinical Data	Responders (n=9)	Non-responders (n=26)	p-value
Age, years	60.3 (5.9)	67.7 (9.9)	**0.045**
Male sex n(%)	5 (55.6)	23 (88.4)	**0.046**
Body mass index (kg/m^2)	25.5 (4.7)	28.9 (3.7)	**0.034**
Currently smoking, n(%)	0 (0)	1 (3.8)	
Alcohol consumption, singles/week	5.1 (5.3)	4.4 (4.7)	0.69
Disease duration, years	5.2 (7.9)	4.6 (4.1)	0.77
Motor subtype			0.36
PIGD, n(%)	5 (55.6)	7 (26.9)	
Non-PIGD, n(%)	4 (44.4)	19 (73.1)	
Tremor dominant, n(%)	3 (33.3)	13 (50)	
Indeterminate, n(%)	1 (11.1)	6 (23.1)	
Levodopa equivalent dose, mg/day	534.6 (210.2)	540.1 (239.9)	
Medication			
On levodopa alone, n(%)	4 (44.4)	13 (50)	0.77
On dopaminergic agonists, n(%)	2 (22.2)	6 (23.1)	0.95
On Stalevo, n(%)	0 (0)	4 (15.4)	0.35
On Comtan, n(%)	1 (11.1)	2 (7.7)	0.75
On levodopa and dopaminergic agonists, Stalevo or Comtan, n(%)	0 (0)	2 (7.7)	0.62
On dopaminergic agonists, Stalevo or Comtan, n(%)	1 (11.1)	10 (38.5)	0.78
Montreal Cognitive Assessment	3 (33.3)	25.3 (2.7)	0.24
Epworth Sleepiness Scale	8.1 (4.5)	8.6 (4.6)	0.79
PDSS-Revised	63.6 (14.4)	7.1 (1.2)	0.17
Motor MDS-UPDRS	18.4 (7.7)	30.3 (12.6)	**0.012**
MDS-UPDRS part IV	3 (2.6)	3.3 (2.9)	0.78
Total MDS-UPDRS score	42.1 (19.9)	53.7 (19.3)	0.13
REM sleep behaviour disorder (RBD)			0.65
RBD, n(%)*	3 (33.3)	6 (23.1)	
Probable RBD, n(%)	2 (22.2)	4 (15.4)	
No RBD, n(%)	4 (45.5)	16 (61.5)	
Comorbidities			
Hypertension, n(%)	0 (0)	9 (34.6)	**0.04**
Heart disease, n(%)	1 (11.1)	4 (15.4)	0.75
Diabetes, n(%)	0 (0)	3 (11.5)	0.54
Prostate issues*, n(%)	1 (11.1)	7 (26.9)	0.35
Depression, n(%)	1 (11.1)	3 (11.5)	0.97
Anxiety, n(%)	2 (22.2)	1 (3.8)	0.13

*Prostate issues include benign prostatic hyperplasia and prostate cancer.
Abbreviations: PIGD Postural instability/gait difficulty PDSS-Revised Parkinson's Disease Sleep Scale – Revised, MDS-UPDRS Movement Disorder Society-Unified Parkinson's Disease Rating Scale

Table 10. Comparison of baseline polysomnographic data of responders (defined as patients who had a reduction in AHI of at least 10 events/hour or at least 50% of baseline) and non-responders (n=35).

Polysomnographic data	Responders (n=9)	Non-responders (n=26)	p-value
AHI (events/hour)	30.4 (15.9)	31.3 (13.6)	0.87
ODI (events/hour)	4.3 (3.7)	12.8 (8.9)	**0.0092**
RDI (events/hour)	46.2 (20.2)	39.9 (12.7)	0.28
RDI REM index (events/hour) (n=35)	59.3 (12.4)	47.4 (20.6)	0.12
RDI NREM index (events/hour)	44 (22.6)	38.7 (13.8)	0.41
RDI supine (events/hour) (n=35)	49.1 (19.8)	52.5 (23.1)	0.69
RDI non-supine (events/hour) (n=29)	47 (22.1)	36.5 (18.5)	0.21
%TST under 90% SaO_2	0.02 (0.07)	0.9 (1.7)	0.16
Total sleep time (minutes)	299.9 (71.9)	292.7 (77.9)	0.81
Sleep efficiency (%)	71.6 (11.9)	73.7 (8)	0.54
Wake-time after sleep onset (minutes)	116.7 (53.7)	104.1 (54.7)	0.55
Stage N1 (%TST)	31.5 (11.4)	24.4 (12.7)	0.15
Stage N2 (%TST)	40.8 (11.6)	44.2 (12.1)	0.47
Stage N3 (%TST)	15.9 (14.6)	21.8 (14.5)	0.31
Stage REM (%TST)	11.8 (6.6)	10.1 (8.4)	0.59
%TST in supine	49 (23.2)	59.1 (36.7)	0.45
Total arousals index (events/hours)	62 (20.4)	48.5 (16.6)	0.055
Respiratory arousals index (events/hour)	46.3 (21.8)	35.5 (14.1)	0.094
PLM arousals index (events/hour)	5.2 (10.2)	5 (9.2)	0.96

Abbreviations: AHI apnea-hypopnea index, ODI oxygen desaturation index, RDI respiratory disturbance index, REM rapid-eye movement, NREM non-rapid eye movement, TST total sleep time, SpO2 blood oxygen saturation, PLM periodic limb movement

Table 11. Mixed models assessing changes in sleep variables (n=34).

	Beta value	95% Confidence Interval	p-value
ODI	-0.8	-3.4; 1.8	0.53
RDI	3.7	-2; 9.3	0.21
RDI REM	-4.9	-13.9; 4.1	0.29
RDI NREM	4.8	-1.2; 10.8	0.12
RDI supine	2.6	-8.8; 13.9	0.66
RDI non-supine	1.5	-6.7; 9.7	0.72
%TST SpO_2 below 90%	0.05	-0.4; 0.5	0.81
Total sleep time	-13.1	-43.9; 17.6	0.41
%TST in supine position	7.4	-1.3; 16.1	0.099
Sleep efficiency	0.1	-6.6; 6.9	0.97
Wake-time after sleep onset	-7.2	-33.4; 18.9	0.59
Stage N1 (%TST)	1.9	-2.9; 6.8	0.44
Stage N2 (%TST)	1.4	-2.7; 5.4	0.51
Stage N3 (%TST)	-2.8	-7.2; 1.6	0.22
Stage REM (%TST)	-0.49	-3.2; 2.3	0.73
Total arousals index	4.9	-1.8; 11.6	0.15
Respiratory arousals index	4.8	-0.9; 10.5	0.1
Periodic limb movement index	-0.8	-3.7; 2.1	0.59

Abbreviations: ODI oxygen desaturation index, RDI respiratory disturbance index, REM rapid-eye movement, NREM non-rapid eye movement, TST total sleep time, SpO_2 blood oxygen saturation

Table 12. Mixed models assessing changes in cognition, daytime sleepiness, subjective sleep and PD motor/nonmotor symptoms (n=34).

	Beta value	95% CI	p-value
ΔMoCA score	-0.01	-0.8; 0.8	0.98
ΔESS score	-0.43	-1.3; 0.4	0.32
ΔPDSS-R score	0.01	-0.3; 0.3	0.96
ΔUPDRS motor	1.3	-1.1; 3.7	0.29
ΔUPDRS part 1	0.3	-1.2; 1.8	0.7
ΔTotal UPDRS	1.9	-1.8; 5.7	0.31

Abbreviations: MoCA Montreal Cognitive Assessment, ESS Epworth Sleepiness Scale, PDSS-R Parkinson's Disease Sleep Scale – Revised, UPDRS Unified Parkinson's Disease Rating Scale

Chapter 4. Discussion

4.1. Sleep architecture, OSA, and PD motor subtypes

4.1.1. Sleep architecture and PD motor subtypes

Our results suggest that the PIGD subtype may be associated with more consolidated sleep, given the significantly greater proportion of N3 sleep in subsets 1 and 3, and the smaller proportion of N1 sleep in subset 3. After removing medication effects, differences emerged in wake-time after sleep onset and the number of total arousals as well. Objective sleep parameters have not been widely explored in motor subtypes of PD, however, studies analyzing subjective sleep quality suggest that patients with the PIGD subtype tend to have worse sleep in general. Huang et al.[71] assessed NMS in 132 patients with early PD, classifying them by TD, PIGD and indeterminate motor subtypes. Patients with the PIGD subtype were found to have more severe sleep impairment and fatigue, urinary symptoms, and worse NMS overall compared to patients with the TD subtype, according to different domains of the NMS Scale. The severity of sleep impairment was validated using the Pittsburgh Sleep Quality Index where sleep impairment remained independently and significantly more severe in PIGD patients compared to TD patients. The authors attribute this to a deficiency in norepinephrine in the central and peripheral nervous system that has been shown to account for both the PIGD phenotype and sleep impairment in PD[152]. In their 110-patient study, Herman and colleagues[67] stratified patients into PIGD and TD subtypes, and further separated them into predominantly PIGD and predominantly TD subgroups. The PIGD subgroup had a significantly higher overall score on the NMS Questionnaire compared to the TD subgroup and used more sleep medication in general. In their whole cohort, there was no difference in the Pittsburgh Sleep Quality Index among PIGD and TD patients[67].

Taken together, these studies imply that patients of the PIGD subtype tend to have more impaired sleep according to self-reporting and may be more frequently prescribed sleep

medication. However, it is difficult to compare the results of the abovementioned studies with our objective assessments. While questionnaires like the Pittsburgh Sleep Quality Index are valuable clinical tools, they do not allow for objective diagnoses and cannot confirm whether these patients experience disrupted sleep from an objective standpoint. In our study, subjective sleep quality was assessed using the PDSS and PDSS-R, where no difference was found between the PIGD and non-PIGD groups, nor in levels of sleepiness assessed using the ESS. The lack of difference may be explained by potential self-selection of more symptomatic individuals across subtypes for participation in sleep research, and high prevalence of OSA in our cohort. Indeed, in previous observational work, we have found the ESS to be associated with OSA in PD patients[129], and the PDSS to improve with OSA treatment[153]. However, sleep-related patient-reported outcomes are multifactorial in PD[4]. Moreover, sleep-wake misperception may be at play, analogous to what occurs in paradoxical insomnia[154]. Thus, one hypothesis may be that, pathophysiologically, the PIGD subtype may lead to the perception of poor sleep, but sleep architecture is not as affected. Other studies assessing sleep using PSG and comparing objective and subjective sleep parameters within the motor subtypes would be valuable to validate our exploratory findings.

RBD prevalence was also found to be higher in non-TD subtypes[155]. In a cohort of 447 patients with PD, the tremor score, and the proportion of the UPDRS score accounted for by tremor were significant factors inversely correlated with the presence of RBD[156]. RBD may lead to greater sleep-related symptoms but may not correlate with sleep architecture overall or with respiratory disturbances. There were no significant differences in RBD frequency between our study groups, but our study was not specifically designed for RBD detection. Other NMS that contribute to sleep disruption but may not necessarily correlate with sleep architecture – nocturia[157] and hallucinations[158,159] – are also more prevalent in patients with the PIGD subtype. Moreover, RLS

was also shown to be more prevalent in the PIGD subtype[157]. We did not detect significant differences in the number of periodic limb movements between subtype groups throughout the night. Nonetheless, the abovementioned NMS may explain why objective sleep may be better in PIGD subtypes.

4.1.2. Respiratory parameters, OSA, and PD motor subtypes

The severity of OSA, measured by the AHI, was significantly lower in patients with the PIGD motor subtype, primarily when medication effects were removed. The differences between groups were attenuated when adjusting for differences in sleep variables, including when the effects of medication were removed. However, several differences remained statistically significant, suggesting that these sleep variables do not explain the differences between groups. The RDI was also lower in the PIGD group, suggesting fewer respiratory-related events overall. The oxygen desaturation index and time with oxygen saturation under 90% were also less affected by medication effects because they were already generally low in this population. OSA was also less frequent in the PIGD group, which was significant across 2 subsets.

OSA is multifactorial and may be a result of motor dysfunction in PD. Indeed, the musculature of the upper airway may be affected by involuntary movements leading to abnormal "saw-tooth" flow-volume patterns on spirometry, that have also been associated with OSA in a general population[61], and an upper airway obstruction pattern. Moreover, upper airway obstruction may be a result of levodopa-induced dyskinesia in some cases[160]. In our sample, we saw more motor complications (higher UPDRS part IV score) in the non-PIGD group, although this was not statistically significant. This may have implications for our results. Patients with the TD motor subtype are more likely to develop levodopa-induced dyskinesia. Patients who are younger at the onset of PD (also associated with the TD subtype) typically respond well to levodopa and are more at risk of developing dyskinesias and motor fluctuations early on since they are on levodopa for a

longer period[64]. Dyskinetic movements can persist during the night, occurring mostly after awakenings and in lighter stages of sleep, namely stage N1[161]. Dystonia is a form of dyskinesia and is also associated with younger onset of PD[64]. In a case report, Marchese-Ragona et al. presented a patient with adductor laryngeal dystonia during sleep and OSA, whose AHI decreased from 43 to 9 events/hr 2 months after botulinum toxin injection[162]. Dystonia of the vocal cords can also occur in multiple systems atrophy, a neurodegenerative parkinsonian disease where SDB is common[163]. Another case report presented a patient with OSA and oromandibular dystonia, where OSA was found to be associated with dystonia symptom severity after several sleep studies[164]. Milder and unrecognized PD motor complications may explain increased OSA severity (more respiratory disturbances) in the non-PIGD group in our study. Future work is required, however, to assess this hypothesis in a larger sample.

The differences between PIGD and non-PIGD groups in sleep and respiratory characteristics were greater when patients on psychoactive medication or on levodopa and DAs at bedtime were excluded from the analysis. This could be due to adverse effects of medication on sleep preferentially in the PIGD group. Alternatively, individuals with less sleep and respiratory objective disturbances might be less likely to be prescribed these medications but only in the PIGD subset. The medications, that include antidepressants, benzodiazepines, and anticonvulsants, have known effects on sleep, but we do not have information regarding the reason for use of these medications in our study participants. Lastly, in non-PIGD participants, disturbances appeared consistent irrespective of medication use (Figures 1 and 2), hence it is possible that these medications have no impact on sleep disturbances in the non-PIGD subtype.

Finally, evaluating OSA endotypes in PD and associating these with motor subtypes would possibly provide a more detailed understanding of the pathophysiological mechanisms of OSA

and the neurodegeneration that occurs in PD. This information may guide individualized therapies based on mechanisms underlying OSA[124] which may allow for patients with PD, who have difficulties with CPAP treatment, to receive more suitable treatment options.

4.2. Long-acting levodopa and OSA in PD (discussion pertaining to Chapter 3)

4.2.1. The magnitude of the effect of LALD on OSA in PD

We conducted the first randomized controlled pilot trial of LALD on OSA in a cohort of PD patients. Here, we observed the difference in the change in AHI from baseline to LALD versus from baseline to placebo to be 3.2 events/hr, indicating that, overall, LALD does not lead to a reduction in AHI in this cohort. Adjusting for expected confounders, including age, sex and BMI[165,166] did not alter these results, nor did adjusting for the UPDRS motor score, which was found to be a potential predictor of AHI in another study[1]. However, adjusting for the proportion of sleep in stage N3, the proportion of sleep in stage REM and the proportion of sleep in the supine position alters the point estimate the most – to 0.6 events/hr. Despite this, the change remains insignificant and does not suggest an improvement in AHI on LALD.

Several studies have been published that assessed the effect of levodopa on pulmonary function. Earlier research has yielded conflicting results in PD – Obenour et al. reported that respiratory function did not improve with levodopa treatment[127], whereas Nakano et al. reported an improvement in respiratory function after levodopa intake compared to placebo[167]. Herer and colleagues also reported an improvement in upper airway obstruction and respiratory function in patients with PD after levodopa therapy, as evidenced by alterations in the "saw-tooth" pattern of flow-volume loops. In our study we did not have spirometry results and we do not know if participants had any degree of upper airway obstruction in wakefulness.

Previously published results of our group's observational study found the AHI to be lower by 18.8 events/hr on overnight PSG in patients with PD taking LALD at bedtime, compared to those

not taking this medication, with results accentuated in the second half of the night[1]. The hypothesis was that the effect of LALD on AHI may be more apparent in the second half of the night when residual effects of any late daytime dosing of short-acting levodopa disappear, as LALD effects last up to 4 hours[1,168]. While this was controlled for in both studies, as patients whose drug regimen included a dose of bedtime levodopa or any levodopa 4 hours before bedtime were excluded, residual effects of earlier daytime dosing were still possible. The difference between the two studies may relate to the respective patient populations. In the observational study, there was a clinical indication for LALD at bedtime, while in the randomized controlled ELO-PD trial, there was not, as patients were recruited if they were not on bedtime levodopa or DA medication. In the ELO-PD trial, PD duration was lower, indicating that patients were earlier in the disease course. However, PD motor and NMS, as evidenced by the total MDS-UPDRS and motor MDS-UPDRS scores were greater in the ELO-PD cohort, suggesting a more symptomatic population which may have implications for our results. In ELO-PD, greater motor symptoms might mean that some patients may be at a greater risk of developing motor complications due to medication effects or disease progression, which can also affect the upper airway musculature and persist during the night. The response to LALD was heterogeneous in our cohort, with some patients experiencing a reduction in AHI after treatment with LALD, and others experiencing an increase, which might explain the differences in motor symptoms and complications. A study with larger sample size and more specific patient selection could be useful to further our understanding of LALD effects.

4.2.2. Responders and non-responders

Several differences were found between patients who responded to LALD and those who did not. The group of responders whose AHI was reduced by at least 10 events/hr or by 50% of baseline were significantly younger, had a significantly lower BMI, and fewer were male and had hypertension. Age[169], male sex[170], obesity[91], and hypertension are all known risk factors for OSA.

Hypertension can contribute to the development of OSA through several mechanisms[171] such as inhibitory effect on genioglossus EMG, decreasing upper airway muscle tone[172], and redistribution of retained fluid in the legs to the upper body impacting neck circumference and airway caliber, thus predisposing to pharyngeal obstruction during sleep[173]. LALD may be less beneficial for patients who are at risk of OSA due to more traditional risk factors independent of PD. Hence, characteristics of responders may imply that OSA in those patients is caused by dysfunction of the upper airway musculature occurring due to the PD process itself. In their study, Herer et al. show that upper airway obstruction was reduced in 60% of patients treated with levodopa, which they suggest may be due to levodopa's ability to ameliorate motor disability, albeit not completely. Specifically, they explain that upper airway obstruction in PD may be caused by tremor and rigidity affecting the upper airway muscles[62]. Bahia et al. reported a higher UPDRS motor score among patients with PD and laryngopharyngeal motor dysfunction, as well as more upper airway dysfunction assessed by spirometry. In their study, patients with laryngopharyngeal motor dysfunction were three times more likely to have OSA than those without laryngopharyngeal motor dysfunction[174]. While we did not measure laryngopharyngeal motor dysfunction in our study, any therapeutic effects of LALD with respect to OSA might be due to an amelioration in upper airway motor dysfunction. In their study, Vincken et al.[126] suggest that levodopa might be able to reverse upper airway obstruction, and the time course of the spirometric respiratory improvements were consistent with the peak plasma concentrations of levodopa. Considering LALD maintains a greater plasma concentration over time, it remains possible that it can reduce upper airway obstruction for longer periods, stabilizing breathing during sleep. Thus, we can hypothesize that LALD stabilizes breathing, explaining why some patients responded to the treatment in our study. Our results support the idea that the PD process itself plays a role in the

development of OSA in a proportion of individuals. Future work is required to confirm this hypothesis.

The same group of responders also had a significantly lower motor MDS-UPDRS score. As mentioned previously, the motor MDS-UPDRS score has been found to be a potential predictor of AHI[1], supporting the idea that motor impairment contributes to the progression of OSA in PD. If OSA in PD is indeed caused, to some degree, by motor dysfunction in the upper airway, then perhaps LALD is not sufficient in treating more severe upper airway motor issues. Thus, patients with advanced motor impairment might not benefit from LALD to a clinically appreciable degree.

When stratifying patients according to whether the AHI decreased from baseline by any amount, we found that sleep efficiency was worse in responders, and they had more wake-time after sleep onset. A low arousal threshold can lead to a reduction in sleep efficiency caused by recurrent arousals throughout the night, reflected by the increased wake-time after sleep onset[175]. Moreover, responders also had more total arousals at baseline than non-responders, albeit insignificantly. Interpatient variability is likely present in the pathological mechanisms of OSA such that a low arousal threshold is implicated in patients who responded to LALD. LALD may help sleep continuity by reducing nocturnal motor symptoms, leading to more stable sleep, thus less respiratory instability and OSA. Indeed, Lees[176] reported that patients experienced less nocturnal bradykinesia, rigidity, and tremor on Madopar HBS (a sustained-release formulation of levodopa and benserazide) at nighttime. This may be true for our population as well, although we did not directly assess nocturnal motor symptoms.

Responders had a lower oxygen desaturation index at baseline when the response was defined by AHI reduction by at least 10/hr or 50% of baseline. This further promotes the idea that responders may have an "endotype"[177] where low arousal threshold is a contributing cause to OSA

because hypoxemia is associated with greater obesity and because patients who tend to be aroused from sleep more easily will have oxygen levels decrease by smaller amounts[178]. Exploring OSA endotypes thus may be a worthy avenue to direct future research.

The distribution of PD motor subtypes was not significantly different among responders and non-responders. Thus, while OSA may be more severe in patients with the TD and indeterminate subtypes, those patients may not be more likely to respond to treatment with LALD. Moreover, assessing the different endotypes of OSA and determining the response to LALD within these endotypes may be a worthy avenue to explore, since these endotypes could be relevant predictors of how clinical interventions will work therapeutically[124].

4.2.3. Feasibility and tolerability

All the patients that completed the protocol in its entirety adhered to the LALD or placebo regimen more than 90% of the time during each treatment period, thus ensuring considerable compliance to the study protocol. This degree of compliance allows us to suggest that this form of treatment is feasible in the short term in the context of a trial for patients with PD, and that the treatment approach is feasible in patients with PD. Only three adverse events were reported throughout the span of the trial, and none were directly related to LALD.

4.2.4. LALD, sleep and other non-motor symptoms

LALD did not seem to exert a significant effect on different sleep parameters, including various respiratory indices. Wailke and colleagues reported that PD patients on LALD at nighttime had shorter sleep duration, but less fragmented sleep compared to PD patients who were off LALD at nighttime. However, no other significant changes in sleep macrostructure were found in their cohort. These results are consistent with the results from our study population.

LALD did not lead to any significant changes in outcomes such as cognition, daytime sleepiness, and subjective sleep quality. In their double-blind crossover trial, Stocchi and

colleagues[179] reported a significant reduction in nocturnal akinesia on LALD (Sinemet CR) compared to on placebo and most patients rated their overall sleep as more satisfactory on LALD than on placebo. On average, their time asleep was greater on LALD, although this was not statistically significant. Their findings suggest that LALD may improve subjective sleepiness by alleviating motor disturbances, but the lack of effect of LALD on subjective sleep quality in our population may be because overall sleep quality, given the average PDSS-R score, does not suggest poor sleep quality at baseline.

LALD at night did not significantly impact cognition. Levodopa is not expected to have a significant direct effect on cognition. Kulisevsky and colleagues[180] conducted a parallel, randomized open study in 20 patients with PD who were assessed before administration and at various timepoints after administration of short-acting levodopa monotherapy, and pergolide. While both treatments improved cognitive function, this improvement was not sustained. However, if sleep quality had improved, cognition might have also improved, but this was not the case in this pilot trial. The small sample and short duration of this study make our results inconclusive.

4.3. Strengths and limitations

4.3.1. General

The studies presented have several strengths and weaknesses. OSA was objectively diagnosed by overnight PSG and all questionnaires and PD assessments at each study visit were overseen by a trained research coordinator. These components ensure that the data collected is standardized and accurate, thus increasing the validity of our findings.

The findings for these studies result from several outcomes and statistical tests, which may raise the risk of making a Type I error and reporting a falsely significant result[181]. However, correcting for multiple comparisons can also lead to an increase in the risk of making a Type II

error[182,183]. Our study on sleep and OSA in the PD motor subtypes was exploratory and hypothesis-generating. Moreover, sleep quality outcomes are related and not independent.

4.3.2. Sleep architecture, OSA, and PD motor subtypes

For our analyses, patients were stratified by motor subtype according to two groups: PIGD and non-PIGD. This was done for two reasons. First, subjective sleep was reported to be worse in the PIGD motor subtype and in the akinetic-rigid subtype, which encompasses similar motor symptoms via a different classification system. Moreover, worse NMS are also associated with PIGD motor subtypes. Thus, we hypothesized that OSA may be worse in these patients, given that OSA is a common NMS of PD. To assess this, we sought to compare patients assigned the TD and indeterminate motor subtypes to those assigned the PIGD motor subtype. Doing so allowed our results to be compared to the existing literature on sleep, NMS and PIGD subtypes. Second, there were few patients assigned the indeterminate motor subtype in comparison to TD and PIGD. Thus, comparing the three groups led to an imbalance of sample size considering the indeterminate group had half the number of subjects as the PIGD and TD groups. It was therefore ideal to dichotomize our cohort into a PIGD group and non-PIGD group.

This study has some limitations. First, the data for our analyses were taken from clinical trials assessing patients with OSA in PD. It is probable that participants recruited for these studies were more likely to have sleep issues. Therefore, our estimates may be prone to collider bias. While the prevalence of OSA in our study is high, it is consistent with a high prevalence of OSA in other elderly populations[84]. An additional limitation is that the populations studied in the COPE-PAP trial and ELO-PD trial were not identical and we did not account for interstudy group differences in our analysis. This being said, there were no major discrepancies between these two study populations. Moreover, patients were analyzed at a fixed timepoint in their disease progression as opposed to being followed longitudinally over a certain number of years or

analyzing data from patients with the same number of years of disease duration. This may affect results considering motor subtypes have been shown to evolve as PD progresses[184]. The indeterminate subtype (included in the non-PIGD group in our analyses) was found to be particularly unstable[184], thus assessing sleep alterations and OSA as PD progresses may provide additional information regarding their association with certain PD motor subtypes. It is also important to consider that motor subtyping is not the only way by which the heterogeneity of PD is classified. Data-driven approaches such as clustering are frequently employed to stratify PD patients by predominant features, both motor and non-motor, to define clinical subtypes. Fereshtehnejad et al.[185] executed a prospective cohort study where they enrolled 113 patients with idiopathic PD and evaluated numerous motor and non-motor features including motor severity, motor complications, motor subtypes, autonomic symptoms, olfaction, sleep and sleep disorders, and neurocognition. They reassessed 76 patients after a mean follow-up period of 4.5 years. With these results, they employed cluster analysis and defined three subtypes: mainly motor/slow progression, diffuse/malignant, and intermediate, based on orthostatic hypotension, mild cognitive impairment, RBD, depression, anxiety, and UPDRS Part II and III baseline scores. While our study provided information about sleep among patients with varying motor profiles, assessing OSA within these distinct PD phenotypes would provide more context regarding which array of symptoms, including NMS profiles, are more likely to co-occur in PD and perhaps provide a more comprehensive understanding of the pathology underlying OSA in PD. However, our interest was to assess if OSA was related to a specific motor subtype to help understand the potential underlying PD-specific pathophysiology of this sleep disorder.

4.3.3. ELO-PD trial

This trial is the first randomized controlled trial, to our knowledge, to assess the effects of LALD on OSA in a PD population. Thus, our results provide novel insight regarding a potential

alternative treatment to CPAP in a population that has disease-specific difficulties with CPAP adherence[132], in addition to the traditional issues with CPAP adherence experienced by the general population. Our OSA diagnostic criteria ensures that only patients with at least moderate OSA were included in this study, enabling us to determine whether this drug can lead to a meaningful decrease in AHI and a reduction in OSA severity. Considering the extensive and somewhat burdensome protocol, we had a minimal number of dropouts and/or cases of protocol deviation. Only two patients were excluded after randomization and both completed at least one segment of the protocol, minimizing the amount of missing data thus making our intention-to-treat analyses more robust.

The ELO-PD trial has some limitations. First, our findings may not be representative in all PD populations, given the involved protocol. Patients with advanced PD can have cognitive and physical limitations, which could make it difficult to adhere to the study procedures. Patients with advanced PD make up between 10%[186] and 51.3% of the PD population[187–189], therefore our cohort is not representative of up to half the general PD population. Moreover, our cohort was not as ethnically diverse as needed to make our results generalizable to all PD populations. Future studies with clinical cohorts from large centers would be necessary. This being said, our results suggest that LALD may not be beneficial for patients with more severe motor dysfunction, and therefore more severe PD. Studies determining the effects of LALD in this patient population may still be beneficial, however, to support our findings.

Second, some patients had extended periods of time from their PSG at baseline to their PSG on treatment in either study period due to COVID-19 pandemic-related delays. Specifically, the longest period between baseline PSG and treatment PSG (either in the LALD or placebo period) was approximately 5 months. This extended time may have resulted in changes in the AHI

irrespective of the treatment. For example, it is possible for one's BMI to change in this period, considering weight loss is common in PD[190]. Only one patient had any changes in their PD drug regimen from baseline until study completion (and pre-maturely terminated the study), while no patients had changes in their non-PD drug regimens, thus any differential influence of medication should not be present.

Lastly, we did not meet our randomization goal of 42 subjects. Only 36 patients were randomized due to delays in recruitment influenced by public health measures that were in place for most of the recruitment period, all caused by the COVID-19 pandemic. Moreover, the need for multiple sleep tests in this study made it difficult to recruit patients, though the study was well tolerated by patients who began the protocol. These issues should thus be considered in future studies on OSA in PD patients. It is important to consider that 36 patients were randomized in this study with only a 6% drop-out rate, and our primary analyses were intention-to-treat. Furthermore, patients were 100% compliant to the protocol on PSG nights specifically, ensuring validity of our analyses regarding the AHI. Our results may also be skewed by outliers present in the dataset, which could represent physiologic variants of interest or other reasons. A study with a larger sample will be needed to clarify the effects of LALD on AHI.

Chapter 5. Conclusions & Future Directions

The work presented in this thesis reveals a relationship between OSA severity and TD and indeterminate motor subtypes compared to the PIGD motor subtype. Our results illustrate that the AHI is significantly higher in patients with the non-PIGD subtype after adjusting for several confounders, and in analyses excluding patients on psychoactive medication or levodopa and/or DAs at nighttime. Patients with the PIGD subtype may have more consolidated sleep, as shown by greater N3 sleep, although other sleep parameters remained unchanged. Additionally, results from the ELO-PD trial suggest that LALD does not reduce the AHI in this cohort. Treatment with LALD was a feasible and tolerable treatment among patients. Moreover, this drug did not improve nor worsen other outcomes including different parameters of sleep architecture, cognition, subjective sleep quality, daytime sleepiness, and PD motor and NMS over a 2-week period. However, effects were heterogenous and participants who responded to this medication, evidenced by a meaningful decrease in AHI, were, on average, younger, had a lower BMI, were mostly female, and had less hypertension. These patient characteristics suggest that OSA in this population may be due to the neurodegenerative process of PD and are less likely to be due to risk factors affecting the general population.

These studies highlight the relevance of such research investigating the mechanisms and therapeutic approaches for OSA in PD. Future work in this area should focus on outlining which subtypes of PD, motor and non-motor, may be associated with changes in sleep architecture, if any, and more severe OSA in larger study populations assessed longitudinally or cross-sectionally to account for the evolution of motor symptoms over time. Moreover, evaluating OSA endotypes in PD would be beneficial to better understand the pathophysiology of OSA and could provide a better understanding of the mechanisms that contribute to the differential development and severity

of OSA across PD patients. Next steps for the ELO-PD trial include analyzing the effects of LALD in the first and second half of the night. Follow-up trials should focus on more precisely evaluating OSA pathophysiology in individual patients with PD, to predict response to LALD.

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Appendix

Appendix material 1. Article: An Overview of the Effects of Levodopa and Dopaminergic Agonists on Sleep Disorders in Parkinson's Disease

Citation: Scanga A, Lafontaine A-L, Kaminska M. An overview of the effects of levodopa and dopaminergic agonists on sleep disorders in Parkinson's disease. J Clin Sleep Med. 2023;19(6):1133–1144.
DOI: https://doi.org/10.5664/jcsm.10450

An Overview of the Effects of Levodopa and Dopaminergic Agonists on Sleep Disorders in Parkinson's Disease

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All authors have seen and approve the manuscript.
Financial Support: none
Conflict of Interest: AS – none; ALL - Advisory board honoraria: Abbvie, Sunovion, Paladin Labs, Merz; Speaker honoraria: Sunovion, Paladin Labs; MK – none.

Abstract
Sleep disorders are among the most common non-motor symptoms in Parkinson's disease (PD) and are associated with reduced cognition and health-related quality of life. Disturbed sleep can often present in the prodromal or early stages of this neurodegenerative disease, rendering it crucial to manage and treat these symptoms. Levodopa and dopaminergic agonists are frequently prescribed to treat motor symptoms in PD and there is increasing interest regarding how these pharmacological agents affect sleep and their effect on concomitant sleep disturbances and disorders. In this review, we discuss the role of dopamine in regulating the sleep-wake state and the impact of neurodegeneration on sleep. We provide an overview of the effects of levodopa and dopaminergic agonists on sleep architecture, insomnia, excessive daytime sleepiness, sleep-disordered breathing, rapid-eye movement sleep behaviour disorder, and restless legs syndrome in PD. Levodopa and dopaminergic drugs may have different effects, beneficial or adverse, depending on dosing, method of administration and differential effects on the different dopamine receptors. Future research in this area should focus on elucidating the specific mechanisms by which these drugs impact sleep in order to better understand the pathophysiology of sleep disorders in PD and aid in developing suitable therapies and treatment regimens.

Keywords: Parkinson's disease, sleep disorders, levodopa, dopaminergic agonists

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder[1] and is characterized by progressive neurodegeneration. PD is most commonly known for its cardinal motor features resulting from dopamine depletion. However, non-motor symptoms (NMS), including mood disorders, autonomic dysfunction, sensory deficits and sleep disturbances are now recognized as major contributors to disease symptomatology, and continue to gain research interest. Sleep disturbances in PD can manifest as changes in normal sleep architecture, insomnia and excessive daytime sleepiness (EDS), or as specific sleep disorders including sleep-disordered breathing (SDB), rapid eye movement sleep behaviour disorder (RBD), and restless legs syndrome (RLS).[2] Sleep disturbances affect approximately 90% of patients with PD[3] and have been linked to cognitive decline.[4] Moreover, sleep problems negatively impact health-related quality of life, beginning during the early stages of PD.[5] Thus, the management of these symptoms is relevant and necessary in order to reduce disease burden and improve patient wellbeing. This article reviews the effects of levodopa and dopaminergic agonists (DAs) on sleep disorders in PD, and provides an overview of the impact of neurodegeneration on the development of sleep issues in PD.

Sleep Disturbances in Parkinson's Disease

Sleep disturbances are among the most common NMS.[6,7] In PD, sleep disruptions are considered multifactorial and are influenced by factors including motor and non-motor symptoms, autonomic dysfunction, circadian dysfunction, and iatrogenic insult.[8] Sleep disorders commonly occur in the prodromal phase of PD, before the onset of motor symptoms, and tend to progress with advancing stages of PD.[2] A primary cause is the progressive neurodegeneration of sleep/wake centers.[9]

The neuropathological hallmark of PD includes the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and dopaminergic depletion of the nigrostriatal pathways.[15] Dopamine is a catecholamine involved primarily in arousal and promoting wakefulness, specifically through cortical activation and behavioural arousal.[10] The ventral tegmental area (VTA) and the mesencephalic SNpc are the major dopaminergic nuclei.[11] Dopaminergic cells in the VTA and SNpc have efferent and afferent projections to and from different brain structures involved in the control of sleep and wakefulness, including the dorsal raphe nucleus, the pedunculopontine and laterodorsal tegmental nuclei, the locus coeruleus, the lateral and posterior hypothalamus, the basal forebrain, and the thalamus.[12] Dopaminergic neurons do not alter their mean firing rate across sleep-wake states,[13] but rather are thought to modify their tonic and phasic pattern of discharge in accordance with inputs from serotonergic, cholinergic, orexinergic, glutamatergic and noradrenergic neurons in the abovementioned brain regions.[11]

Extranigral structures including in the brainstem[14] and hypothalamus [15] are important in the pathology of sleep disruptions in PD. In a post-mortem study, PD patients with sleep disturbances exhibited greater pathological changes in specific regions of the brainstem and the hypothalamus than PD patients without sleep disturbances.[16] Degeneration in hypothalamic regions such as the ventrolateral preoptic[17,18] and median preoptic areas[19] may lead to insomnia and sleep disturbances in PD.[8] Neurons projecting from these regions innervate and inhibit major monoamine arousal systems leading to the generation and promotion of sleep. Thus, pathological

alterations in the hypothalamus can alter sleep-wake states and circadian rhythms, and decrease consolidated sleep[17] in PD.[20]

While dopamine is one of many neurotransmitters playing a crucial role in the sleep-wake cycle, sleep disturbances can also result from degeneration of nondopaminergic pathways including serotonergic[21], noradrenergic[22] and cholinergic.[23]Additionally, EDS in PD may in part be attributed to a deficiency in hypocretin-containing neurons.[24] A loss of hypocretin neurons is involved in hypersomnolence and the pathogenesis of narcolepsy. In some instances, PD patients with EDS can experience sleep attacks, a narcolepsy-like symptom[25]. Other specific neurological regions affected in PD include the noradrenergic locus coeruleus and subcoeruleus complex,[22] which are involved in sleep-wake state regulation, particularly in promoting arousal and vigilance,[26] with relevance to cognition.[27] Locus coeruleus neurons are in turn affected by sleep disturbances.[28–30] In addition, these neurons have been found to be involved in the pathogenesis of RBD. Neuroimaging has shown decreased signal intensity in the abovementioned regions in patients with PD and RBD.[31]

The brainstem is home to important components of respiratory control, including the respiratory pacemaker and central chemoreceptor.[32] Thus, SDB in PD may be attributed to the degeneration of neurons in specific brainstem structures involved in the control of ventilation.[33]

As per the Braak hypothesis, which suggests that neurodegeneration in PD begins in lower brainstem structures and follows an ascending pathway,[14] brainstem regions could be among the first to be affected by neurodegeneration in PD,[14] potentially acting as a predisposition to the development of sleep disorders. However, Braak's hypothesis is likely not the only way by which this neurodegenerative process progresses. A post-mortem study by Kalaitzakis et al. found that lower brainstem structures were not affected in a subset of PD cases, indicating that different trigger sites and progression patterns of PD exist,[34] which could also account for differences in sleep-related manifestations.

Dopamine Receptors and Sleep Regulation in Animal Models

Much of what is known about the effects of the different dopaminergic receptors in sleep comes from animal data. In rats, administration of D1 and D2 receptor agonists induces wakefulness and reduces slow-wave sleep and rapid-eye movement (REM) sleep.[13] However, D2 receptors exhibit biphasic effects, such that a reduction in wakefulness and increases slow-wave sleep and REM sleep have been observed with small doses of D2 receptor agonists, and the opposite observed with higher doses.[13] Animal data have shown that levodopa and DAs facilitate sleep at lower doses but have the opposite effect at higher doses, through the biphasic action of presynaptic D2 receptors.[35,36] Similarly, low doses of the D2 receptor agonist quinpirole decreased wakefulness and increased sleep by acting presynaptically, while higher doses promoted wakefulness by acting postsynaptically.[37] In primate models, quinpirole was shown to increase sleep latency and wakefulness after sleep onset, exhibiting a deleterious effect on sleep parameters. The DA pramipexole which has D2 and D3 receptor affinity also exhibited a biphasic effect in rats with increased sleep at lower doses and greater alertness at higher doses.[38] The D1 receptor agonist SKF38393 increased slow wave sleep, reduced periods of wakefulness after sleep onset, albeit insignificantly, and restored levels of REM sleep to baseline values in a primate model of PD.[39] This effect is contrary to what was previously found in other animal models.[40–42] Thus, further experimentation is required to elucidate the effects of the different dopaminergic receptors, particularly in humans.

Pharmacology of Levodopa and Dopaminergic Agonists

Levodopa is the gold standard in the treatment of PD due to its effectiveness and ability to alleviate the hallmark motor symptoms. Levodopa is decarboxylated in the striatum to form dopamine which stimulates dopaminergic receptors. This pharmacological agent has a half-life of 50 minutes, however, this can be increased to approximately 90 minutes when administered with a decarboxylase inhibitor such as carbidopa.[43] The combination of levodopa and carbidopa enables levodopa to cross the blood-brain barrier without being metabolized prematurely by the gastrointestinal system.[44] Gastrointestinal adverse effects of levodopa are less frequent with the use of carbidopa.[45] Adverse drug reactions occurring with advancing PD include motor fluctuations and symptoms recurring due to the "on-off" phenomenon. After taking levodopa, patients will be in the "on" phase when symptoms are alleviated, but due its short half-life, its effects begin to wear off after a few hours and patients experience the "off" phase where symptoms can become unpredictably more severe. Common "on" complications include a delay in the onset of symptomatic relief or a less powerful relief of symptoms than usual upon intake of medication.[46] Levodopa-induced dyskinesia (LID) is a common, but physiologically complex complication in PD,[47] occurring in 3%[48] to 94% of PD patients.[49] LID occurs when dopamine concentrations are at their maximum in the brain, termed peak-dose dyskinesia, which occurs in a dose-dependent fashion,[47,50] and also depends on the methods of drug delivery.[47]

Long-acting levodopa (LALD) has a longer half-life than that of regular levodopa, maintaining a greater plasma concentration over a greater amount of time.[51] LALD exhibits the same safety and tolerability as immediate-release levodopa but also has similar rates of motor complications. Its role as an alternative for immediate-release levodopa remains unclear due to less predictable absorption and effect.[52]

DAs are dopaminergic drugs that can be administered either in monotherapy or with levodopa, depending on the symptomatic profile of the individual patient.[53] DAs act directly to continuously stimulate the central dopamine receptors[54] in situations of insufficient endogenous dopamine such as PD. DAs can be divided into two groups: ergoline and non-ergoline-derived agonists. Common ergoline class drugs are bromocriptine, cabergoline, pergolide and lisuride,[55] all now rarely prescribed in PD due to their severe adverse complications including cardiovascular,[56] retroperitoneal[57] and pleuropulmonary[58] fibrosis.[54]

Currently, the widely used non-ergot-derived DAs include pramipexole, ropinirole, apomorphine, and rotigotine. These drugs bind with high affinity to the D2-like dopamine receptor family and modestly interact with the D1-like family.[54] In contrast to levodopa, DAs are appreciated for their longer half-life and can be used to reduce motor fluctuations caused by levodopa therapy.[55]

Pramipexole is among the therapies with the longest half-life – 12 hours.[55] It also binds with high affinity to D3 receptors found in the limbic system[55] and is often prescribed for unipolar and bipolar depression, making it a treatment option for PD patients with mood disorders.[59] Ropinirole is pharmacologically similar in many ways to pramipexole, although it has a shorter half-life of approximately 6 hours and exhibits a preferential affinity for D2 receptors. Adverse effects of both these drugs include orthostatic hypertension, dizziness, nausea and somnolence.[53]

Unlike pramipexole and ropinirole, apomorphine and rotigotine are not administered orally. Apomorphine is among the shortest acting DAs, with a half-life of 30-60 minutes, and is administered subcutaneously. It is used in cases where patients exhibit uncontrollable "off" episodes.[55] Rotigotine is primarily a D2/D3 receptor agonist administered in the form of a daily

transdermal patch. It has a biphasic half-life beginning with an initial distribution of three hours followed by 5 to 7 hours of continuous drug availability. Rotigotine is a valuable option for patients with issues adhering to their daily drug regimen.[55] Apomorphine and rotigotine may cause reactions at the site of administration, and other adverse effects include dizziness and orthostatic hypertension.[53] Treatment with DAs can also lead to the development of impulse control disorders.[60]

Sleep Architecture and Objective Sleep Quality

In PD, progressive alterations in architectural parameters of sleep structure have been evaluated and confirmed in numerous studies, with changes in sleep efficiency, total sleep time, sleep fragmentation, prolonged sleep latency and a reduction in the percentage of REM sleep.[61–63] Architectural sleep changes advance progressively with disease duration,[61] indicating that the neuropathological process of PD may play a pivotal role in structural sleep changes. When compared to healthy control subjects, drug-naïve patients with PD present a significantly reduced sleep efficiency, a greater sleep latency and decreased time in REM sleep, supporting the hypothesis that the neurodegenerative process of PD contributes to changes in sleep architecture.[64]

Conflicting evidence exists regarding the effect of levodopa and DAs on sleep architecture. In their early study, Nausieda et al.[65] concluded that sleep disruptions were associated with chronic antiparkinsonian therapy because of the increased prevalence of patient-reported sleep disturbances with longer treatment duration.[65] Furthermore, the onset of antiparkinsonian treatment in early PD patients has been linked to a statistically significant increase in awakenings and decrease in stage 1 non-REM sleep evidenced by polysomnography (PSG) recordings.[66] However, in some studies, PSG data exhibited no significant correlation with levodopa or DA dosage, suggesting that dopaminergic therapy does not result in sleep "destructuring".[61,67] Moreover, Ferreira et al. found that in drug naïve patients started on levodopa for 2 months prior to undergoing a sleep study, sleep efficiency improved from 75.4% to 86.4% ($p = 0.012$), with improvements in wakefulness after sleep onset and sleep latency noted as well.[64] This was attributed to improved motor symptoms rather than direct changes in sleep architecture. Improvement of sleep fragmentation with dopaminergic treatment was previously shown to be related to normalization of muscle activity in sleep.[68] A study assessing the effect of LALD, on microstructural sleep parameters found that this preparation of levodopa had no significant impact on objective sleep, that is LALD did not cause alterations in sleep architecture, but it also did not reverse sleep disturbances, nor rescue sleep structure.[69]

In a recent meta-analysis, it was found that the levodopa equivalent daily dose (LEDD) contributed significantly to the heterogeneity of PSG changes in PD, and that increased LEDD was associated with increased wakefulness after sleep onset and REM latency, and decreased total sleep time.[70] Self-reported and objective sleep parameters assessed by SCOPA-SLEEP questionnaire and PSG, respectively, worsened with increasing dosage of dopaminergic medication taken within four hours of bedtime.[71] However, contradictory evidence was reported when the effects of levodopa and DAs were compared separately. While levodopa was not significantly associated with altered sleep macrostructure in a cohort of 351 PD patients, DAs were associated with more awakenings ($p<0.001$) and decreased time spent in REM sleep ($p = 0.012$).[72] However, rotigotine resulted in improved objective quality of sleep with a 10% increase in sleep efficiency, decreased wakefulness after sleep onset and sleep latency, and increased REM sleep compared to placebo.[73] Though improved sleep through improved motor symptom

control remains a possibility, the authors suggest a direct effect on D1 receptors,[73] which have been shown to be involved in sleep mechanisms in a primate PD model.[39]

Overall, the effects of levodopa and DAs on sleep architecture appear to be variable in PD, depending on factors including PD disease duration, the dosage of medication used and the specific pharmacodynamic profile of levodopa formulation or DA. As evidenced experimentally, the dose of levodopa and DAs is critical in both sleep promotion and sleep disruption. Thus, further experiments should focus on determining the optimal dose, formulation and pharmacologic profile that can maintain consolidated sleep while alleviating motor symptoms.

Subjective Sleep Quality and Insomnia

Insomnia, the most prevalent sleep disorder among PD patients,[74] refers to difficulties in sleep initiation, sleep maintenance, or early awakenings.[75] Subjective sleep quality and insomnia are related. Patients with PD experiencing sleep dysfunction and insomnia report issues primarily regarding sleep maintenance and consolidation.[76] Insomnia can be caused by other sleep disorders such as RLS, particularly for sleep onset insomnia, and OSA,[77] as well as depression,[78] pain and nocturia. Patients experiencing insomnia will often report daytime sleepiness,[79] altering their ability to perform daily tasks.

Levodopa may impact subjective sleep quality.[67] Increasing doses of levodopa administered chronically over time in PD negatively correlate with subjectively assessed sleep quality[67,80,81] and sleep maintenance.[67] The motor complications of levodopa can lead to a reduction in subjective sleep quality out of proportion to PSG-measured sleep architecture impact, related for example to akinesia, cramps, dystonia, and pain related to "off" periods.[67] However, LALD administered at bedtime appears to improve nocturnal akinesia and increase total sleep time, but has no effect on sleep fragmentation, sleep initiation, and sleep maintenance. It can also reduce rigidity, and promote sleep in some patients.[52,82] Conversely, in cross-sectional analyses, Schaeffer et al.[80] have found that LALD may not be adequate in reducing nocturnal akinesia and impaired subjective quality of sleep, and results in increased perception of nocturnal akinesia.[80] While some patients may benefit from LALD to control nocturnal motor symptoms, others may not benefit sufficiently from it to experience better subjective sleep quality.

In a longitudinal study, subjects with early PD who reported insomnia had a greater overall LEDD in comparison with subjects who did not experience sleep disturbances, indicating a potential correlation.[74] Insomnia severity assessed in PD using the Insomnia Severity Index (ISI)[83] was not associated with LEDD.[84] Therefore, while LEDD may be correlated with the presence of insomnia, it may not necessarily correlate with insomnia severity. Moreover, sleep maintenance insomnia, in a cohort of 182 drug-naïve PD patients, increased by 50% from baseline after the introduction of DAs.[75] Other investigators have established that treatment with DAs may be an independent risk factor for insomnia.[78]

Three randomized controlled trials observing the effects of ropinirole prolonged-release,[85] rotigotine,[86] and pramipexole,[87] either together with levodopa or as monotherapy in early PD, reported insomnia as one of the most common adverse events experienced by participants in the groups receiving the intervention. However, a later randomized controlled trial testing rotigotine in a cohort of advanced PD patients reported no difference in reported insomnia between PD subjects who received the intervention and those who did not.[88] The difference in study population, early versus late PD, might account for different effects. In the RECOVER trial, rotigotine improved nocturnal PD symptoms assessed by PDSS-2.[89,90] Moreover, other randomized controlled trials using rotigotine and ropinirole prolonged-release showed an

improvement in the general quality of self-reported sleep evidenced by significant improvements in PDSS scores.[73,91,92]

Insomnia is multifactorial, and PD drug regimens may differentially influence sleep depending on the balance of beneficial versus adverse effects in a given individual. Once motor disturbances are alleviated with levodopa and/or DAs, including throughout the night, patients may be more likely to experience fewer nocturnal disturbances, reducing symptoms of insomnia and ameliorating the perceived quality of sleep. However, motor fluctuations and other adverse effects may lead to poor sleep outcomes. Side effects can also include hallucinations, that are more prevalent in PD patients taking DAs,[93] and may aggravate any insomnia experienced. A direct drug effect promoting alertness may also impair sleep.

In treating insomnia, nonpharmacological approaches should be favored, including optimization of sleep hygiene and cognitive behavioural therapy[94]. Pharmacological treatment options are limited and associated with potential adverse effects (Table 1). Research to further our understanding of the specific etiologies contributing to the development of poor sleep quality and insomnia in individuals with PD could aid in developing targeted and personalized therapies that will leave patients with more consolidated sleep overall.

Excessive Daytime Sleepiness

EDS is classified as a state of daytime hypersomnolence where daily, unintentional sleep episodes occur inappropriately.[95] A recent meta-analysis found that out of 59 analyzed studies, the estimated prevalence of EDS in PD was 35.1%, which represents a higher prevalence in PD than in the general population.[96] EDS can pose a threat to the safety of patients, particularly while driving.[97] The pathophysiology of EDS in PD is multifactorial, and evidence suggests that it can arise because of the nigrostriatal dopamine depletion occurring in the neurodegenerative process of PD,[98] co-existing sleep disorders, nocturnal motor symptoms,[99,100] and the use of ergot[101] and non-ergot DAs.[102,103]

Routine use of DAs in PD resulted in the observation of a severe adverse effect: sleep attacks. Eight PD patients on pramipexole or ropinirole reported falling asleep while driving without feeling any drowsiness or fatigue.[104] The same effect of hypersomnolence while driving was reported in three other patients with PD on bromocriptine, lisuride and piribedil, ergot DAs.[101] Paus and colleagues[105] surveyed 2952 PD patients regarding the occurrence of sleep attacks, or sleep episodes, and found that this phenomenon occurred with all DAs available on the market at the time and with levodopa monotherapy. The latter was associated with the lowest risk of developing sleep attacks while the greatest risk was associated with combination therapy of levodopa and DAs. Treatment with DAs was one of the main determining factors of sleep attacks in this cohort.[105] However, this finding has been challenged by other investigators arguing that neither pramipexole nor levodopa monotherapy make patients with PD more susceptible to sleep attacks.[106] Amara and colleagues longitudinally assessed EDS in PD patients over three years and determined that at years two and three, the total LEDD was significantly higher in PD patients with EDS, setting forth the possibility of a dose-dependent association between EDS and total LEDD.[107] Notably, consistent evidence suggests that levodopa monotherapy confers less of a risk of somnolence in comparison with DAs alone, and when compared to DA and levodopa combination therapy.[108,109] However, levodopa may exert sedative effects contributing to EDS and sleep episodes in patients with PD.[101] Other investigators have determined that the dosage of DAs is associated with EDS, while the dose of levodopa is not.[110] Although there is conflicting evidence regarding levodopa and increased somnolence, the potential sedative effects of levodopa, and the sedative effects of DAs, indicate

that somnolence may occur due to a drug class effect.[111] Bliwise et al.[112] have challenged this idea, however, suggesting that daytime alertness is differentially affected by DAs and levodopa: increasing doses of DAs resulted in reduced daytime alertness while higher doses of levodopa increased daytime alertness, as measured using the Maintenance of Wakefulness Test.[113] The authors thus propose a divergent, dose-dependent effect of drug class on daytime alertness.[112] This is different from animal data where higher doses of DA led to greater alertness, as discussed above. Differences may relate to lower dosages per kg used in the Bliwise study in humans compared to the animal studies, and possibly patient/PD-related factors.

EDS can also be attributed to the neurodegeneration occurring in PD. EDS is frequent in PD even before treatment initiation,[103] and associated with longer PD duration.[96] Mean sleep latency from the mean sleep latency test (MSLT), an objective sleepiness measure,[114] did not differ significantly between the rotigotine group and the placebo group in an RCT during a 4-months period,[115] suggesting this DA had no effect on EDS. EDS has been found to be related to dopaminergic nigrostriatal degeneration in PD, as assessed using DAT scanning.[98] Recently, a PET imaging study found reductions in hypothalamic D3 receptor availability to be associated with EDS, irrespective of LEDD.[116] This is consistent with previous studies finding daytime sleepiness was not correlated with sleep disorders, nor with levodopa or DAs, but rather appeared to be a consequence of the pathology of PD.[117] It has been suggested that PD patients with greater neurodegeneration, such as has been identified in ascending arousal systems, may be more susceptible to the effect of dopaminergic therapy in promoting EDS.[116]

Insomnia and EDS are both associated with DAs.[77] DAs, as well as levodopa, may promote insomnia in several ways. They increase the risk of hallucination, which can cause sleep disturbances.[118,119] Motor fluctuation such "off" periods related to medication can also lead to poor sleep. Moreover, as discussed above, DAs have a biphasic effect on D2 receptors such that higher doses may lead to insomnia while lower doses could exert a soporific effect.[36,37,78] Both EDS and insomnia in PD can be caused by disturbed sleep from motor or other symptoms, including other sleep disorders, and neurodegeneration. Specific alterations in sleep/wake circuitry may result in different clinical manifestations. For example, hypothalamic D3 receptors appear to be involved in EDS but not insomnia.[116] Consequently, the manifestations of insomnia and EDS in a given patient might result from the interaction of the specific neurodegeneration pattern and medication type, dose and method of delivery.

Sleep Disordered Breathing

SDB in PD can present in different forms, with the most prevalent form being OSA, affecting between 20% to 60% of all PD patients.[120–122] It is suggested that OSA in PD can develop and worsen due to factors such as upper airway motor instability and impaired ventilatory control.[32] Whether OSA is more prevalent in PD than in the general population remains a topic of debate. Nevertheless, OSA results in fragmented sleep and intermittent hypoxemia, which can exacerbate symptoms of poor sleep, EDS and cognitive dysfunction, greatly impairing quality of life.[32] In our group's work and that of others, greater cognitive dysfunction was found in PD patients with OSA, and greater cognitive impairment was positively associated with increasing OSA severity.[123,124] Furthermore, treatment of OSA in PD using continuous positive airway pressure was found to improve non-motor symptoms, reduce global cognitive dysfunction[125] but not specific cognitive domains,[124] and reduce daytime somnolence.[122]

The effect of levodopa and DAs on SDB in PD has not been well described. Vincken et al. reported a positive effect of levodopa on upper airway obstruction in one PD patient. Spirometry was performed on this patient before intake of levodopa, immediately after and approximately one hour later. The flow rate increased substantially after levodopa treatment, in parallel with parkinsonian symptoms and dyspnea improvement. The authors thus showed that upper airway muscles are involved in disorders affecting motor activity, such as PD.[126] In a cohort of 21 PD patients, five were found to have evidence of upper airway obstruction after levodopa withdrawal. Reintroduction of levodopa resulted in improvement in upper airway obstruction.[127] However, airways obstruction may not ameliorate following levodopa treatment, and may be due to comorbid chronic obstructive pulmonary disease (COPD).[128] Additionally, it has been postulated that the DA apomorphine can improve dysfunction of the musculature in the airway, potentially reversing obstruction that could result in OSA.[127,129] Interestingly, irregular and tachypneic breathing has been reported as a symptom of levodopa-induced dyskinesia in two PD patients. The authors postulate that, in some patients, respiratory dysfunction induced by levodopa may be a result of neurodegeneration of dopaminergic neurons in the respiratory control centers. Dopamine is involved in both the peripheral and central circuitry of respiration. Exogenous dopamine may result in denervation hypersensitivity of peripheral chemoreceptor dopaminergic neurons, causing levodopa-induced respiratory dyskinesia.[130] Moreover, the degeneration of dopaminergic neurons in the brainstem that control breathing, and compromised dopamine receptor function may also contribute to the development of levodopa-induced respiratory dysfunction.[131]

Higher LEDD is associated with less severe OSA.[132] A retrospective study conducted by Valko et al.[133] compared patients with PD, with or without SDB (PD-SDB and PD-wo, respectively). Patients in the PD-SDB group were divided further into cohorts of central and obstructive SDB predominance. Here, AHI was calculated using overnight PSG, where central apnea was characterized by an absence of respiratory effort after the event, and obstructive apnea was characterized by the presence of respiratory effort after the event. Patients with central SDB predominance (n = 7) had a greater overall LEDD than patients with obstructive SDB predominance (n = 50). Moreover, 100% of patients exhibiting central SDB were on dopaminergic treatment compared to only 56% with obstructive SDB ($p = 0.03$). The authors suggest that central SDB predominance may be more likely to occur in patients on both levodopa and DAs, however further studies with a larger sample size are required to confirm this finding. Additionally, Valko and colleagues speculate that PD patients with central SDB may be predisposed to sleep attacks, considering EDS was highly prevalent in the central SDB group. Interestingly, in PD-SDB patients treated with DAs, the author's observed a significant decrease in the AHI during REM sleep, occurring exclusively in this group. The authors attribute this lower REM SDB severity to the close interplay between the neurodegenerative processes affecting REM-sleep-related structures in the brainstem, and the effect of DAs.[133] While important observations were made in this study, the exact effect of DAs and levodopa on SDB in PD remains ambiguous and warrants further investigation, considering the impact of SDB on cognition, amongst other clinical variables.

Recently, our group found that patients with PD taking LALD before bedtime had a lower incidence of OSA events with a lower AHI and fewer respiratory arousal events compared to patients not taking LALD. These results suggest that LALD might be a potential treatment for OSA in some PD patients. Moreover, dopaminergic agonists were not significant predictors of OSA in this cohort, and adjusting statistical models for LEDD did not alter results, suggesting

that DAs do not impact OSA in PD.[134] A randomized controlled trial assessing the effect of LALD on OSA in PD is ongoing.

Rapid Eye Movement (REM) Sleep Behaviour Disorder

RBD is characterized by the loss of muscle atonia during REM sleep accompanied by enactments of dreams with or without vocalizations,[95] which can be bothersome for patients and family members. The incidence of RBD increases throughout disease progression[135] and it is estimated that up to 50% of PD patients will eventually be diagnosed with RBD.[136,137] RBD may be a prodromal feature of PD. The loss of dopaminergic midbrain neurons is associated with idiopathic RBD. Consistent with the hypothesis that RBD precedes disorders involving nigrostriatal dopamine depletion such as PD,[138] up to 82% of patients diagnosed with idiopathic RBD develop a neurodegenerative syndrome, including parkinsonism after 12 years, on average, of follow-up.[139]

Patients with PD frequently experience psychosis, most commonly in the form of visual hallucinations[140] – a phenomenon that has been investigated with RBD in PD.[141,142] RBD in PD is significantly related to the development of hallucinations. RBD and visual hallucinations likely have overlapping neuropathological mechanisms, including cholinergic dysfunction and degeneration.[143] The latency with which psychosis in PD develops depends on differing clinical correlates. In early-onset psychosis, RBD was more frequently present than in patients with late-onset psychosis. Moreover, the development of hallucinations was found to be correlated with the dosage of DA therapy.[141] Later onset of psychosis in particular correlated significantly with LEDD. Generally, as disease duration increases and PD progresses, there will be an increase in LEDD. Therefore, this correlation may be influenced more so by disease duration rather than the actual drug effect.[144]

LEDD was found to be among the statistically significant clinical correlates of RBD when comparing patients with PD who either did or did not have RBD.[145] Longer disease duration was also a significant clinical correlate, further contributing to the likelihood that the association of LEDD and RBD may be confounded by disease duration. A recent preliminary study[146] has confirmed the finding that LEDD is associated with RBD symptoms. Meloni and colleagues sought to evaluate how dopamine replacement therapy affects the presence of symptomatic RBD in a cohort of 250 patients with PD. Intriguingly, levodopa therapy was directly and positively associated with RBD severity, as measured with the RBD screening questionnaire (RBDSQ), after adjusting for age and PD severity.[146] Unlike levodopa, DA therapy was not associated with RBDSQ scores.[146]

The potential prodromal nature of RBD in PD further points toward an association with dopaminergic loss. Patients with idiopathic RBD appear to experience progressive nigrostriatal dopaminergic dysfunction.[147] Hence, DAs has been evaluated in the treatment of RBD in patients with and without PD. In 10 patients with RBD only, pramipexole was highly efficacious, with 89% of these patients reporting that RBD symptoms were moderately reduced or completely resolved.[148] These results were in line with other findings indicating that clinical manifestations of RBD decreased in both frequency and intensity,[149] as well as the severity of RBD symptoms[150] after treatment with pramipexole. However, Kumru et al. assessed the effect of pramipexole in a cohort of PD patients undergoing PSG and found that while parkinsonism improved in all patients, the frequency and severity of RBD symptoms remained unchanged.[151]

Rotigotine may be beneficial for RBD symptoms in PD, as reported in an exploratory, open-label study assessing RBD-related symptoms in PD subjectively and objectively, using the

RBD Questionnaire – Hong Kong[152] and PSG, respectively.[153] The preliminary findings of this study present an improvement in the severity of RBD symptoms with rotigotine.

The presented studies on DAs in RBD are observational, lack a control group and involve small sample sizes. Furthermore, studies evaluating idiopathic RBD[148–150] differ from the study of Kumru and colleagues,[151] where secondary RBD (RBD present with another neurological disorder) was assessed. Idiopathic RBD and secondary RBD may present distinct stages of this disorder, potentially changing response to treatment.[154]

The potential improvement of RBD symptoms in PD with the administration of rotigotine suggests that a potential relationship exists between dopamine and the pathogenesis of RBD.[153] Likewise, Meloni et al. speculate that the lack of association between selective D2/D3 receptor agonists and RBD scores implicates the involvement of D1 receptor activation in the underlying pathophysiology of RBD in PD.[146] Indeed, REM sleep is modulated by D1 receptor activation,[40] a hallmark of rotigotine's mechanism of action, as confirmed by *in vivo* modelling.[155] Randomized controlled trials evaluating the effects of rotigotine in PD patients with RBD should be employed to confirm these observations,[153] and further experimentation is required to clarify these neurological mechanisms.

Restless Legs Syndrome

RLS is a sleep-related movement disorder characterized by waking dysesthesia and an urge to move the legs that occur at rest and, primarily in the evening and at night, resulting in delayed sleep onset. These symptoms can be relieved by movement.[95] They may be accompanied by periodic limb movements (PLM) of sleep. RLS is commonly diagnosed in PD patients, with its prevalence ranging from 0% to 52%.[156] RLS in PD is typically associated with an older age of onset, a lower rate of family history and a lower PLM index on PSG.[157]

It is postulated that RLS is an early clinical feature of PD, however recent evidence suggests that symptoms of RLS do not predate a new diagnosis of parkinsonism.[158] Moreover, the pathogenesis of RLS in PD likely differs from that of idiopathic RLS.[159] Dopamine dysregulation, not dopamine deficiency, may be the predominant mechanism underlying idiopathic RLS,[160] differing from the hypodopaminergic state of PD. The lack of association between RLS and PLM in PD also suggests different pathophysiology in PD.[161]

Treatment of RLS should initially focus on correction of exacerbating factors, including iron deficiency.[162] Pramipexole,[163,164] ropinirole[165] and rotigotine[166] are all approved for the treatment of RLS[167] and have shown considerable efficacy and safety.[168] However, long-term use of these drugs often leads to augmentation: the apparent worsening of RLS symptoms related to RLS treatment symptoms.[169] Additionally, the risk of impulse control disorders with DAs also remains an issue in RLS treatment. Augmentation also often occurs with levodopa treatment.[167] Thus, recent guidelines indicate that alpha$_2$-delta ligands should be the first-line agents used to treat chronic persistent RLS, and DAs should only be prescribed if alpha$_2$-delta ligands are contraindicated.[170]

Maestri et al. have reported that extended-release formulations of DAs may resolve the issue of augmentation due to their longer half-life.[171] There appears to be an inverse relationship between drug half-life and the development of augmentation. In a cohort of 24 patients with RLS, augmentation was resolved after switching from immediate-release DA treatment to extended-release pramipexole.[171] However, further investigation is required to determine if the risk of augmentation is reduced using extended-release DAs, including in PD.

The pharmacological treatment of RLS in PD aligns with that of idiopathic RLS.

While RLS in PD can be treated by optimizing and adjusting dopaminergic drug regimens to alleviate symptoms, the same adverse effects exist as in idiopathic RLS.[172] Small doses of pramipexole and ropinirole have shown great efficacy and tolerability. In the double-blind, placebo-controlled RECOVER trial, rotigotine showed a significant overall improvement of sleep complaints in PD (assessed by PDSS-2), including on specific questions regarding RLS symptoms such as the urge to move arms and legs, and restlessness felt in the arms and legs.[90] In patients already on dopaminergic therapy, it has been proposed that the schedule of levodopa intake can be altered to optimize its effectiveness in alleviating RLS, with administration of an evening dose.[172] In older PD patients with greater cognitive dysfunction, DAs can lead to confusion and hallucinations, and, in rarer cases, impulse control issues.[172] Levodopa could then be considered over DAs. Nonetheless, to reduce the risk of augmentation and avoid increasing what may be an already high LEDD for some PD patients, it is recommended that other treatment options are thoroughly discussed and considered, namely alpha$_2$-delta ligands.[173] Studies have shown that subthalamic nucleus deep brain stimulation can also reduce RLS symptoms in PD,[174,175] although this requires further investigation.

Conclusion

Sleep disturbances and disorders are prevalent NMSs warranting safe and efficacious treatments to prevent cognitive decline and improve quality of life. The development of sleep issues in PD is likely multifactorial and influenced by the complex interplay of neurodegeneration, disease progression and iatrogenic insult. Levodopa and DAs continue to be effective in the treatment of motor symptoms and preliminary studies suggest they may be beneficial for certain sleep disorders such as OSA and RBD. However, these drugs can pose a risk for developing sleep disturbances including daytime somnolence, a common adverse effect of DAs. Moreover, insomnia may also be an adverse effect associated with DA use. Insomnia can result from a multitude of adverse events in PD such as LID and nocturnal motor complications, and thus may be likely to improve when motor symptoms are alleviated by treatment. Overall, larger randomized controlled trials and longitudinal studies are necessary to evaluate the effects of levodopa and DAs on sleep and sleep issues in PD. Additional experimental evidence is required to elucidate the specific mechanisms of sleep disorders in PD, and, consequently, develop a greater understanding of how levodopa and dopaminergic drug therapy may influence these neuropathological mechanisms.

Abbreviations

Parkinson's disease PD
Non-motor symptoms NMS
Excessive daytime sleepiness EDS
Sleep-disordered breathing SDB
Rapid-eye movement sleep behaviour disorder RBD
Restless legs syndrome RLS
Dopaminergic agonist DA
Ventral tegmental area VTA
Substantia nigra pars compacta SNpc
Rapid-eye movement REM
Levodopa-induced dyskinesia LID
Long-acting levodopa LALD

Polysomnography PSG
Levodopa equivalent daily dose LEDD
Parkinson's Disease Sleep Scale PDSS
Epworth Sleepiness Scale ESS
Insomnia Severity Index ISI
Mean Sleep Latency Test MSLT
Chronic obstructive pulmonary disease COPD
Obstructive sleep apnea OSA
RBD Screening Questionnaire RBDSQ
Periodic limb movement PLM

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Table 1. Summary of the pharmacological treatment options and effects of levodopa and dopaminergic agonists on sleep disorders in Parkinson's disease.

Sleep Disorder	**Pharmacologic Treatments**	**Overall Effect of Levodopa (Better or Worse)**	**Overall Effect of DAs (Better or Worse)**
Insomnia	Eszopiclone* (Off label)[94,176] Melatonin* (Off label) [94,176]	Better	Worse
Excessive daytime sleepiness	Modafinil (Possibly useful)[176] Caffeine (Off label)[176] Solriamfetol[177] Sodium oxybate (Off label)[178] THN102 (Investigational)[179]	Worse	Worse
Sleep disordered breathing	No pharmacological treatment recommended.	Better (Under investigation)	No effect
REM sleep behaviour disorder	Clonazepam[176] Melatonin[176]	Worse	Better
Restless legs syndrome	Alpha$_2$-delta ligands:[180] Gabapentin enacarbil, pregabalin, gabapentin Dopaminergic agonists:[180] Pramipexole, ropinirole, rotigotine Opioids[180]: Prolonged-release oxycodone-naloxone	Better	Better in short term but risk of augmentation (Second-line treatment)**
Circadian rhythm disorders	Melatonin***[181,182] (Off label) Melatonin agonists (Investigational)†[183] REV-ERBα agonists (Investigational)$^{+}$[184]	Worse[185,186]	Worse[186]

*Drugs with the greatest supporting evidence for treating insomnia in PD. Other pharmacological agents such as zolpidem, ramelteon, trazodone and doxepin may be useful but there is insufficient evidence. Safety issues may also arise such as risk of falls.
**Doses of DAs should be kept low and other treatments should be considered before additional DAs are prescribed.
***Melatonin has not been directly assessed as a modulator of the circadian rhythm in Parkinson's disease. Rather, clinical trials have observed the effects of melatonin on sleep-wake cycle alterations.
†Experiments performed *in vivo* in animal models only and assessed the effects of a melatonin agonist on age-related changes of the circadian rhythm.
$^{+}$ Experiment performed *in vivo* in animal models only and assessed the ability of synthetic REV-ERBα agonists to regulate circadian behaviour.

Appendix material 2:

Table A1. Linear regression models comparing sleep architecture between the motor subtypes of Parkinson's disease.

	Model of adjustment	PIGD vs. Non-PIGD											
		Full sample (n=146)			Subset 1 (n=73)			Subset 2 (n=101)			Subset 3 (n=60)		
		β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
Total sleep time, mins	Model 1	-12.5	-35.9; 10.8	0.29	-13.9	-48.8; 21	0.43	0.4	-28.1; 28.9	0.98	1.1	-36.9; 39	0.96
	Model 2	-11.4	-34.9; 12.2	0.34	-20.2	-56.4; 15.9	0.27	-1.4	-30.3; 27.4	0.92	-4.6	-44.4; 35.1	0.82
TST in supine position, %	Model 1	8.2	-3.4; 19.9	0.17	-4.2	-21.3; 12.9	0.63	6	-8.5; 20.4	0.42	-6.5	-25.5; 12.5	0.49
	Model 2	8.5	-3.4; 20.4	0.16	-0.6	-18.4; 17.3	0.95	7.2	-7.5; 21.8	0.33	-4.5	-24.3; 15.2	0.65
Sleep efficiency, %	Model 1	1	-4.1; 6.1	0.69	0.44	-6.5; 7.4	0.9	5.4	-0.6; 11.4	0.075	4.1	-3.3; 11.4	0.27
	Model 2	1.6	-3.5; 6.7	0.53	-0.9	-8.2; 6.2	0.79	4.8	-1.2; 10.8	0.11	2.6	-4.9; 10.2	0.49
Wake-time after sleep onset, mins	Model 1	-2.5	-24.7; 19.8	0.83	-6.9	-38.5; 24.5	0.66	-24.2	-47.9; -0.5	**0.046**	-23.3	-55.8; 9.2	0.16
	Model 2	-6.4	-28.4; 15.6	0.57	-1.9	-34.9; 30.9	0.91	-22.4	-46.4; 1.6	0.067	-17.3	-50.8; 16.3	0.3
Stage N1, %	Model 1	-1.9	-6.5; 2.6	0.4	-5.6	-10.6; -0.5	**0.03**	-4	-8.3; 0.2	0.061	-6.9	-12.3; -1.4	**0.01**
	Model 2	-2.1	-6.7; 2.5	0.37	-4.8	-10; 0.4	0.07	-3.7	-8; 0.6	0.089	-6.5	-12.2; -0.7	**0.03**
Stage N2, %	Model 1	-1.6	-6.3; 3.1	0.5	-0.1	-6.6; 6.3	0.97	0.6	-4.6; 5.8	0.83	0.7	-6.1; 7.5	0.84
	Model 2	-1.2	-5.9; 3.5	0.6	0.2	-6.2; 6.5	0.96	1.3	-3.8; 6.3	0.62	1.6	-5.2; 8.5	0.64
Stage N3, %	Model 1	4.5	-0.2; 9.3	0.063	8.1	1.5; 14.7	**0.02**	3.3	-2.4; 9	0.25	8.9	1.9; 15.8	**0.01**
	Model 2	4.1	-0.6; 8.8	0.088	6.7	0.1; 13.3	**0.047**	2.6	-3.2; 8.3	0.38	7.7	0.6; 14.8	**0.04**
Stage REM, %	Model 1	-1.7	-4.3; 0.8	0.18	-3.1	-6.8; 0.7	0.11	-0.5	-3.6; 2.5	0.73	-2.7	-6.7; 1.3	0.18
	Model 2	-1.6	-4.1; 0.9	0.22	-2.9	-6.8; 0.9	0.13	-0.7	-3.8; 2.3	0.63	-2.8	-6.9; 1.4	0.18
Total arousals index, /hr	Model 1	-2.5	-10.1; 5	0.51	-10.9	-21; -0.9	**0.03**	-8.8	-16.7; -0.9	**0.03**	-14.6	-24.5; -4.7	**0.005**
	Model 2	-3.6	-11.1; 3.9	0.35	-10	-20.5; 0.5	0.06	-8.5	-16.5; -0.4	**0.04**	-13.9	-24.4; -3.4	**0.01**
Periodic limb movement arousals index, /hr	Model 1	0.2	-1.5; 1.8	0.84	1.3	-0.7; 3.3	0.19	-0.3	-2.2; 1.7	0.8	1.2	-1.2; 3.5	0.31
	Model 2	0.2	-1.5; 1.9	0.81	1.6	-0.5; 3.6	0.13	-0.2	-2.2; 1.8	0.85	1.3	-1.1; 3.7	0.28
Periodic limb movement index, /hr	Model 1	4.9	-2.8; 12.7	0.21	9.5	-3.6; 22.6	0.15	4.4	-6.2; 15	0.41	9.2	-6.3; 24.7	0.24
	Model 2	4.6	-3.2; 12.5	0.25	11.2	-2.5; 24.9	0.11	4.9	-5.8; 15.6	0.37	10.8	-5.5; 27.1	0.19

Subset 1: Excluding patients on psychoactive medication (n=73), Subset 2: Excluding patients on levodopa and dopaminergic agonists at nighttime (n=101), Subset 3: Excluding patients on psychoactive medication and patients on levodopa and dopaminergic agonists at nighttime (n=60).
Adjusted for age, sex, and body mass index.
Bold values are statistically significant.
Abbreviations: PIGD postural instability and gait difficulty, TST total sleep time, REM rapid-eye movement

Appendix material 3:

Table A2. Linear regression models comparing different OSA-related sleep variables between the motor subtypes of Parkinson's disease.

	Model of adjustment	PIGD vs. non-PIGD											
		Full sample (n=146)			Subset 1* (n=73)			Subset 2* (n=101)			Subset 3* (n=60)		
		β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
AHI, /hr	Model 1	-5.2	-12.3; 1.8	0.15	-10.4	-20.5; -0.4	**0.04**	-10.4	-17.7; -3	**0.006**	-13.9	-22.7; -5	**0.003**
	Model 2	-6.7	-13.6; 0.1	0.05	-10.2	-20.5; 0.05	0.05	-10.4	-17.8; -3.1	**0.006**	-13.4	-22.6; -4.3	**0.005**
	Model 3	-6.6	-13.1; -0.1	**0.047**	-8.1	-16.9; 0.7	0.07	-9.7	-16.6; -2.9	**0.006**	-12.3	-20.3; -4.3	**0.003**
ODI, /hr	Model 1	-2.4	-6.3; 1.4	0.21	-2.3	-8.1; 3.5	0.43	-3.8	-7.6; 0.08	0.06	-2.9	-7.6; 1.9	0.23
	Model 2	-3.4	-7.2; 0.3	0.08	-2.2	-8.1; 3.8	0.47	-3.8	-7.7; -0.03	**0.048**	-2.6	-7.4; 2.2	0.29
	Model 3	-3.4	-7.2; 0.3	0.08	-1.4	-7.4; 4.6	0.64	-3.6	-7.5; 0.3	0.07	-2.6	-7.8; 2.6	0.32
RDI, /hr	Model 1	-4.8	-11.6; 2	0.17	-11.6	-21.3; -1.9	**0.02**	-10.1	-17.5; -2.7	**0.008**	-14.8	-24.3; -5.4	**0.003**
	Model 2	-6.2	-12.9; 0.4	0.07	-9	-17.6; -0.5	**0.04**	-10.1	-17.6; -2.6	**0.009**	-14.2	-23.9; -4.4	**0.005**
	Model 3	-5.3	-11.3; 0.7	0.08	-8.1	-16.4; 0.2	0.06	-8.9	-15.4; -2.3	**0.009**	-11.5	-19.9; -3	**0.009**
Respiratory arousals index, /hr	Model 1	-3.9	-11.4; 3.5	0.3	-12.5	-23; -1.9	**0.02**	-10.1	-18; -2.2	**0.01**	-16.1	-26.2; -5.9	**0.002**
	Model 2	-5.3	-12.7; 1.9	0.15	-12	-22.9; -1.2	**0.03**	-10	-18; -2	**0.02**	-15.3	-25.9; -4.7	**0.005**
	Model 3	-4.1	-10.7; 2.5	0.23	-8.2	-17.3; 0.9	0.08	-8.6	-15.5; -1.7	**0.02**	-11.9	-21; -2.9	**0.01**
RDI REM, /hr	Model 1	-11.3	-33.4; 10.8	0.31	-28.6	-68.9; 11.8	0.16	-17.3	-47.7; 13	0.26	-31.4	-80.2; 17.5	0.2
	Model 2	-10.9	-33.3; 11.6	0.34	-30.1	-71.8; 11.6	0.15	-17.3	-47.9; 13.3	0.26	-22.6	-74.4; 29.1	0.38
	Model 3	-7.8	-30.7; 15.1	0.5	-19.6	-62.5; 23.3	0.37	-13.8	-44.6; 16.9	0.37	-20.9	-73.8; 32	0.43
RDI NREM, /hr	Model 1	-7.8	-17.4; 1.8	0.11	-16.8	-33.3; -0.33	**0.046**	-15	-27; -2.9	**0.015**	-22.2	-40.6; -3.7	**0.019**
	Model 2	-8.8	-18.2; 0.7	0.07	-16.8	-33.7; 0.1	0.05	-14.9	-26.9; -2.9	**0.016**	-22.6	-41.3; -3.8	**0.019**
	Model 3	-7.1	-16.3; 1.9	0.12	-11.9	-28.1; 4.4	0.15	-12.7	-24.1; -1.2	**0.03**	-16.1	-35; 2.8	0.09
RDI supine, /hr	Model 1	-14.3	-32.2; 3.6	0.12	-24.1	-60.2; 12.1	0.19	-24.6	-49.6; 0.4	0.05	-31.1	-74.5; 12.2	0.16
	Model 2	-15.7	-33.7; 2.2	0.09	-28.1	-65.8; 9.6	0.14	-24.9	-49.7; -0.3	**0.048**	-35.3	-79.3; 8.7	0.11
	Model 3	-9.8	-27.7; 8.1	0.28	-16.7	-52.9; 19.5	0.36	-17.5	-42.2; 7.2	0.16	-20.8	-64.7; 23.1	0.35
RDI non-supine, /hr	Model 1	-10.6	-23.6; 2.5	0.11	-18.9	-40.3; 2.4	0.08	-20.7	-38; -3.3	**0.02**	-26.3	-51.9; -0.7	**0.044**
	Model 2	-12.2	-25.2; 0.8	0.07	-19.8	-41.7; 2.2	0.08	-22.5	-39.8; -5.1	**0.012**	-29.4	-54.7; -4.2	**0.024**
	Model 3	-11.2	-24.5; 2.1	0.097	-12.8	-36.3; 10.6	0.28	-17.9	-35.5; -0.3	**0.047**	-16.1	-46.8; 14.5	0.29
TST SpO_2 below 90%, %	Model 1	-0.3	-1.2; 0.5	0.45	0.06	-1.3; 1.4	0.93	-0.5	-1.6; 0.7	0.43	-0.1	-1.8; 1.5	0.86
	Model 2	-0.5	-1.3; 0.4	0.27	-0.1	-1.5; 1.4	0.89	-0.5	-1.7; 0.08	0.39	-0.3	-2; 1.4	0.73
	Model 3	-0.5	-1.4; 0.3	0.22	0.2	-1.3; 1.7	0.79	-0.5	-1.7; 0.6	0.37	0.01	-1.8; 1.8	0.99

Subset 1: Excluding patients on psychoactive medication (n=73), Subset 2: Excluding patients on levodopa medication at nighttime (n=101), Subset 3: Excluding patients on psychoactive medication and patients on levodopa and dopaminergic agonists at nighttime (n=60).
All patients – Model 1: Unadjusted Model 2: Adjusted for age, sex, and body mass index; Model 3: Adjusted for age, sex, body mass index, total sleep time in stage N3, total sleep time in stage REM, and total sleep time in the supine position.
*All subsets – Model 1: Unadjusted; Model 2: Adjusted for age, sex, and body mass index; Model 3: Adjusted for total sleep time in stage N3, total sleep time in stage REM, and total sleep time in the supine position.
Bold values are statistically significant.
Abbreviations: PIGD postural instability and gait difficulty, AHI apnea-hypopnea index, ODI oxygen desaturation index, RDI respiratory disturbance index, REM rapid-eye movement, NREM non-rapid eye movement, SpO_2 blood oxygen saturation

Appendix material 4:

Table A3. Linear regression models evaluating the relationship between the apnea-hypopnea index and MDS-UPDRS IV scores.

	Model of adjustment	UPDRS part IV score											
		Full sample (n=146)			Subset 1 (n=73)			Subset 2 (n=101)			Subset 3 (n=60)		
		β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
AHI, /hr	Model 1	0.3	-0.7; 1.3	0.56	-0.2	-1.7; 1.2	0.75	-0.1	-1.3; 1.1	0.86	-0.3	-1.7; 1.1	0.66
	Model 2	0.5	-0.5; 1.4	0.3	0.1	-1.4; 1.6	0.87	-0.06	-1.2; 1.1	0.93	-0.02	-1.5; 1.4	0.98

Model 1 = Unadjusted, Model 2 = Adjusted for age, sex, and body mass index
Abbreviation: AHI apnea-hypopnea index