Chapter

The Relationship between Amyotrophic Lateral Sclerosis and Parkinson's Disease and Sleep Disorders: Pathophysiological and Clinical Approach

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Abstract

This chapter focuses in the interrelationship between sleep and two neurodegenerative disorders: Amyotrophic Lateral Sclerosis [ALS] and Parkinson's disease [PD]. Sleep disorders have deleterious effect on the quality of life and survival in these neurodegenerative disorders, while the reverse is also true where neurodegenerative disorders significantly impair the sleep, leading to a vast sleep complains that worsen the clinical course of these conditions. Other neurodegenerative disorders such as dementias, spinocerebellar ataxias, atypical parkinsonism, etc. will not be cover in this chapter.

Keywords: sleep, amyotrophic lateral sclerosis, hypoventilation, Parkinson's disease, parkinsonism

1. Introduction

Given the effect of neuromuscular disease on respiratory muscle strength (including the diaphragm, upper airway and accessory muscles), it is an undeniable fact, that neuromuscular disease can cause disruption of sleep. In general, sleep disorders are underrecognized in this population, as their secondary effects can mimic symptoms of the underlying disease. Recognizing sleep-related disorders in patients with neuromuscular disease such as Amyotrophic Lateral Sclerosis (ALS) is of utmost importance, as they are potentially treatable problems and their correction can improve quality of life and even increase survival time [1].

ALS is an incurable neurodegenerative disorder of upper and lower motor neurons, which is characterized by degeneration of the corticospinal tracts, resulting in loss of motor neurons in the brain, brainstem and anterior horn cells of the spinal cord. Age of onset of disease is in the sixth decade of life and is usually

sporadic, though a minority of patients have familial disease. Numerous abnormalities exist in cellular and molecular function in ALS, including protein aggregation, mitochondrial dysfunction, DNA and RNA processing and central nervous system inflammation [2].

The hallmark of clinical disease is the presence of both upper and lower motor neuron signs. Weakness in ALS starts as asymmetrical or focal, and then progresses to generalized weakness, ultimately affecting all skeletal muscles. Loss of motor neurons in the brainstem and spinal cord causes weakness of the pharyngeal, laryngeal, intercostal and diaphragmatic muscles. This predisposes patients with ALS to respiratory dysfunction (the physiology behind this to be detailed below). When respiratory dysfunction becomes severe, tracheostomy and permanent ventilation are required. From the time of the diagnosis the median survival time is 3 to 5 years. The most common cause of death in ALS is respiratory failure [3, 4].

There are two FDA approved medications for ALS. Riluzole was approved in 1997 and provides a modest survival benefit of 3 months. A second medication, Edaravone, a free radical scavenger, was approved in 2017, but is only approved for use in ALS patients without respiratory insufficiency, and is controversial for clinical use due to its burdensome administration schedule and questionable clinical efficacy [5]. Numerous clinical drug trials have failed to demonstrate marked clinical benefit in ALS. However, provision of non-invasive ventilation has shown survival benefit in some ALS patients [6]. The dearth of effective treatment options for ALS underscores the importance of modifying those factors that optimize quality of life and extension of survival, particularly sleep and respiration.

2. Pathophysiology

Adequate involuntary ventilation is essential for effective sleep. The pathway by which voluntary ventilation occurs involves the cerebral cortex, brainstem and corticospinal tracts to motor neurons in the C3-C5 spinal segments which supply the phrenic nerve. The phrenic nerve innervates the diaphragm. In the state of wakefulness (in which both voluntary and involuntary ventilation persists), the diaphragm is the major inspiratory muscle and is assisted by accessory muscles. The accessory inspiratory muscles include the intercostals, trapezius, scalenes, sternocleidomastoid and pectoralis major muscles. Involuntary or automatic breathing involves the respiratory centers in the brainstem (pons and medulla). This is the central respiratory drive. Oxygen and carbon dioxide levels sensed by chemoreceptors (peripheral and central) directly influence automatic breathing (which is then carried out through the spinal segments formerly mentioned innervating the diaphragm through the phrenic nerve). During non-REM sleep, muscle tone is decreased and during REM sleep muscle tone is almost completely lost. Automatic ventilation during sleep is almost completely dependent on the diaphragm (particularly in REM sleep) therefore diaphragmatic dysfunction (such as that seen in ALS) can predispose to hypoventilation and nocturnal hypoxemia. The sensitivity of chemoreceptors is also reduced during sleep [1].

Effective sleep also depends on maintaining a patent upper airway. Patency of the upper airway is dependent on secondary muscles of respiration, which include the muscles of the pharynx. Pharyngeal muscle tone is maintained by trigeminal sensory afferents during inspiration, when negative pressure is generated. This prevents upper airway collapse. Weakness of pharyngeal muscles (such as in ALS) leaves one susceptible to airway collapse and the upper airway resistance seen in obstructive sleep apnea [1].

3. Clinical features of sleep disturbances in amyotrophic lateral sclerosis

Sleep disorders are quite prevalent in patients with ALS, but often under-reported, misdiagnosed, and undertreated. It has been shown that the onset of nocturnal breathing abnormalities often precedes the onset of overt daytime respiratory dysfunction [3]. A recent study showed that sleep disorders occur in 70 percent of patients with ALS, where 65 percent have insomnia, 50 percent have sleep-breathing disorders including hypoventilation, and 85 percent suffer from night-time awakening related to ALS symptoms [7].

The most common form of sleep disturbance encountered in ALS is due to hypoventilation, rather than obstructive nocturnal events [8]. As ALS progresses, the involvement of the respiratory muscles is unavoidable; this results in nocturnal hypoventilation [9, 10]. Hypoventilation is the primary etiology of nocturnal oxygen desaturation (hypoxemia) in patients with ALS. This is due to bilateral phrenic nerve dysfunction resulting in diaphragmatic weakness or paralysis [11]. Nocturnal hypoventilation is first present when supine, as this is where the diaphragm is put at its worst mechanical disadvantage resulting in a drop in lung volumes [3, 12]. Diaphragmatic dysfunction in ALS is of particular concern in regard to sleep-disordered breathing as the diaphragm is the sole active respiratory muscle during REM sleep (where accessory and intercostal muscles are naturally inhibited) [13]. For this reason, nocturnal hypoventilation is especially worse during REM sleep [12, 14].

Quality of sleep in those without advanced disease can be normal (although quality of life is impacted by respiratory muscle weakness) [11]. As the disease progresses fragmentation of stage N3 of sleep occurs due to loss of circadian rhythms [13]. All stages of sleep are eventually affected resulting in daytime hypercapnia which is defined as an elevated $CO2 > 45$ mm Hg. Hypoxemia and hypercapnia result from respiratory failure and the hypoventilation syndrome caused by restrictive thoracic disease from weakness of respiratory muscles. This hypoventilation syndrome results in a decrease in sensitivity of chemoreceptors due to chronic hypercapnia [15]. Hypoventilation is further complicated with the co-existence of sleep-breathing disorders.

Sleep-breathing disorders are common in ALS. Oropharyngeal weakness affecting dilatory muscles leads to obstructive sleep apnea that presents like in non-ALS OSA patients with snoring, snorting, apneas, and frequent nocturnal arousals [16]. In a study of 18 patients with ALS, it was found on polysomnography that total sleep time was decreased, and frequency of sleep-disordered breathing and arousals were higher than in age-matched controls. Eight of these patients were found to have periods of hypoventilation (most often during REM sleep). There were no recorded apneas. Bulbar involvement did not show a significant association with degree of sleep-disordered breathing [2]. Bulbar weakness does however predispose to obstructive sleep apnea due to weakness of tongue protrusion and palatal control. Bulbar weakness is also associated with increased secretions and weak cough [13]. That being said, since patients with bulbar ALS have tongue atrophy, they have less prevalence of OSA [17, 18]. Central sleep apneas in ALS patients may result from central motor neuron impairment, though they are less frequent than OSA [15].

Particular importance should be placed on addressing respiratory muscle weakness (hypoventilation) rather than the number of apneas or hypopneas on polysomnography in ALS patients [11]. OSA is common in ALS and if untreated shortens the survival of ALS patients [3, 12]. Non-invasive positive pressure ventilation can prolong time to tracheostomy and provide benefit in regard to quality of life in the setting of respiratory muscle weakness and sleep-disordered

breathing [11]. Therefore, when OSA is suspected a polysomnogram should be requested to confirm its diagnosis.

In regard to the effects of sleep-disordered breathing on quality of life, ALS patients often complain of excessive daytime sleepiness resulting from nocturnal sleep fragmentation and insomnia. Nocturnal hypoventilation results in orthopnea, morning headaches, excessive daytime sleepiness, and cognitive dysfunction [12, 17]. A study showed the most common nocturnal complaints in ALS patients were nocturia, sleep fragmentation, and cramps (each seen in about half of the patients) [19]. **Table 1** shows the common sleep disturbances seen in ALS.

Nocturnal restlessness, sleep fragmentation with multiple awakening, snoring, and apneas leads to excessive daytime sleepiness, difficulties to arouse in the morning, difficulties to arouse from sleep, cognitive problems and poor work performance. In severe cases when insomnia and sleep continuity is severely impaired patients develop lethargy, cyanosis, early morning headaches, nausea and vomiting and leg edema. **Table 2** shows the most common sleep features in ALS patients.

Patients with ALS suffer from other conditions that also affect the sleep such as restless leg syndrome (RLS), REM-sleep behavior disorder (RBD), cramps, immobility-associated discomfort, pain, depression-related sleep disorders and dementia-related sleep disorders which may affect the sleep continuity. Even patients newly diagnosed with ALS have shown poor sleep quality related to depression and poor nocturnal mobility [12, 17, 19].

There are important secondary cardiopulmonary effects of chronic nocturnal hypoxemia that should not be overlooked. These include pulmonary hypertension, right heart failure and arrhythmia. There is also an increased risk of stroke, myocardial infarction and lethal cardiac arrhythmias. This highlights the critical

Insomnia
Excessive daytime sleepiness
Sleep fragmentation
Sleep related hypoventilation
Sleep breathing disorders

Table 1.
Sleep disturbances in ALS.

Nocturnal features	**Daytime features**
Nocturnal restlessness	Excessive daytime sleepiness
Sleep fragmentation	Increase daytime napping
Increase WASO	Fatigue
Insomnia	Poor concentration
Apneas/hypopneas	Poor work performance
Snoring/snorting	Morning lethargy
Orthopnea	Morning headaches
Respiratory interruptions	Cognitive dysfunction
Difficulty to aroused in the morning	
Nocturnal cyanosis	
Choking	
Nocturia	
Nocturnal cramps	
Nightmares	

WASO: wake after sleep onset.

Table 2.
Sleep-related features in ALS.

need to diagnose and treat sleep-disordered breathing early particular in ALS where lifespan is devastatingly shortened [20].

4. Diagnosis

Essential to the identification of ALS patients with sleep abnormalities is maintaining a high index of suspicion and taking a detailed sleep history. This ideally takes place with a family member or caregiver present (or anyone who may share a bed with the patient). This second party can provide history regarding the patient's behaviors during sleep and functioning in the daytime (some of which the patient himself/herself may not be aware of). Specific questions regarding the presence of excessive daytime sleepiness, cognitive dysfunction, orthopnea, apneas and snoring are essential. Frequent awakenings, snoring and choking are clues for suspecting obstructive sleep apnea. Nocturnal orthopnea is often an early sign of respiratory dysfunction causing hypoventilation. Commonly used screening tools for sleep disorders include STOP-BANG, Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index Scale [3]. All patients with respiratory dysfunction or bulbar weakness should be screened for sleep disorders. Close attention should be placed on examining for signs of respiratory dysfunction such as accessory muscle use (particularly when supine). Increased work of breathing can result in weight loss and cachexia. Patients with bulbar dysfunction progressively develop changes in their voice, difficulty clearing secretions, weak cough and difficulty swallowing [21].

There are multiple modalities that can be utilized in the diagnostic evaluation of respiratory muscle weakness and sleep disorders in ALS. The use of more than one modality increases the precision and accuracy of the diagnosis and prevents over- or underestimation of respiratory muscle strength [20]. **Table 3** outlines the different laboratory investigations used to diagnose sleep disorders in ALS.

If hypoventilation is suspected, then spirometry should be requested. Clinical indicators include excessive daytime sleepiness, morning headaches, frequent nocturnal waking, and vivid dreams [22]. Forced vital capacity (FVC) has long been used to predict survival and disease progression in ALS patients. Faster progression of disease has been associated with FVC < 75 percent of predicted value. A more accurate measure of weakness of the diaphragm is supine FVC however this can be difficult to evaluate [21, 22]. The difference between standing and supine FVC correlates with orthopnea and a fall from sitting to supine >20 percent has a sensitivity of 90 percent for identifying diaphragmatic weakness [12], whereas sitting FVC < 50 percent has only a sensitivity of 58 percent. Despite wide availability in obtaining FVC it is not as sensitive for early respiratory dysfunction and values may be inaccurate in patients with bulbar dysfunction who cannot maintain a tight seal on the mouth piece [21].

Arterial Blood Gas (ABG)
Pulmonary Function Tests
• Sitting and supine forced vital capacity (FVC)
• Maximal inspiratory pressure (MIP)
• Maximal expiratory pressure (MEP)
Sniff Nasal Pressure (SNP)
Overnight Pulse Oximetry
Polysomnography (PSG)

Table 3.
Investigations commonly used to detect sleep disorders in amyotrophic lateral sclerosis.

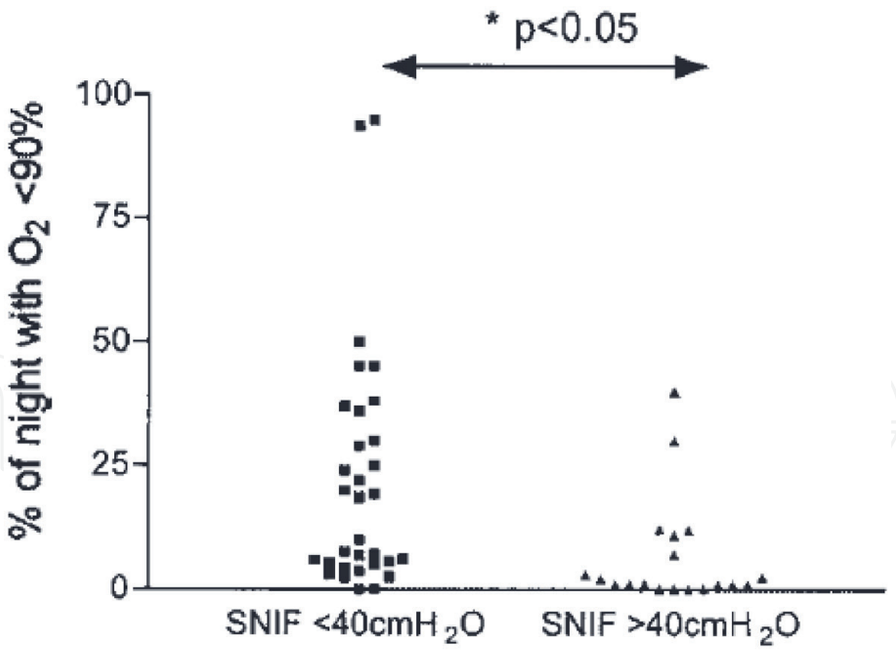

Figure 1.
Scatterplot of the proportion of the night spent with nocturnal hypoxemia (defined as oxygen saturation < 90 percent) in ALS patients with SNIF <40 cm H2O compared to those with SNIF >40 cmH2O [24].

The sniff nasal transdiaphragmatic pressure (SNIP) is a strong predictor of diaphragmatic muscle strength. It is a non-invasive inspiratory volitional test. It can also be used to monitor progression of disease [21]. In addition, SNIP testing is not limited by the requirement of securing an adequate seal over the instrument's mouthpiece, rendering it advantageous for evaluation of patients with prominent cranio-bulbar weakness. The sniff test has a sensitivity of 97 percent for a sniff value <40 cm H2O for predicting six-month mortality, compared to 58 percent sensitivity of VC < 50 percent [23, 24]. SNIP value <40 cm H2O is strongly correlated with nocturnal hypoxemia in ALS patients [24] (see **Figure 1**). This predictive value for nocturnal hypoxemia was not seen with other measures of respiratory sufficiency such as MIP and FVC [24].

Maximal inspiratory pressure (MIP) and maximal expiratory pressures (MEP) are useful for predicting early respiratory muscle weakness. MIP is done by inspiring from residual lung volume. MEP is done by having the patient maximally expire against a closed airway. MIP > 80 cm H2O or MEP > 90 cm H2O excludes significant respiratory muscle weakness [21]. MIP < 40 cmH2O also identifies people at risk of hypoventilation. This test may underestimate the degree of respiratory muscle weakness as it involves a mouthpiece and those with facial or bulbar weakness may not form a tight seal around it. This test does require effort on the part of the patient [21].

Nocturnal pulse oximetry and capnography can also be used for screening for hypoventilation. Nocturnal pulse oximetry is often the first test ordered when sleep disturbance is suspected as it is inexpensive and non-invasive [20]. Nocturnal desaturation <90 percent for >5–10 percent of the time may suggest hypoventilation [23]. A nocturnal desaturation to less than 90 percent for one minute is also helpful to diagnose hypoventilation [22]. Patterns seen in early disease suggestive of hypoventilation are cyclical desaturations with low baseline oxygen saturation. This pattern is also seen in COPD or interstitial lung disease and nocturnal pulse oximetry cannot distinguish between these conditions. There are also some technical problems with nocturnal pulse oximetry as the oximeter can become dislodged or readings can be inaccurate in the setting of anemia. [20] Capnography is utilized

in diagnosing hypoventilation by measuring a nocturnal transcutaneous carbon dioxide [PtcC02] increment of >10 mm Hg above 50 mm Hg for >10 min. This is performed with simultaneous pulse oximetry recording to compensate for possible aberrant valuates seen at times with PtCO2 [25].

Nocturnal and daytime arterial blood gases (ABG) is another tool that can be used to predict nocturnal hypoventilation resulting in hypoxia (PaO2 < 60 mm Hg) and hypercapnia (PaCO2 > 45 mm Hg). Nocturnal hypoventilation is suggested by an increase of PaCO2 by 10 mm Hg when comparing nocturnal to daytime values. This method is more invasive, and disparities can sometimes only be seen late in the disease [20]. Hypoventilation can also be diagnosed by ABG with hypercapnia defined as a cut off of PCO2 > 45 mm Hg while resting in a seated position for 15 min [26].

In-laboratory overnight polysomnography is the gold standard for the diagnosis of hypoventilation and OSA. At home tests are not recommended for patients with neuromuscular disease as these are limited studies. The standard polysomnogram consists of at least 3 electroencephalography (EEG) channels, chin and leg electromyography (EMG), 2 eye (electrooculogram) leads, effort channels, flow channels, electrocardiography and SaO2. This allows for tracking and monitoring the stages of sleep, SaO2 abnormalities and any abnormal movements [20]. Polysomnography [PSG] with capnography [transcutaneous PCO2] detects sleep-related hypoventilation [PCO2 increment more than 10 mmHg during sleep versus wakefulness, especially during REM] and is more sensitive than oximetry. One third of the patients with confirmed sleep hypoventilation have normal oxygenation [12, 19]. Using PSG, the etiologies of sleep disturbances can be distinguished using analysis of this multimodal test and patterns of SaO2 abnormalities. This allows for recognition of hypoxemia that is event related (obstructive sleep apnea) or due to hypoventilation (or a combination of both) [20].

The measurement of diaphragmatic thickening using ultrasound is a new developing technique that predicts hypoventilation, though no cut off value has been established [19].

5. Treatment

Basic sleep hygiene should always be emphasized with the patient and family as the usefulness of these interventions is often overlooked. Treatment of comorbid conditions that may be contributing to sleep disorders or fatigue such as hypothyroidism, depression or obesity should also be addressed.

The mainstay of treatment of sleep-disordered breathing in ALS is through assistance of the weakened respiratory muscles with positive upper airway pressurization [20]. Non-invasive positive pressure upper airway ventilation [NIV] should be considered when hypoventilation is clinically suspected and confirmed with spirometry [19]. Practice parameters recommend initiation of NIV when SNIP falls below 40 cm H2O, FVC < 50%, or in the setting of abnormal nocturnal oximetry [22].

It is well established, that NIV improves symptoms of sleep disturbance, quality of life and cognitive function and is primarily indicated in sleep-disordered breathing and inspiratory muscle dysfunction. NIV may also prolong tracheostomy -free survival [19]. Studies have shown a slower rate of decline of FVC and pulmonary function with use of NIV in ALS patients. Benefit in survival correlated with at least 4 hours of NIV use at night [20]. Most patients with ALS will need NIV at first while sleeping, but later as symptoms progress with more dyspnea and hypercapnia/hypoxemia-related-symptoms NIV will be required for longer periods of ventilation and then continuously [12, 19]. They are at first treated with NIV and

finally with tracheostomy with total ventilator support, if elected by the patient, or with supportive measures in hospice until death.

The aim of NIV is normalization of hypercapnia, hypoxia, and the apnea-hypopnea index. This results in improvement of the sleep architecture and prolonged survival up to one year [19]. NIV is divided in pressure-assisted control where partial pressure is provided and volume-assisted control where the patient receives a predefined gas volume. Volume-assisted control has the advantage of overcoming airflow obstruction and being effective in obstructive events, but it has the disadvantage of an uncomfortable feeling caused by the ventilation and no compensation for leaks [27]. The pressure assisted control is more comfortable and it compensates for leaks. One study showed greater survival with pressure-assisted over volume-assisted ventilation [28]. NIV using nasal ventilation is preferred because it allows speech and induces a lower rate of OSA. Patients require close surveillance in the first few days of use to determine proper the settings and then monthly or quarterly evaluations thereafter. NIV failure is most commonly caused by leaks [29] and the coexistence of untreated OSA that increases mortality.

Bronchial congestion caused by weak coughing and excessive sialorrhea may also cause failure of NIV therapy. Sialorrhea may be treated with drugs [atropine, scopolamine, belladone tincture], and if these drugs fail with salivary glands radiation; Botox injections are not recommended. Keeping the head up to avoid supine position, cervical collars, or mandibular advancement may also be helpful in addition to NIV [19].

To assist cough, mechanical insufflation-exsufflation (MI-E) devices can be prescribed to patients in order to clear airway secretions and prevent development of pneumonia. These devices administer pressure (both positive and negative, as might be done in a voluntary cough) artificially and can be used via face mask or tracheostomy [30].

It is important to mention, that bulbar dysfunction poses some management challenges in regard to the use of NIV. Compliance with use of NIV in these patients is lower due to decreased tolerance. As previously mentioned, hypersalivation in these patients worsens prognosis with NIV and requires symptomatic treatment. The initial study that showed increased survival with use of NIV [31] in patients with ALS did not show benefit in patients with severe bulbar symptoms however more recent studies have contradicted this. For this reason, treating symptoms that limit NIV usage in these patients is essential. Full face masks rather than the nasal mask are necessary for patients with bulbar dysfunction due to incomplete mouth closure [32].

6. Sleep disorders in Parkinson disease

Parkinson Disease [PD] is the second most common neurodegenerative disorder after Alzheimer's disease [33]. PD occurs as a result of chronic, progressive decrease in dopamine levels of the substantia nigra, secondary to loss of dopaminergic neurons in the pars compacta and the occurrence of Lewy bodies in the cytoplasm of remaining neurons [34]. It is primarily diagnosed clinically and patients may present with the characteristic motor deficits, which include the resting tremor, bradykinesia, rigidity and postural instability. However, most will have both motor and nonmotor symptoms. The nonmotor symptoms cause disturbances, which affect sleep, mood, cognition, sensation and autonomic function. Among the nonmotor symptoms in PD, sleep disorders are second in frequency only to neuropsychiatric disorders [35].

It is estimated that between 55 to 80 percent of PD patients suffer from sleep disorders [SD] [36, 37]. Sleep can be affected in a multitude of ways with the most common SD displayed in **Table 4**. Some disturbances will precede the disease, while others are indicators of disease progression. In many cases, more than one sleep

Nocturnal sleep disorders	Diurnal sleep disorders
Insomnia	Excessive daytime sleepiness
Circadian rhythm disorders	Sleep attacks
Sleep breathing disorders	
Restless leg syndrome	
Periodic limb movements of sleep	
Rapid Eye Movement (REM) sleep behavior disorder	
Nocturia	

Table 4.
Sleep disorders in PD.

disorder may coexist in the same patient. Poor sleep, particularly if chronic, will have an impact on daily activities causing excessive daytime sleepiness [EDS] and sleep attacks [SA]. The neurodegenerative process caused by PD itself will exacerbate daily drowsiness, as well as certain medications [38]. Therefore, a detailed sleep history in a patient with PD is imperative to identify symptoms in order to treat accordingly and monitor their progression. There is evidence to suggest that improving a patient's quality of sleep not only will improve their quality of life, but can also lead in an improvement of their motor symptoms.

Another important consideration for patients with bradykinesia and rigidity, who may have trouble turning in bed at night or getting to the bathroom - is using an extended release formulations as their last dose of the day that might disrupt their sleep or, even worse, lead to falls.

Two validated scales were created to assess the severity of the impact of PD [Parkinson Disease Sleep Scale (PDSS) and Scales for Outcome in PD Sleep [SCOPA-S] [39, 40].

7. Sleep architecture changes in PD

Patients with PD often have many sleep architecture changes, the most common ones are shown in **Table 5**. The sleep architecture abnormalities include intrinsic brain changes caused by the underlying neurodegenerative disorder, co-existent sleep disorders, nocturnal motor symptoms, and dopaminergic medications.

8. Nocturnal sleep disorders

8.1 Insomnia

Insomnia affects approximately 50 to 60% of patients with PD, making it the most common sleep disorder and perhaps the most complex to treat given its multifaceted basis [42]. When it lasts for more than three months, it is considered chronic insomnia [43].

It can be further classified into the following patterns:

- Sleep-onset insomnia: when the patient has difficulty falling asleep
- Sleep-maintenance insomnia, also referred as sleep fragmentation: when the patient has difficulty staying asleep
- Terminal insomnia: when the patient awakens involuntarily earlier than usual

Decreased total sleep time
Increased sleep latency
Increased sleep fragmentation
Increase WASO
Decreased sleep efficiency
Decreased spindles
Decreased N3 stage
Decreased REM stage

WASO: wake after sleep onset. N3; NREM slow waves stage [41].

Table 5.
Sleep architecture in PD.

The most common insomnia is sleep-maintenance insomnia seen in 80 percent of patient with PD, whereas sleep onset and terminal insomnia are seen in 18 percent and 40 percent of the PD patients, respectively [36, 37, 44, 45]. Insomnia is more prevalent in women, those with longer PD duration, and those with depression or anxiety. The causes of insomnia is multifactorial and includes the neurodegenerative process of PD itself, co-morbid sleep disorders, nocturia, cramps, limitation in mobility (i.e. difficulty turning in bed), early morning leg dystonia, pain, confusion, urinary dysfunction, sleep breathing disorders [SBD], and drugs [36, 42, 45, 46, 47]. Circadian rhythm disorders and psychiatric disorders [depression, anxiety, hallucinations, etc.] may also contribute in the genesis of insomnia [45–47].

Before deciding on a treatment option for insomnia, it is important to establish the specific pattern of insomnia and other risk factors that may be contributing to the condition. For example, addressing motor symptoms and/or obstructive sleep apnea may significantly improve insomnia therefore reducing or even eliminating the need for pharmacological interventions.

Almost half of patients with PD take medications for insomnia [36, 37, 42]. The use of levodopa-carbidopa controlled release [LD-CD] at bedtime may reduce motor bradykinesia/akinesia with improvement in total sleep time [48]. Dopamine agonists [DA] such as ropinirole-24 hour prolonged release (2-24 mg/day) [49], pramipexole (up to 4.5 mg/day) and transdermal rotigotine patch (up to 16 mg/day) [50] can be used as adjuncts to LD-CD. This combination has shown to improve both nocturnal motor activity and sleep symptoms. Two trials with transdermal rotigotine patch demonstrated improvement not only nocturnal motor symptoms but also wake time after sleep onset [WASO], nocturia, pain, RLS with reduced daily sleep episodes and overall improved quality of life in PD patients [51, 52]. MAO-inhibitor rasagiline has shown to improve total sleep time and reduce sleep latency when used in combination with LD-CD compare to when LD-CD is used alone [53]. Rasagiline's beneficial effects on insomnia are likely related to an increment in melatonin levels.

After motor impairment and co-existent sleep disorders are identified and treated, insomnia can further be managed with cognitive behavioral therapy utilizing sleep hygiene techniques, stimulus control, sleep restriction, relaxation techniques, and cognitive therapy [53, 54]. Soporific drugs such as eszopiclone, zolpidem, doxepin, trazodone, ramelteon, and melatonin have been used with various success in the therapy of insomnia in PD patients [44]. Melatonin at very high doses (50 mg) at bedtime was compared with 5 mg/day at the bedtime in the treatment of insomnia in PD patients. Melatonin 50 mg dose showed a statistical significant improvement in total sleep time compared to lower doses, however melatonin at 5 mg improved subjective sleep disturbance, sleep quantity, and daytime drowsiness compared to placebo. Melatonin may be associated with morning headaches, hallucination, and daily drowsiness [55].

8.2 Nocturia

Nocturia is defined as an increase in the frequency of nocturnal urination. About one third of PD patients suffer from nocturia [56]. Nocturia in PD is most likely a result of autonomic dysfunction caused by detrusor hyperreflexia from lack of dopamine which decreases the inhibition of micturition. However, it is important to rule out secondary organic causes of nocturia (such as urinary tract infections, prostrate disorders, anxiety, congestive heart failure, etc.) before altering anti-Parkinson medication doses [45, 48].

Subcutaneous apomorphine at a dose of 3-8 mg at bedtime has been used to treat nocturia as it reduces the hyperreflexia in the detrusor muscles [57]. Rasagiline at a dose of 1 mg/day can increase bladder capacity and decreases residual volume [58]. Intranasal desmopressin and botulinum toxins in the detrusor muscles may be beneficial. Anticholinergic drugs [oxybutynin, solifenacin, darifenacin, tolterodine], can potentially help with nocturia, although the side effects of these drugs (drowsiness and cognitive impairment) might be an impediment [35].

8.3 Restless leg syndrome

Restless leg syndrome [RLS] is a sensorimotor disorder characterized by an unpleasant leg sensation associated with an urge to move the legs, relieved by leg movement, worsen by inactivity and worse at night [43]. RLS is seen in about 20% of patients with PD, which is a higher rate than in the general population [59]. Primary RLS is a genetic disorder, whereas secondary RLS results from other conditions such as renal disease, iron deficiency, co-existence of neuropathies, medications, etc. [43, 60]. PD patients who develop RLS tend to have later PD onset, poor sleep quality and more cardiovascular and anxiety disorders [45, 59]. RLS need to be differentiated from common complain seen in PD patients such as uncomfortable nocturnal motor symptoms secondary to immobility, akathisia and dystonia. The treatment of RLS in PD patients is similar to the treatment for non-PD patients. Identify and treat any underlying secondary causes of RLS first. Iron supplementation is required when ferritin levels are below 50 microg/ml. Antidepressants may worsen RLS symptoms therefore adjustment in dosage or replacement with bupropion with dopaminergic effect is warranted [60, 61]. Antidopaminergic and antihistaminic medications can also worsen RLS [45]. L-dopa-carbidopa is no longer recommended to treat RLS due to the high risk of augmentation (treatment complication from dopaminergic drug with worsening of the RLS symptoms [45, 60, 61]. Dopamine agonists (ropinirole, pramipexole, transdermal rotigotine patches) and GABAergic products (pregabalin, enacarbil, gabapentin) can be used as first line of therapy. The latter being particularly useful in patients with a coexistent neuropathic pain [60, 61]. Other drugs as clonazepam and opioids may be used to induce sleep and treat pain, respectively. New devices that apply pressure to the legs may also relieve RLS symptoms [62].

8.4 Periodic leg moment of sleep

Periodic leg moment of the sleep [PLMS] is a sleep disorder characterized by repetitive leg movements while patient is asleep that result in sleep fragmentation and daily drowsiness. Whereas the diagnosis of RLS is clinical the diagnosis of PLMS is polysomnographic. A PLMS index [leg movements per hour of sleep] of 15 or more is considerate abnormal [43]. PLMS is seen in 80% of patients with RLS [43] and the incidence of PLMS is 30–80% of patients with Parkinson disease [45, 63].

Age and dopamine loss may contribute to PLMS [64]. The mainstay treatment for PLM is the use of dopamine agonists [65].

8.5 REM behavior disorder

REM Behavior Disorder (RBD) is a REM-parasomnia characterized by the ability of the patient to reenact the content of his dreams with complex and violent motor behaviors which varies from vocalization, throwing punches, kicking, flailing, screaming, to jumping from the bed and running. This can cause injuries to the patient and/or to the bed partners [43]. RBD is commonly seen in PD [66] and is more prevalent in the second half of the night when REM sleep occurs [43]. Studies have demonstrated that RBD may manifest years prior to the development of PD symptoms with an estimated 75–90% of RBD patients developing PD after 10 to 14 years from onset [43]. RBD may precede the onset of others alpha-synucleinopathies such as Lewy Body dementia and multiple system atrophy [43]. RBD should be considered in patients presenting with history of "acting out their dreams or motor activation while sleeping" and confirm it with video polysomnography, though not require for its diagnosis. Creating a safe sleeping environment is the first step in management. This condition responds to low dose of clonazepam [0.25-2 mg qhs]. Clonazepam improves total sleep time, sleep efficiency, increase in NREM sleep, and decrease WASO [67, 68]. However, this medication was associated with sedation, cognitive deficits, and increments in falls [45]. Melatonin 3 to 12 mg at night or at higher doses is also helpful in RBD and can be used with dementia and obstructive sleep apnea where clonazepam is not recommended. Melatonin may be used as solo or co-adjuvant therapy for insomnia and at high doses may be associated with morning headaches, sedation, or delusion/hallucinations [45, 69]. Patients who failed clonazepam and melatonin may respond to rivastigmine [70] or ramelteon [71] at night.

8.6 Sleep-breathing disorders

Obstructive sleep apnea (OSA) is the most common sleep breathing disorder (SBD). Other forms of SBDs are also seen in PD such as snoring, central and mixed apneas [43]. OSA is characterized by intermittent and repetitive events of pharyngeal airway collapse with complete upper airway obstruction (apnea) or partial upper airway obstruction (hypopneas) during sleep, especially during REM sleep when the effect of the atonia is more pronounced. Patients present with nocturnal snoring, snorting, sleep fragmentation, insomnia, and daily consequences of daytime sleepiness, fatigue, poor concentration, poor memory, and mood changes. If severe, it is associated with sleep attacks [spells of sudden sleepiness] [43]. The prevalence of OSA in PD varies between 20–60% depending on the methodology used to score respiratory events [45] and according to two recent studies it is more common in PD patients than in the general population [72, 73]. An additional study showed that SBDs are also more common in other forms of parkinsonism such as vascular parkinsonism than controls [74]. From all forms of SBDs [snoring, central sleep apneas and obstructive sleep apneas] OSA is the most common form in PD [74]. This is likely related to multiple factors seen in patients with PD: most PD patients are elders [advanced age is a risk factor for OSA], PD present with autonomic dysfunction [autonomic dysfunction increases the risk for OSA], PD patients share loss of motor neurons from brainstem involved in respiration [reduced respiratory drive] and control oropharyngeal muscles [fluctuating respiratory muscle coordination increases risk for OSA], PD patients have restrictive lung disease caused by chest wall rigidity and upper airway abnormalities as shown spirometry

abnormalities in up 65% patients with PD [75]which increased the risk for upper airway obstruction [42, 74]. The diagnosis of OSA is suspected through history and specific screening questionnaires such as STOP-BANG and Berlin's questionnaire. In PD, STOP-BANG has a high sensitivity, but low specificity in the diagnosis of OSA, whereas the Berlin's Questionnaire has a higher sensitivity in the diagnose of PD, but it sensitivity declines as the severity of PD declines [76]. And it is confirmed with polysomnography at a sleep center or level III portable monitoring at home [77, 78]. OSA may worsen PD as it worsens sleep fragmentation and causes intermittent hypoxia [45, 79, 80] which is associated with worsening in the cognitive function [81, 82]. Sleep disorders are considered one of the most disabling of the non-motor symptoms of PD [83]. The treatment of OSA with PD is the same than in patients without PD: body weight loss, positional therapy, continuous positive airway pressure (CPAP), and surgery [45, 84]. The cognitive impairment often reported in patient with Parkinson disease [81, 82] also improves with positive airway pressure therapy [85].

8.7 Circadian rhythm disorder

Circadian rhythm disorders (CRD) are implicated in the pathophysiology of PD [86], but their real prevalence in PD patients remains unknown [87]. Motor and non-motor features [autonomic function, visual performance, sleep-awake cycles, and response to dopaminergic drugs] experienced a diurnal fluctuation from the circadian system [88]. Dopamine is an intermediary of light providing input to the retinal circadian clock which provides a direct input to the suprachiasmatic nuclei (SCN). Thereby, via retinal dopamine-containing amacrine cells, information is conveyed across a series of clock genes that control the circadian rhythm. Dopamine deficiency, seen in Parkinson disease, affects specific clock genes (dysregulation of Bmal gene expression) resulting in dysfunction of the central sleep–wake cycle control [86, 87]. Studies using actigraphy to record times of wrist motor activity [wakefulness] and times of motor inactivity [sleepiness] showed lower peaks of physical activity during rest time and higher levels of activity at night compared with control [89, 90]. Motor symptoms in Parkinson disease worsen in the afternoon and evening in stable patients and patients with wearing off [advanced PD] indicating that the response to dopaminergic drugs declines throughout the daytime [91]. This decrease in diurnal activity and increase in nocturnal activity observed in PD patients is influenced by dopaminergic drugs [86]. A variability in the pharmacokinetics of levodopa, i.e. faster during daytime and while standing compared with being supine at night, play the role in levodopa variability [92]. Patient with PD with hallucinations show more fragmentation of the rest activity with more unpredictability in the circadian pattern [93].

Autonomic dysfunction, a common feature in PD, also follows a circadian pattern with a nocturnal blood pressure reversal pattern i.e. blood pressure equal or higher than daytime blood pressure as demonstrated in most of the patients in one study [94]. An attenuation of sympathetic nervous system activity in PD patients was demonstrated by a heart rate variability study where power spectral analysis using a 24-hour ambulatory EKG revealed a decrease in total frequency component and low frequency/high frequency ratio [86, 94]. Studies in PD patients have shown a reduction in core body temperature. This reduction in core temperature correlated with higher rates of self-reported RBD symptoms, reduction in percentage of REM sleep, and prolonged latency compared with controls [95].

Hormonal changes are also affected by circadian rhythms in PD. PD patients have shown elevated serum cortisol levels and reduced serum melatonin levels compared with controls [96, 97]. Furthermore, melatonin diurnal fluctuations are

blunted in PD patients [98] which correlates with the self-reported symptoms of EDS [97]. The amplitude in melatonin decreases and melatonin phase advanced in PD treated patients compared with non-treated patients indicating that as PD progresses melatonin decreases with a phase advancement [99]. Dopamine drugs affect the regulation of melatonin circadian pattern and sleep onset patients in PD patients [100].

Circadian rhythm changes affect also visual performance in PD [101] most likely caused by impairment in retinal dopamine content that follows a circadian rhythm independent of light/dark cycles [102] Dopamine agonists may regulate the rhythmic expression of melanopsin in retina ganglion cells [88].

In summery the causes of CRD in PD are multifactorial and some are included below list:

- Disorders of the sleep-awake neuronal circuity controlling the circadian rhythm.
- Hypothalamic dysregulation with a decline of the SCN that lead to reduction in melatonin production and sleep-awake disruption.
- Dysregulation of the genes that control the awake-sleep cycles such as Bmal1 gene and clock genes expression [dopamine regulates the Bmal1/clock activity]
- Disconnection of SCN with neuronal circuitries and hormonal signals
- SCN degeneration associated with clock gene dysregulation
- Striatum dysregulation [dopamine controlled clock proteins Per1/Per2 gene expression]
- Decrease rhythmic expression of retinal melanopsin [regulated by dopamine] that affect the entrainment of diurnal circadian rhythm
- Animal models of PD revealed changes in the neurons firing pattern of the SCN associated with changes in the circadian rhythm amplitude [86, 87, 103]

Light therapy is a non-invasive technique proven to be safe, well tolerated, and effective on the treatment of daily drowsiness and impair alertness in PD [104–106].

9. Diurnal sleep disorders

9.1 Excessive daytime sleepiness in PD

Excessive daytime sleepiness (EDS) involves symptoms of frequent napping, feeling abnormally sleepy and sleep attacks. It is seen in 33–76% of patients with PD [100, 107] and is likely a result of damaged to the orexin-producing neurons from the posterior lateral hypothalamus involved in the wakefulness [108]. Other brainstem stimulating monoaminergic neurons are also implicated in promoting wakefulness in damaged in PD [109]. EDS is common in advanced PD and is a marker of dopamine loss [110, 111]. **Table 6** display the condition more commonly associated with EDS in PD.

Severe PD
PD-related disability
Cognitive decline
Frequent hallucinations
Dementia
Depression
Polypharmacy
Co-existence sleep disorders
High comorbid disease burden
High doses of antiparkinsonian Drugs

Table 6.
Cause of excessive daytime sleepiness in PD.

Sleep attacks, which are defined as sudden irresistible drowsiness without awareness of falling sleep, are seen in 21% of PD patients. These are particularly concerning as they can cause serious injuries or even death, for example, as a result of a car accident when the patient falls asleep while driving [45, 55]. The Inappropriate Sleep Composite Score (ISCS) have a high specificity to detect the risk of car accidents related to EDS while driving [112]. A study with drug-naïve patients with early PD showed that patient who developed EDS after 5 years of treatment had higher baseline levels of drowsiness [113].

Management of EDS includes improving sleep hygiene, daytime regular exercises, avoid strenuous exercises a few hours before bedtime, reducing sedating medications both psychiatric (i.e. antidepressants, benzodiazepines, antipsychotics, etc.) as well as anti-Parkinson medications (particularly dopaminergic medications and levodopa), especially when used in combination [45, 114]. Stimulating anti-Parkinson medication earlier into the day such as amantadine and selegeline may help with EDS and if appropriate may be used instead of DAs [115]. If above plan fails, consider starting stimulants such as:

- Caffeine at a dose of 200 mg twice a day [116]
- Modafanil at a dose of 100–400 mg/day [117, 118].
- Methylphenidate at a dose of 1 mg/kg TID [119]
- Sodium oxybate at a dose of 3–9 grams per night at bedtime and 4 hours later [120].

Treatment of co-existent sleep disorders is essential.

Increase total sleep time
Increase sleep efficiency
Reduce sleep fragmentation
Decrease WASO
Increased slow wave sleep
Increase REM sleep
Improve insomnia
Improve restless leg syndrome
Improve daytime sleepiness

Table 7.
Deep brain stimulation, sleep architecture and sleep disorders.

9.2 Deep brain stimulation

Deep brain stimulation (DBS) is the most common surgical intervention for the treatment of PD. The procedure involves the surgical placement of electrodes, either unilaterally or bilaterally, in certain target areas in the brain. Most commonly placed in the subthalamic nucleus (STN) or the internal globus pallidus (GPi). The electrodes are then connected to a pulse generator implanted in the chest. DBS is known to improve motor symptoms and overall quality of life however we have only recently established that it also improves non-motor symptoms, including sleep [121]. STN DBS especially has shown significant improvement in sleep quality, sleep efficiency and sleep duration [121].

The beneficial effect on sleep architecture and sleep disorders [45] are displayed **Table 7**.

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