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REVIEW

Sleep Disturbance in Parkinson's Disease: Consequences for the Brain and Disease Progression – A Narrative Review

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Abstract: Sleep disturbance in Parkinson's disease (PD) is recognized to be one of the most common non-motor complications. It occurs before disease onset as a prodromal symptom, during and then throughout the disease course. Causes are multifactorial and can be multiple in the same patient. Specific sleep disorders that are known to occur in those with Parkinson's disease include REM sleep behavior disorder, sleep disordered breathing including obstructive sleep apnea, restless legs and periodic limb movements, nightmare disorder, insomnia alongside direct side-effects of the medication used for therapy. One key question is whether these sleep disorders impact upon the motor and non-motor symptoms of Parkinson's disease. There has been significant interest in recent years in using certain sleep disorders, in particular, REM sleep behavior disorder, as a biomarker both for those at risk of Parkinson's disease but also influencing the subsequent severity and speed of progression. However, other sleep disorders in the general population may also increase the risk of developing Parkinson's disease. It is important to understand whether the treatment of sleep disturbance and specific sleep disorders modifies the long-term risk of developing Parkinson's disease or its progression.

Keywords: sleep disorders, Parkinson's disease, REMBD, sleep therapies

Introduction

James Parkinson noted that "the sleep becomes much disturbed" in 1817 when first describing the characteristic features of the shaking palsy that would later bear his name.[1]

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder.[2] It is estimated that there will be between 8.7 and 9.3 million PD cases in western Europe's five, and the world's ten, most populous nations by 2030.[3] Sleep disturbance is a broad symptom characterized by impairment of the normal architecture of sleep and is one of the most common non-motor complications of PD. Sleep disturbance and specific sleep disorders (see below) are now recognized to occur throughout the disease course, including as prodromal symptoms, although they increase in frequency with disease progression.[4] The causes of sleep disturbance are often multifactorial, including the degeneration of the neural structures that modulate sleep, the side effects of some medications on sleep, the parkinsonian symptoms themselves that can interfere with normal movement in bed, and the sleep and circadian rhythm disturbance that occurs during normal ageing and with other medical comorbidities.[5]

"Sleep disturbance" as above, is a broad and widely used terminology but it may be better to consider distinct sleep disorders, given they have both diagnostic criteria and specific therapies. A broad range of sleep disorders are seen in PD including rapid eye movement (REM) sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), sleep disordered breathing including obstructive sleep apnea (OSA), restless legs syndrome, circadian rhythm disorder and insomnia disorder. In addition, questionnaire-based data suggest nightmares occur in 17.2% of people with PD.[6]

RBD has been of particular interest given this disorder is now established as one of the most specific and early prodromal features of PD and other parkinsonian disorders. It occurs in some patients many years before PD diagnosis

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and seems to predict worse long-term outcomes.[7] This has led to large cohort studies of those with REM sleep behavior disorder to enable future neuroprotective treatment trials.[8]

Additionally, there is increasing interest in sleep disturbance as a specific and potentially modifiable risk factor for neurodegeneration more broadly. In Alzheimer's disease, the discovery of the glymphatic system highlighted the necessary role of sleep in the clearance of amyloid,[9] however its relevance to the pathophysiology of Parkinson's disease remains debated.[10] Longitudinal cohort studies of the normal ageing population have shown disturbance of sleep and circadian rhythm to be an independent risk factor for worse cognition and increased mortality.[11]

The first review of longitudinal studies using both validated sleep questionnaires and objective measures of sleep in PD was published in 2011.[12] This suggested that those with increased rates of sleep disturbance had a more aggressive disease course with increased prevalence of other non-motor features. Since then, PD-specific sleep questionnaires have been published,[13] multiple further longitudinal cohorts studied,[4] and the gold standard objective measure of sleep of video polysomnography (vPSG) used to more precisely characterize sleep and specific sleep disorders in PD patients over time. There are effective treatments for many sleep disorders and so this leads to the key question of whether treatment of specific sleep disorders can impact on future risk of PD or the motor or cognitive decline in PD. To date, few studies have assessed this rigorously with many confounding factors, but there is some evidence that therapy for some of the sleep disorders may change or improve long-term PD outcomes.[14]

The purpose of this narrative review is to look at the impact of sleep disturbance in PD over time and consider the impact of the specific sleep disorders on disease progression. To this end, a literature search was conducted in PubMed, Web of Science, and Scopus databases from inception to November 2024. The focus was upon longitudinal studies investigating the association between baseline objectively measured sleep parameters and Parkinson's disease. This included an assessment of study methodology given that many earlier studies were cross-sectional rather than longitudinal and did not have objective markers of sleep. More recently, objective measures of sleep have been used to examine the frequency of both individual and multiple sleep disorders and their association with motor and non-motor symptoms over time. We explored the specific sleep biomarkers within vPSG that are associated with the subsequent development of dementia, and we also examined the relationship between specific sleep and circadian rhythm disorders and the subsequent risk of PD over time. Finally, we reviewed the published treatment trials of sleep disorders in PD considering whether the treatment of sleep disturbance impacts PD disease progression.

Two of the authors (KA and LG) cross-referenced "Parkinson's disease" and "sleep disorder", "sleep disturbance", "obstructive sleep apnea", "restless legs syndrome", "insomnia" and "insomnia disorder" as well as "nightmares", "parasomnia" and "REM sleep behavior disorder", "REMBD" and "RBD". Additionally, "treatment" and "therapy" were also cross referenced against "Parkinson's disease" and "sleep". Papers describing therapy were excluded if they were case reports, had no clear definition of the sleep disorder or there was no explanation of study design or lack of a control group.

Insomnia Disorder

Insomnia disorder remains a subjective self-report of a persistent difficulty initiating sleep, and/or maintaining sleep typically with frequent, prolonged nighttime awakenings that then cause daytime impact, typically fatigue, poor concentration and impact on mood. This needs to be present more than 3 days a month and for more than 3 months to be a chronic insomnia disorder.[15] Population-based studies suggest the prevalence of insomnia in the general population is up to 30%.[16] Many other sleep disorders can mimic insomnia, and so the medical assessment in the Parkinson's clinic must exclude lack of opportunity to sleep, physical disruption to sleep – in particular the night time discomfort of bradykinesia, nocturia, sleep disturbance due to medication or other sleep disorders including obstructive sleep apnea and restless legs.

Insomnia as a Risk Factor for PD

One important question remains as to whether insomnia in isolation increases the risk of dementia or all-cause mortality. Some recent studies within the UK Biobank cohort challenge a widespread view that insomnia disorder in itself increases the risk of cognitive impairment and mortality. In one study, after a careful control of the confounding factors of

cardiovascular risk, there was no association between self-report of insomnia and the subsequent development of Alzheimer's disease.[17] Another prospective study from the same large UK Biobank cohort showed an increased risk of PD over time with self-reported long sleep but actually showed a lower risk of PD with both shorter sleep and insomnia symptoms.[18] Both a meta-analysis of multiple sleep disorders, and a recent large, single-center study by Dodet et al using vPSG to study multiple sleep disorders in PD found that insomnia was common, increased with disease duration but was not associated with worse motor or autonomic scores.[19,20] This was in contrast to excessive daytime sleepiness. Thus, at present, the association between insomnia and the subsequent risk of developing PD remains unclear.

Genetic association studies provide another opportunity to look at overlapping causality between sleep disorders and the development of PD. If insomnia, for example, was directly contributory to the development of PD or other neurodegenerative disorders, then one may expect some overlap between genetic variants that predispose to insomnia and those that predispose to PD. Insomnia is an extremely polygenic trait, and at least 554 risk loci for insomnia have been identified.[21] These genetic variants are enriched in gene networks that co-ordinate synaptic function and neuronal differentiation that are involved in neuropsychiatric processes, but do not appear to overlap genes established to predispose to PD. However, it is likely that the majority of genetic variation that contributes to insomnia risk remains to be determined,[22] and thus it is possible that further overlapping genetic variants are identified in larger studies.

Prevalence and Associations of Insomnia in PD

Existing studies of insomnia prevalence in PD have used different methodologies to confirm the diagnosis, including semi-structured interviews and questionnaires and have reported conflicting results. A longitudinal study found the prevalence of insomnia in drug-naïve PD patients was 31%, and the overall prevalence of insomnia was not shown to change over time.[23,24] There were, however, quite marked fluctuation in one of the cohort studies over the 8 years.[24] In a further study, there was an increase in the prevalence of insomnia in patients with PD over 5 years, where it was found 51% had insomnia at some point.[25] The sleep-altering side effects of dopaminergic medication could potentially be contributing to the discrepancy in insomnia prevalence.[26] Multiple epidemiological studies in the general population have shown that the presence of insomnia or poor sleep quality increases the lifetime risk of depression, increases the risk of depressive relapse and that women are more likely to report insomnia than men.[27] Exactly the same associations are seen within the PD studies. For example, baseline depression and anxiety predict the development of insomnia in early PD.[28] In addition, insomnia was associated with motor fluctuations and higher levodopa use.[25]

In addition, certain known genetic causes of PD have been shown to have higher rates of insomnia than idiopathic PD, in particular, the leucine-rich repeat kinase 2 (LRRK2) gene, recognized as the most common cause of both sporadic and familial PD.[29] Interestingly, RBD was seen less in LRRK2-associated PD than idiopathic PD in the prodromal state, suggesting less brainstem-specific pathology.[29]

Treatment Approaches for Insomnia in PD and Impact on Disease Progression

First-line therapy for insomnia disorder is CBT for insomnia (CBTi), also shown to be effective as a digital therapy with hypnotic therapy as second line. However, despite high prevalence, to date, there have only been two small randomized controlled trials (RCTs) exploring CBTi in PD with no assessment of impact on PD symptoms. There have also been small studies of bright light therapy and exercise therapy.[30] Deep brain stimulation has been shown to improve sleep and insomnia as a non-motor symptom.[31]

A review of the available studies in 2020 proposed a treatment algorithm for CBTi in PD but highlighted a lack of known impact on other PD symptoms.[30] Pharmacological approaches such as melatonin have also been used to treat both insomnia and other sleep disturbance in PD, particularly RBD.[32,33] There has been interest in its potential neuroprotective role based on animal studies,[34] and there have been RCTs exploring benefit on sleep disturbance in patients which have shown inconsistent results, although not primarily treating insomnia. In 2023, a meta-analysis of the five available RCTs concluded that the higher doses of 10mg and immediate release melatonin had a positive impact on the United Parkinson's disease rating scale (UPDRS) scores. However, these were small studies, used variable doses of melatonin, and only two had follow-up to 12 weeks and beyond.[35] A recent single further RCT using 3mg immediate release melatonin showed benefit on sleep disturbance and the Non-Motor Symptom Scale (NMSS).[36] Future studies may well

explore the impact of the newly available dual-orexin receptor antagonists and orexin receptor antagonists which are now licensed for insomnia.[37] Interestingly, the orexin system has also been implicated in alpha-synucleinopathy, possibly with an early neuroprotective impact.[38]

To date, however, there are no treatment trials which show that treating insomnia modifies PD disease progression; however, given the increasingly widespread availability of effective digital versions of CBTi, this is a promising area for future research.

Restless Legs Syndrome

Restless legs syndrome (RLS) is characterized by unpleasant sensations producing the urge to move the legs, relieved by movement and with a striking circadian rhythm typically starting late in the evening or in the first half of the night.[39] The 2014 diagnostic criteria for RLS highlight the need to exclude other mimics of foot and leg pain or cramp, this is particularly important in PD patients where cramp and dystonia is common and so asking for all of the diagnostic features and what patients mean by RLS is key. The prevalence in the general population is 1.5–4% but increases with age and it is more common in women.[40] Periodic limb movements of sleep (PLMS) occur in 80–90% of patients with RLS and can be quantified with vPSG that measures the periodic limb movement index.[41] However, PLMS in themselves are nonspecific, can occur in isolation, can be asymptomatic when infrequent and can be associated with certain medications or a number of other medical problems common in the ageing population.[39]

RLS as a Risk Factor for PD

Dopaminergic dysfunction and response to dopaminergic medications are shared features of RLS and PD, and complications of dopaminergic medications are also seen in both conditions including augmentation in RLS and dyskinesia in PD.[42,43] However, there is still no clear evidence of a shared tangible pathophysiology between RLS and PD from brain imaging studies, and findings from functional imaging studies in RLS have been uncertain.[42] There remains significant debate about motor leg restlessness as a feature of PD and interestingly, epidemiological studies suggest an association between RLS and other movement disorders including essential tremor, dystonic syndromes and chorea.[44] There has been debate about whether RLS may be a prodromal phenomenon in some capacity for the subsequent development of PD,[45] and two large epidemiological studies have reported greater risk of subsequent PD in individuals with RLS.[46,47] The prospective Health Professionals Follow-up Study looked at individuals over 8 years and showed that men with frequent RLS symptoms more than 15 days a month had an increased risk of PD (adjusted relative risk 1.47).[46] Another retrospective population study using a large Veterans data base also showed increased PD risk in those coded as having RLS (HR 2.57).[47] A further study in 2023 followed up adults aged over 60 for 12 years and showed that the risk of all-cause dementia was higher in those with RLS compared to controls (adjusted HR 1.46).[48] There was no association between the use of dopamine agonists in RLS and risk of dementia within this study. A single study using vPSG measures at baseline to look at PLMI as a prognostic factor for PD showed that the number of periodic limb movements at baseline did not differ between PD patients and matched controls, but increased periodic limb movements were a predictor of subsequent cognitive decline.[49] In addition, genetic association studies have failed to show a genetic correlation between RLS and PD. Thus, the associations observed in epidemiological studies are likely to be non-genetically mediated.[50]

Prevalence and Associations of RLS in PD

The most recent meta-analysis of 46 studies of patients with PD and RLS suggested a pooled RLS prevalence of 20%, therefore increased compared to the background population and associated with female sex.[43] Eight of these studies also assessed the motor phenotype in PD. There was no significant association between PD-RLS and disease stage, age of PD onset or PD stage but the combination of PD and RLS was associated with more severe motor symptoms, worse daytime sleepiness and fatigue, increased neuropsychiatric symptoms and worse quality of life. A large single-center vPSG study from Dodet et al in 2024 compared early PD patients to healthy controls and assessed multiple sleep disorders, identifying an association between RLS and insomnia but not with worse motor scores, dopaminergic therapy, age or other sleep measures or sleep disorders.[19]

Treatment Approaches for RLS in PD and Impact on Disease Progression

In terms of specific therapy – both RLS and PD will improve with dopaminergic therapy and when moderate or severe, RLS clearly impacts on sleep fragmentation and has been shown to affect cognition.[51] To date, however, there have been no RCTs measuring the impact on motor or cognitive outcomes in PD when treating RLS. However, these data suggest that treating clinicians should be aware of RLS as a distinct movement disorder that has increased prevalence in PD patients which contributes to sleep fragmentation, neuropsychiatric symptoms, and worse quality of life. Distinct to PD, there is high-quality evidence for the use of alpha 2 delta ligands such as pregabalin and gabapentin in RLS.

Recently the American Academy of Sleep Medicine (AASM) published updated guidance regarding the treatment of RLS, which advocated for the use of gabapentin or pregabalin as first line, and iron replacement (where indicated). They now they advise against the use of levodopa and dopamine agonists.[52] While ropinirole and pramipexole were previously considered standard treatments,[53] recent longitudinal studies have shown high risks of impulse control disorder and augmentation.[52] This clearly presents a challenge when managing RLS in patients with comorbid PD, emphasizing the need for further research in this area.

Circadian Rhythm Disorder

The timing of sleep is precisely controlled by direct links from a subset of specialized retinal ganglion cells to the suprachiasmatic nucleus (SCN) within the hypothalamus. While a number of physical external signals including temperature, physical activity and temperature all act as time keepers (known as zeitgebers), the most powerful of these is the changing spectrum of light over 24 hours.[54] It is worth remembering that sleep and circadian rhythms change significantly across the life span with altered circadian responses to light.[55] Older age is also associated with decreased nocturnal sleep duration, advanced sleep onset, and increased sleep fragmentation with a marked decline in nocturnal melatonin levels.[56] A circadian rhythm disorder describes a change to the timing of sleep beyond that expected for age. Delayed sleep-wake phase disorder (DSWPD) involves later onset of sleep and waking relative to what is expected, while advanced sleep-wake phase disorder (ASWPD) is characterized by earlier onset of sleep and waking. Irregular sleep-wake rhythm disorder (ISWRD) describes numerous short episodes of sleep and wakefulness due to failed sleep consolidation. Non-24 hour sleep-wake rhythm disorder (N24SWD) results from an unregulated circadian rhythm, for example, in absence of light-dark cues due to blindness (but can also occur in individuals with normal sight).[57] Both sleep logs or sleep diaries with people documenting lights out time, sleep onset, wake time and any daytime naps alongside actigraphy are used to make the diagnosis. Actigraphy is a validated measure of rest activity rhythms using accelerometer devices. It remains an indirect measure of sleep onset, sleep duration and sleep timing but one that is validated when used over days to weeks with greater sensitivity than sleep logs or sleep diaries alone. While survey studies suggest the prevalence circadian rhythm disorder is up to 3% in adults, the figure may actually be up to 10% in adults (and 16% in adolescents) as a result of misdiagnoses.[58,59]

Circadian Rhythm Disorder as a Risk Factor for PD

There has been debate over the years about both duration and quality of sleep but also the timing and regularity of sleep and circadian rhythm and whether dysregulation of circadian rhythm is an independent risk factor for future neurodegeneration or whether it worsens PD.[60] Sleep was shown to have a role in clearance of amyloid from cerebrospinal fluid via the glymphatic system and proposed as key for Alzheimer's disease pathophysiology.[61] Some recent animal and human models have suggested that glymphatic function is also reduced in PD.[62] This provides a putative link between sleep disturbance as potentially being directly neurotoxic.

Long-term epidemiological studies show inconsistent results when considering whether abnormal circadian rhythm in itself increases the risk of future PD, and this may reflect methodology with self-report versus objective measures using techniques such as actigraphy. For example, the large United States Nurses Health Study showed that those who reported working shifts for 15 years or more actually had a lower risk of PD.[63] Two studies using the UK Biobank cohort of over 400,000 individuals looked at subjects over 11.8 years and demonstrated higher risk of Parkinson's with self-reported long sleep, poor sleep pattern and decreased physical activity.[18] Conversely, self-reported insomnia was associated with

reduced risk. An objective assessment using the same cohort but with actigraphy looked at all-cause mortality and described regularity of sleep (getting up and going to sleep at the same time most days) and therefore a stable circadian rhythm as an important predictor of mortality and a stronger predictor than that of sleep duration.[11] This was corroborated with objective assessments of actigraphy which identified an increased risk of PD in men with abnormal circadian rhythms followed up over 11 years.[64] Sleep regularity therefore may be a simple and effective target for improving general health and reducing future PD risk although there are no current randomized control treatment trials in PD patients with additional circadian rhythm disorder.

Prevalence and Associations of Circadian Rhythm Disorder in PD

PD patients have been shown to have abnormal circadian rhythms in terms of nocturnal hypertension, disrupted thermoregulation, disrupted melatonin rhythms in some but not all studies.[65] However, the timing of sleep onset in PD is affected by multiple environmental factors and multiple different sleep disorders and many of the studies were small and cross-sectional in design. Despite this caveat, studies showed that a greater variability in day-to-day sleep–wake rhythms in PD was associated with poorer executive, visuospatial and psychomotor functions.[66] To date, over 300 loci have been identified as being associated with human chronotypes.[67] Whilst the majority of these genes are not associated with the development of PD, several variants such as the CLOCK 3111T/C variant do appear to predispose to an earlier onset of disease and thus are potential disease modifiers in PD,[68] further supporting that circadian rhythm variation may modify disease course. Moreover, several studies have found abnormal expression of circadian rhythm genes in peripheral blood lymphocytes from PD patients. Bmal1 and brain and muscle Arnt-like protein 2 (Bmal2) are significantly decreased in PD, while Bmal1 levels have been positively correlated with PD severity and sleep quality.[69] In another study, the expression levels of "clock" genes BMAL1, CLOCK, cryptochrome 1 (CRY1), PER1 and period 2 (PER2) were significantly decreased in the peripheral blood mononuclear cells of PD as compared to controls. Based on these results, the clock genes have been proposed as potential biomarkers for evaluating the sleep-wake rhythm disturbances in PD patients (ref). At present, there is no data for the prevalence of circadian rhythm disorder in PD.

Treatment Approaches for Circadian Rhythm Disorder in PD and Impact on Disease Progression

A recent review identified twelve studies investigating bright light therapy (BLT) in PD using light intensity between 1000 and 10,000 Lux. BLT can be delivered with either light boxes or more modern smart glasses.[70] Five studies which addressed EDS used a placebo group, and two of these showed both significant and clinically important improvement in EDS scores. One study with a placebo group showed significant improvement in insomnia scores with BLT, but no improvement on actigraphy. Furthermore, of the five studies that looked at PD motor scores with a placebo group, all except one showed improvements in motor symptoms.[70] This suggests that BLT may possibly have an additional impact on PD itself and could improve sleep quality, although larger better designed studies are needed over longer time periods. However, BLT is a low cost, safe and well-tolerated therapy.

Melatonin is used both as chronobiotic to adjust the timing of sleep onset and in PD patients with RBD. AASM guidelines advise the use of strategically timed melatonin to treat DSWPD. However, the use of melatonin in elderly patients with dementia is discouraged, and sleep-promoting medications such as hypnotics are contraindicated in this group. Instead, light therapy is considered a suitable treatment for elderly ISWRD patients, in addition to individuals with ASWPD.[68]

Given the potential beneficial effects of melatonin for PD patients discussed earlier in the paper, it may prove therapeutic in co-morbid patients with DSWPD/N24SWD and PD. The evidence opposing the use of melatonin in ISWRD patients with dementia is partly based on a study that failed to show an effect on total sleep time. The majority of study participants had Alzheimer's disease, and there were no participants with Lewy body dementia or Parkinson's disease dementia.[69] The AASM guidelines also cite a study demonstrating worsening mood and withdrawn behavior in patients with dementia given melatonin.[70] However, one that measured depression outcomes in PD patients given melatonin showed 12 weeks of melatonin supplementation resulted in a significantly improved depression score.[71]

Excessive Daytime Sleepiness

EDS is a symptom rather than a specific disorder, and it is estimated to affect up to 18% of people.[71] There are multiple possible causes including sleep disorders such as obstructive sleep apnea, sedative medication, physical causes of a fragmented night or restricted sleep for need.

EDS is defined as the inability to stay awake and alert during the major periods of wakefulness in the day, leading to unintended lapses into drowsiness or sleep.[15] In PD, this is mostly defined by the simple, self-rated subjective Epworth sleepiness scale (ESS) questionnaire,[72] rather than objective measures. The gold standard test of abnormal EDS outside of population norms is overnight vPSG followed by the mean sleep latency test which assesses sleepiness during the next day.[73] The ESS by contrast estimates average sleepiness over multiple daily activities.[74]

EDS as a Risk Factor for PD

Due to cost and complexity, there are very few cohort studies or longitudinal studies of aging populations that use objective measures of sleepiness. Subjective EDS is, however, thought to be a risk factor for subsequent development of PD. For example, elderly male subjects had a 3-fold increase in developing PD if they self-reported EDS in the Honolulu-Asia Aging study.[75] Within the UK Biobank participants, there was an increased PD risk over time with self-reported long sleep time, and this was in contrast to a fragmented night sleep and short sleep time which did not look to increase risk.[18] In addition, a genetic polymorphism in the preprohypocretin gene was associated with the development of 'sleep attacks' in patients with PD,[76] suggesting again that genetic variation may be modifying the sleep-phenotype of disease.

Prevalence and Associations of EDS in PD

Multiple longitudinal studies have more broadly investigated EDS in PD patients. Although one early study suggested a possible role for dopamine agonists in increasing sleepiness,[77] but subsequent studies have not confirmed this association, although a greater total dose of all dopaminergic medications is robustly associated with EDS.[78] A 2023 meta-analysis of the longitudinal studies of both EDS and additional sleep disorders in PD showed that the prevalence of EDS was 35% and there was an association with older age, longer disease duration, worse motor and autonomic symptoms, higher levodopa dose, reduced autonomy, and more severe neuropsychiatric symptoms.[20] A study from a single expert center looking at vPSG measures in relation to EDS did not show a clear link between the PSG measures themselves and the self-reported EDS (defined as Epworth sleepiness scale >10) and this might reflect the multifactorial drivers of daytime sleepiness.[19] However, it did show again that EDS was associated with higher levodopa use and worse PD as measured by increased UPDRS scores. This therefore highlights the need to explore further with patients their self-reported sleepiness to consider distinct and potentially treatable causes, with one of the most important and well-studied being sleep disordered breathing including obstructive sleep apnea.

Treatment Approaches for EDS in PD and Impact Upon Disease Progression

Management of EDS in PD would depend on the cause, and treatment of Obstructive sleep apnoea (OSA) is covered in the following section. Other therapy approaches might include reduction or removal of any sedative medications where possible and treatment of any physical causes of sleep disturbance, including nocturnal reflux, pain and nocturia. It is also important to ensure adequate sleep duration.

Psychostimulants such as modafinil have been studied in 4 RCTs of PD patients with a systematic review concluding that there was significant improvement in daytime sleepiness but no improvement or worsening of UPDRS scores.[79]

Obstructive Sleep Apnea (OSA)

OSA is a common sleep disorder with snoring and recurrent collapse of the upper airway leading to pause or cessation in breathing (hypopnea/apnea).[80] OSA syndrome (OSAS) describes symptomatic unrefreshing, fragmented night sleep with subsequent daytime sleepiness. Many have additional nocturia or dry mouth, and some have awareness of night-time choking. OSA remains under-diagnosed,[81] but data suggests it affects 9–38% of the population (up to 49% in the older

age group).[82] Key risk factors include male gender, increasing age, obesity and medications that decrease muscle tone such as benzodiazepines or opioids.[80] The significant nocturnal hypoxemia and surges in nocturnal blood pressure that occur in OSA cause a chronic inflammation and oxidative stress.[83] The potential for this oxidative stress to trigger or worsen neuronal degeneration has led to increasing interest in the role of OSA as a potential risk factor for the development of PD together with several other neurodegenerative disorders.

OSA as a Risk Factor for PD

The association between OSA and PD has been studied by multiple different groups from Canada, the US, South Korea and Taiwan. Four reported studies have used data obtained from the Taiwan type 1 longitudinal health insurance data base,[84–87] and all four of these separate studies reported OSA as a risk factor for subsequent PD (OR 1.35 to 3.54). Large study numbers were available, but it should be noted that the absolute numbers of incident PD were low and the hazard ratio for risk of PD was only slightly elevated, suggesting that OSA was not a particularly strong risk factor for developing PD. The severity of OSA was also not quantified in these studies. There have been conflicting results according to gender,[84,87] with the most recent studies suggesting no specific difference based on gender, and no clear relationship between the severity of OSA as measured by apnea-hypopnea index and the subsequent risk of developing PD.

Prevalence and Associations of OSA in PD

At 45%, the prevalence of OSA itself does not look to be increased in PD patients compared to the age matched population.[88] This may simply be due to OSA being a common disorder in older adults. There has been debate about the role of OSA in cognition and mood in patients with PD. OSA in isolation is described to worsen depression and anxiety and to cause deficits in memory, executive function and attention.[89] Treatment of OSA with devices such as continuous positive airway pressure (CPAP) at least partially reverses some of these cognitive and psychological deficits and improves a range of quality of life measures.[89–92] One would therefore expect worse cognition in PD patients with OSA, and a number of studies have now shown this in terms of reduced cognitive testing using the Montreal Cognitive Assessment (MoCA).[93] Furthermore, genetic association studies have observed that OSA risk is associated with variants in the ANGPT2 gene,[94] which function to modulate endothelial permeability.[95] ANGPT2 expression has been observed to be upregulated in the brain of patients with PD,[96] and may provide a mechanistic link between OSA risk, and cerebral vascular permeability abnormalities seen in PD and many other neurodegenerative disorders.[97,98]

A recent meta-analysis of seventeen studies looking at PD patients with and without OSA studied a combined sample of 1448 patients and found the prevalence of any level of OSA as 45%. OSA was associated with older age, male sex, higher body mass index (BMI), more severe motor disturbances and periodic limb movements, reduced risk of rapid eye movement sleep behavior disorder, intake of dopamine agonists, and worse excessive daytime sleepiness. No relationship emerged with cognitive functioning and neuropsychiatric manifestations. However, it should be noted that only the minority of studies in this meta-analysis looked at cognitive function and neuropsychiatric symptoms, and the severity of OSA was not clearly defined.[88]

Treatment Approaches for OSA in PD and Impact Upon Disease Progression

OSA is effectively treated with CPAP, alongside lifestyle measures such as weight loss. The effect of OSA on cognition in the general population and as a risk factor for dementia is increasingly debated and OSA is now considered to be a modifiable factor in cognitive impairment.[99,100] One study that measured cognition in PD patients with OSA treated with CPAP did not show improvement in a neuro cognitive battery at 6 weeks. Given the time needed to fully treat OSA this may simply reflect too short a time period for an effect to be observed, as in a further prospective study of 67 PD subjects followed up for a year, CPAP therapy was shown to stabilize motor function as compared to the patient groups who did not have CPAP therapy or were not diagnosed with OSA.[101] A review of published studies that have assessed PD patients on CPAP suggested that there may be improvement in both motor and cognitive function with CPAP, and possibly an impact on sleep disordered breathing directly due to dopaminergic medication.[93] The additional long-term impact on nocturnal blood pressure suggests that screening for and treating OSA in PD patients is likely to improve long-term cognitive outcomes.

REM Sleep Behavior Disorder (RBD)

Individuals with RBD present with loss of the normal REM sleep atonia, resulting in motor and vocal dream enactment often with injury to patient or bed partner.[102] A study using questionnaire and polysomnography data found the prevalence of RBD to be 1.06% in their sample of middle to older age participants.[103]

RBD as a Risk Factor for PD

In 1986, Carlos Schenck described five patients with violent dream enactment behavior and loss of the normal REM atonia seen on vPSG. Four of the patients subsequently developed a parkinsonian neurodegeneration.[104] "Isolated" RBD is now established as a prodromal stage before neurodegeneration occurring most commonly in alpha-synucleinopathies such as PD, multiple system atrophy and dementia with Lewy bodies.[105,106] One of the largest and best characterized longitudinal, multicenter studies was published in 2019 and recruited 1280 cases of vPSG confirmed RBD. They were followed up prospectively for an average of 4.6 years with phenoconversion to a neurodegenerative disorder occurring at a rate of 6.3% per year. Up to 73.5% had therefore phenoconverted when followed up to 12 years after their RBD onset.[105] Multiple earlier, retrospective longitudinal series of apparently idiopathic RBD cases have also demonstrated high rates of conversion to neurodegeneration,[107–110] for example 80.8% of RBD patients followed up over 16 years by Schenck's group.[107] Additional multimodal imaging studies of RBD have shown that those presenting with RBD but no or few other symptoms already have established abnormalities in both the locus coeruleus and peripheral autonomic nervous system which are equivalent to those observed in PD.[111]

Genetic association studies have observed a significant overlap between genetic variation associated with the development of RBD and also PD, with variants in genes such as SNCA, GBA and SCARB2 all acting as risk factors for both disorders and supporting a causal link at the genetic level.[112] In addition, patients with PD who carry a mutation in GBA are 6.24 times more likely to develop RBD,[113] and patients with PD who carry a GBA mutation are significantly more likely to have both RBD and develop hallucinations compared to non-carriers.[114] More recent data also supports that certain variants in GBA such as the E326K variant, and the SNCA A53T variant also predispose to an increased frequency of RBD compared to non-carriers.[115,116] This further supports that genetic variation contributes to the sleep phenotype observed in PD.

Prevalence and Associations of RBD in PD

The gold standard diagnostic test for RBD remains vPSG to capture the characteristic loss of REM atonia (RSWA), typically alongside video evidence of vocalization and limb movement. It also excludes mimics of NREM parasomnia, severe OSA or periodic limb movements. However, many longitudinal cohort studies in PD have instead used screening questionnaires such as the RBD screening questionnaire (RBDSQ).[117] The RBDSQ has a sensitivity of 0.96 in sleep clinic cohorts, and specificity of 0.56 that increases to 0.92 in the general population in unselected controls.[117] This questionnaire has now been validated for use in PD and more recent studies using the RBDSQ have shown that the prevalence of RBD in PD increases over time.[118,119] These studies differed a little as to whether RBD was persistent or fluctuated. Less robust methodologies were used in earlier studies which might account for this variation. A large meta-analysis of eight studies looked at newly diagnosed PD patients with a combined sample size of 2642. This reported a wide range of prevalence figures between 4.3% and 69.4% across the different studies.[120] However, only one study had utilized vPSG and this reported a baseline prevalence of 25% of RBD.[121] These earlier studies have now been superseded by studies that repeated vPSG at multiple time points, these have conclusively demonstrated that RBD and the PSG hallmark of REM sleep without atonia (RSWA) are both persistent and progressive features in RBD patients. The DeNoPa study group showed that RBD prevalence increased from 25% at baseline to 43% at 2-year follow-up,[121] and then up again to 52% by 6 years.[122] RSWA was independently associated with both disease duration and age but not with any other disease-related factors. Another group showed similar findings studying 22 PD subjects with RBD measuring PSG at baseline and 3 years later and showing that RSWA measurements increased significantly in all subjects over time. The development of RSWA was associated with worsening motor fluctuation, dyskinesias and cognitive function. Importantly, the vPSG measures contrasted with self-reported frequency of RBD, as 42% of PD patients reported RBD as unchanged, with 27% increasing but 27% also decreasing over time. This variability in self-reported disease

progression compared to vPSG might reflect both cognitive impairment, medical therapy or spouse leaving the bedroom, but highlights RSWA rather than patient self-report are likely to be a more robust biomarker for disease progression.[123]

Cross-sectional studies of PD patients have consistently shown that those with RBD have a more severe disease phenotype with both worse motor scores but also greater non-motor symptoms. There is an association of RBD with hallucinations in PD and the presence of RBD predicted the development of hallucinations and was associated with both a worse cognitive outcome and higher mortality. These cross-sectional findings were then confirmed in a prospective cohort of PD patients followed up over 4 years. Half of the cohort with PSG confirmed RBD had developed dementia after 4 years whereas all of the PD subjects without RBD remained dementia free.[121,122] Baseline REM sleep without atonia was also predictive of subsequent dementia. Another large cohort study involving 923 early PD subjects followed up over an average of 4.8 years showed that the presence of possible RBD at baseline predicted greater non-motor, motor progression and was associated with increased risk of cognitive impairment.[124]

One challenge in the use of RSWA measures as a biomarker is that PSG protocol and analysis methods differ across different studies and the current International Classification of Sleep Disorders – 3 (ICSD 3) do not provide clear cut-offs for the scoring of abnormal phasic and tonic EMG. There are therefore no current consensus criteria,[125] but a standardized protocol to diagnose RBD and identify prodromal RBD with increased motor movements in REM sleep has been proposed.[126] This may well impact upon the future estimation of RBD prevalence. The ongoing cost and night to night variability of RBD motor behavior severity on PSG also places limitations on the utility of this as a tool for longitudinal assessment and as a biomarker.[127,128] One future solution may come with AI technology. A recent machine learning algorithm was able to accurately predict phenoconversion from vPSG in isolated RBD subjects. This studied 66 patients, of whom 18 converted to overt alpha-synucleinopathy within 2.7 years. For each patient, a baseline PSG was available and sleep stages were scored automatically alongside EMG.[129]

Treatment Approaches for RBD in PD and Impact Upon Disease Progression

There have been guidelines published by the AASM for the management of REM sleep behavior disorder to prevent injury and reduce the risk of the disorder.[33] These guidelines are based largely on case-control studies with few RCTs although both melatonin and clonazepam have been shown to decrease injury and both are widely used. Despite the neuroprotective potential of melatonin highlighted in some animal studies,[130] there has been no convincing evidence that early treatment of RBD affects long-term PD outcomes or the subsequent development of PD.[131] The ongoing longitudinal studies of RBD patients may well allow this to be studied in more detail in the future.

Characterizing Multiple Sleep Disorders or Complaints

A practical difficulty in any assessment of the role of sleep in PD progression is that individual sleep disorders often do not exist in isolation (see Table 1 for a list of sleep disorders and their prevalence and treatment). Therefore, the study of specific sleep problems may lack clinical relevance. For example, the patient with a fragmented night may have; nocturia, pain due to bradykinesia, OSA and RLS which all combine to cause a fragmented sleep and then EDS. There is a dilemma when considering whether to study individual sleep disorders or every cause of poor sleep in a PD patient considering disease progression and impact on the brain. A number of recent longitudinal studies have investigated sleep holistically with a combination of detailed sleep questionnaires and vPSG.

Our group looked at the burden of EDS, insomnia, and RBD separately in the Parkinson's progression markers initiative (PPMI) cohort to determine the burden of these sleep disorders at the individual patient level over 5 years. We saw that sleep disturbance increased over time, with the frequency of insomnia increasing the most followed by RBD.[132] The number of subjects reporting multiple sleep disturbances also increased over time.[132] There was, however, a large variation in the combination of different sleep problems highlighting need for a targeted sleep history and relevant investigations for each PD patient. In a single expert center, 162 early PD patients were compared to healthy controls, and all had detailed assessment alongside vPSG. They also showed that the number of sleep disorders increased over disease duration and dysautonomia. Insomnia (41%), followed by definite RBD, EDS and RLS were all more frequent than in controls although OSA was similar.[19]

Table 1 Summarizes the Individual Sleep Disorders, Their Prevalence in PD and Published Therapies as Well as Associations with Different Aspects of PD

Disorder	Prevalence in PD	Prevalence in General Population	Potential Associations in PD	Treatment Options
Insomnia	31–51%	30%	Worse motor fluctuation Depression and anxiety	CBTi Hypnotic therapy
Restless Legs Syndrome	20%	3%	Worse motor symptoms Worse neuropsychiatric symptoms	Dopaminergic therapy Gabapentin/Pregabalin
Circadian rhythm disorder	Unknown	3–10%	Worse neuropsychiatric symptoms	Melatonin Bright Light therapy
Excessive daytime sleepiness	35%	18%	Worse motor symptoms Worse autonomic symptoms Worse neuropsychiatric symptoms	Dependent on cause but may consider psychostimulants eg Modafinil
Obstructive Sleep Apnea	45%	9–38%	Worse cognitive function Worse motor symptoms	Weight loss if high BMI CPAP Oral appliance if mild or moderate
REM Sleep Behavior Disorder	25–52%	1.06%	Worse motor fluctuation Worse dyskinesias Worse cognitive function Dementia Hallucinations Higher mortality	Safety advice Melatonin Clonazepam

The Predictive Values of vPSG Data in PD

vPSG remains the gold standard objective measure of sleep physiology and is key for the diagnosis of certain sleep disorders, in particular RBD.[126,133] However, it may also have prognostic value in PD. As was earlier described, the vPSG features seen in RBD can predict dementia,[134] and this has also been seen in a more recent study.[135] This group also studied slow wave sleep in a different cohort and found that lower N3 percentage at baseline was significantly associated with worse cognition over time.[136] Other PSG features including lower sleep spindle amplitude and density were also shown to predict the subsequent development of dementia.[137] In particular, lower sleep spindle density in the occipital and parietal lobes were correlated with worse visuospatial ability in PD patients. This group then demonstrated that specific features within the PSG were predictive of cognitive impairment and dementia. Specifically, higher absolute power in the delta and feta bands in REM sleep and lower dominant occipital frequency and higher delta and slowing ratios during wakefulness.

Until recently, vPSG has remained a time-consuming and costly test, potentially limiting applicability. However, recent use of machine learning algorithms has used baseline PSG in a group of isolated RBD patients to predict phenoconversion.[129] The development of large vPSG databases and deep learning algorithms are now being used to predict mortality risk in the ageing population.[138] These new techniques will increase the ability for changes in sleep physiology to be used as predictive biomarkers for PD patients.

Conclusions and Future Directions

Earlier longitudinal studies of PD have often used sleep questionnaires with a variable range of objective sleep measures and often within a more comprehensive set of biometric assessments. The specific investigation of sleep disorders may not be the main focus of these cohort studies. This possibly accounts for some of the conflicting data seen in PD studies of sleep.

RBD is an established prodromal feature of PD associated with a worse motor and cognitive outcome. It has effective symptomatic therapy and is and will be the target population for neuroprotective treatment trials for the future. Ongoing

longitudinal biomarker studies are studying RBD patients and are also likely to be able to determine if different medical therapies for RBD impact on phenoconversion.

However, when considering ways to prevent neurodegeneration and decrease the risk of developing PD, protecting the quality, quantity and timing of sleep may be an under used therapy for long-term brain health. More comprehensive and objective sleep data including vPSG suggest that long sleep and circadian rhythm disturbance as well as sleep disorders such as obstructive sleep apnea and restless legs may confer an increased risk of neurodegeneration including PD, and for OSA, that treatment may modify cognitive outcome in PD patients. Treatment of OSA is emerging as a strategy to improve cognitive outcomes in both mild cognitive impairment and dementia and so consideration of screening should be considered in all PD patients who complain of sleep disturbance.

Within PD patients themselves, the prevalence of multiple sleep disorders increases over time and sleep disorders are typically associated with a worse motor and non-motor outcome including cognition. Sleep disorders place a substantial burden upon PD patients, and they have effective therapies to improve both sleep and quality of life.

There still remain few trials that have addressed the impact of treating sleep disorders upon the long term PD disease outcome itself. Emerging evidence does suggest that assessment and treatment of OSA may have important benefits in improving the long term cognitive outcomes in PD patients. However, longitudinal studies that look at the development of PD and the disease trajectory after treatment of other sleep disorders are needed. This remains an important unanswered question worthy of further research. We already know that treating sleep disturbance improves how PD patients move, think and feel the next day. We do not yet know whether it changes their future.

Data Sharing Statement

No new data was generated in this paper.

Author Contributions

All authors agreed on the journal to which the article will be submitted, reviewed and agreed on all versions of the article before submission, and during revision, and the final version accepted for publication. All authors agreed to take responsibility and be accountable for the contents of the article and any changes introduced at proofing stage. The contributions of the different authors are as stated; KA conceptualization, writing – original draft, writing – review and editing, literature review, LG, conceptualization, literature review and reference checking, writing – original draft, writing – review and editing, MK supervision, resources, writing – original draft, writing – review and editing.

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References

1. Parkinson J. An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci*. 2002;14(2):223–236. doi:10.1176/jnp.14.2.223
2. Bekris LM, Mata IF, Zabetian CP. The genetics of Parkinson disease. *J Geriatr Psychiatry Neurol*. 2010;23(4):228–242. doi:10.1177/0891988710383572
3. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007;68(5):384–386. doi:10.1212/01.wnl.0000247740.47667.03
4. Xu Z, Anderson KN, Pavese N. Longitudinal studies of sleep disturbances in Parkinson's disease. *Curr Neurol Neurosci Rep*. 2022;22(10):635–655. doi:10.1007/s11910-022-01223-5
5. Iranzo A, Cochen De Cock V, Fantini ML, Pérez-Carbonell L, Trotti LM. Sleep and sleep disorders in people with Parkinson's disease. *Lancet Neurol*. 2024;23(9):925–937. doi:10.1016/S1474-4422(24)00170-4
6. Ylikoski A, Martikainen K, Partinen M. Parasomnias and isolated sleep symptoms in Parkinson's disease: a questionnaire study on 661 patients. *J Neurol Sci*. 2014;346(1–2):204–208. doi:10.1016/j.jns.2014.08.025
7. Bargiotas P, Schuepbach MW, Bassetti CL. Sleep-wake disturbances in the premotor and early stage of Parkinson's disease. *Curr Opin Neurol*. 2016;29(6):763–772. doi:10.1097/wco.0000000000000388

8. Postuma RB. Neuroprotective trials in REM sleep behavior disorder: the way forward becomes clearer. *Neurology*. 2022;99(7 Suppl 1):19–25. doi:10.1212/wnl.0000000000200235
9. Reddy OC, van der Werf YD. The sleeping brain: harnessing the power of the glymphatic system through lifestyle choices. *Brain Sci*. 2020;10 (11). doi:10.3390/brainsci10110868
10. Scott-Massey A, Boag MK, Magnier A, Bispo D, Khoo TK, Pountney DL. Glymphatic system dysfunction and sleep disturbance may contribute to the pathogenesis and progression of Parkinson's disease. *Int J Mol Sci*. 2022;23(21). doi:10.3390/ijms232112928
11. Windred DP, Burns AC, Lane JM, et al. Sleep regularity is a stronger predictor of mortality risk than sleep duration: a prospective cohort study. *Sleep*. 2024;47(1). doi:10.1093/sleep/zsad253
12. Zoccolella S, Savarese M, Lamberti P, Manni R, Pacchetti C, Logroscino G. Sleep disorders and the natural history of Parkinson's disease: the contribution of epidemiological studies. *Sleep Med Rev*. 2011;15(1):41–50. doi:10.1016/j.smrv.2010.02.004
13. Högl B, Arnulf I, Comella C, et al. Scales to assess sleep impairment in Parkinson's disease: critique and recommendations. *Mov Disord*. 2010;25(16):2704–2716. doi:10.1002/mds.23190
14. Amara AW, Chahine LM, Videnovic A. Treatment of sleep dysfunction in Parkinson's disease. *Curr Treat Options Neurol*. 2017;19(7):26. doi:10.1007/s11940-017-0461-6
15. Medicine AAOS. International Classification of Sleep Disorders 2014 Darien, IL, USA
16. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med*. 2007;3(5 Suppl):S7–10.
17. Guo C, Harshfield EL, Markus HS. Sleep characteristics and risk of stroke and dementia: an observational and Mendelian randomization study. *Neurology*. 2024;102(5):e209141. doi:10.1212/wnl.0000000000209141
18. Chen Y, Gao Y, Sun X, et al. Association between sleep factors and Parkinson's disease: a prospective study based on 409,923 UK biobank participants. *Neuroepidemiology*. 2023;57(5):293–303. doi:10.1159/000530982
19. Dodet P, Houot M, Leu-Semenescu S, et al. Sleep disorders in Parkinson's disease, an early and multiple problem. *NPJ Parkinson's Dis*. 2024;10(1):46. doi:10.1038/s41531-024-00642-0
20. Maggi G, Vitale C, Cerciello F, Santangelo G. Sleep and wakefulness disturbances in Parkinson's disease: a meta-analysis on prevalence and clinical aspects of REM sleep behavior disorder, excessive daytime sleepiness and insomnia. *Sleep Med Rev*. 2023;68:101759. doi:10.1016/j.smrv.2023.101759
21. Watanabe K, Jansen PR, Savage JE, et al. Genome-wide meta-analysis of insomnia prioritizes genes associated with metabolic and psychiatric pathways. *Nature Genet*. 2022;54(8):1125–1132. doi:10.1038/s41588-022-01124-w
22. Watanabe K, Stringer S, Frei O, et al. A global overview of pleiotropy and genetic architecture in complex traits. *Nature Genet*. 2019;51 (9):1339–1348. doi:10.1038/s41588-019-0481-0
23. Tholfsen LK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Changes in insomnia subtypes in early Parkinson disease. *Neurology*. 2017;88 (4):352–358. doi:10.1212/wnl.0000000000003540
24. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP. Insomnia in Parkinson's disease: frequency and progression over time. *J Neurol Neurosurg Psychiatry*. 2007;78(5):476–479. doi:10.1136/jnnp.2006.100370
25. Zhu K, van Hilten JJ, Marinus J. The course of insomnia in Parkinson's disease. *Parkinsonism Relat Disord*. 2016;33:51–57. doi:10.1016/j.parkreldis.2016.09.010
26. Chahine LM, Daley J, Horn S, et al. Association between dopaminergic medications and nocturnal sleep in early-stage Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(10):859–863. doi:10.1016/j.parkreldis.2013.05.009
27. Ford DE, Cooper-Patrick L. Sleep disturbances and mood disorders: an epidemiologic perspective. *Depress Anxiety*. 2001;14(1):3–6. doi:10.1002/da.1041
28. Rutten S, Vriend C, van der Werf YD, Berendse HW, Weintraub D, van den Heuvel OA. The bidirectional longitudinal relationship between insomnia, depression and anxiety in patients with early-stage, medication-naïve Parkinson's disease. *Parkinsonism Relat Disord*. 2017;39:31–36. doi:10.1016/j.parkreldis.2017.01.015
29. Pont-Sunyer C, Iranzo A, Gaig C, et al. Sleep disorders in parkinsonian and nonparkinsonian LRRK2 mutation carriers. *PLoS One*. 2015;10(7): e0132368. doi:10.1371/journal.pone.0132368
30. Wallace DM, Wohlgemuth WK, Trotti LM, et al. Practical evaluation and management of insomnia in Parkinson's disease: a review. *Mov Disord Clin Pract*. 2020;7(3):250–266. doi:10.1002/mdc3.12899
31. Bjerknes S, Skogseid IM, Hauge TJ, Dietrichs E, Toft M. Subthalamic deep brain stimulation improves sleep and excessive sweating in Parkinson's disease. *NPJ Parkinson's Dis*. 2020;6(1):29. doi:10.1038/s41531-020-00131-0
32. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(2):307–349. doi:10.5664/jcsm.6470
33. Howell M, Avidan AY, Foldvary-Schaefer N, et al. Management of REM sleep behavior disorder: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2023;19(4):769–810. doi:10.5664/jcsm.10426
34. Hunt J, Coulson EJ, Rajnarayanan R, Oster H, Videnovic A, Rawashdeh O. Sleep and circadian rhythms in Parkinson's disease and preclinical models. *Mol Neurodegener*. 2022;17(1):2. doi:10.1186/s13024-021-00504-w
35. Iftikhar S, Sameer HM, Zainab. Significant potential of melatonin therapy in Parkinson's disease - a meta-analysis of randomized controlled trials. *Front Neurol*. 2023;14:1265789. doi:10.3389/fneur.2023.1265789
36. Sugumaran R, Sai Krishna KS, Saibaba J, Narayan SK, Sandhiya S, Rajeswari M. Melatonin on sleep in Parkinson's disease: a randomized double blind placebo controlled trial. *Sleep Med*. 2024;124:502–509. doi:10.1016/j.sleep.2024.10.020
37. Nie T, Blair HA. Daridorexant in insomnia disorder: a profile of its use. *CNS Drugs*. 2023;37:267–274. doi:10.1007/s40263-023-00987-9
38. Raheel K, See QR, Munday V, et al. Orexin and sleep disturbances in alpha-synucleinopathies: a systematic review. *Curr Neurol Neurosci Rep*. 2024;24(9):389–412. doi:10.1007/s11910-024-01359-6
39. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated international restless legs syndrome study group (IRLSSG) consensus criteria--history, rationale, description, and significance. *Sleep Med*. 2014;15 (8):860–873. doi:10.1016/j.sleep.2014.03.025
40. Broström A, Alimoradi Z, Lind J, Ulander M, Lundin F, Pakpour A. Worldwide estimation of restless legs syndrome: a systematic review and meta-analysis of prevalence in the general adult population. *J Sleep Res*. 2023;32(3):e13783. doi:10.1111/jsr.13783

41. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord*. 1997;12(1):61–65. doi:10.1002/mds.870120111
42. Peeraully T, Tan EK. Linking restless legs syndrome with Parkinson's disease: clinical, imaging and genetic evidence. *Transl Neurodegener*. 2012;1(1):6. doi:10.1186/2047-9158-1-6
43. Maggi G, Barone A, Mastromarino C, Santangelo G, Vitale C. Prevalence and clinical profile of patients with restless legs syndrome in Parkinson's disease: a meta-analysis. *Sleep Med*. 2024;121:275–286. doi:10.1016/j.sleep.2024.07.015
44. Alonso-Navarro H, García-Martín E, Agúndez JAG, Jiménez-Jiménez FJ. Association between restless legs syndrome and other movement disorders. *Neurology*. 2019;92(20):948–964. doi:10.1212/wnl.0000000000007500
45. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol*. 2006;5(3):235–245. doi:10.1016/s1474-4422(06)70373-8
46. Wong JC, Li Y, Schwarzschild MA, Ascherio A, Gao X. Restless legs syndrome: an early clinical feature of Parkinson disease in men. *Sleep*. 2014;37(2):369–372. doi:10.5665/sleep.3416
47. Szatmari S Jr, Bereczki D, Fornadi K, Kalantar-Zadeh K, Kovesdy CP, Molnar MZ. Association of restless legs syndrome with incident Parkinson's disease. *Sleep*. 2017;40(2). doi:10.1093/sleep/zsw065
48. Kim KY, Kim EH, Lee M, Ha J, Jung I, Kim E. Restless leg syndrome and risk of all-cause dementia: a nationwide retrospective cohort study. *Alzheimers Res Ther*. 2023;15(1):46. doi:10.1186/s13195-023-01191-z
49. Mollenhauer B, Zimmermann J, Sixel-Döring F, et al. Baseline predictors for progression 4 years after Parkinson's disease diagnosis in the De Novo Parkinson Cohort (DeNoPa). *Mov Disord*. 2019;34(1):67–77. doi:10.1002/mds.27492
50. Estiar MA, Senkevich K, Yu E, et al. Lack of causal effects or genetic correlation between restless legs syndrome and Parkinson's disease. *Mov Disord*. 2021;36(8):1967–1972. doi:10.1002/mds.28640
51. Wang S, Zheng X, Huang J, et al. Restless legs syndrome and cognitive function among adults: a systematic review and meta-analysis. *J Neurol*. 2023;270(3):1361–1370. doi:10.1007/s00415-022-11484-2
52. Winkelman JW, Berkowski JA, DelRosso LM, et al. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2025;21(1):137–152. doi:10.5664/jcsm.11390
53. Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine clinical practice guideline. *Sleep*. 2012;35(8):1039–1062. doi:10.5665/sleep.1988
54. Van Drunen R, Eckel-Mahan K. Circadian rhythms of the hypothalamus: from function to physiology. *Clocks Sleep*. 2021;3(1):189–226. doi:10.3390/clockssleep3010012
55. Duncan MJ. Interacting influences of aging and Alzheimer's disease on circadian rhythms. *Eur J Neurosci*. 2020;51(1):310–325. doi:10.1111/ejn.14358
56. Li J, Vitiello MV, Gooneratne NS. Sleep in Normal Aging. *Sleep Med Clin*. 2018;13(1):1–11. doi:10.1016/j.jsmc.2017.09.001
57. Basit H, Damhoff TC, Huecker MR. Sleeplessness and Circadian Disorder. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023.
58. Kim MJ, Lee JH, Duffy JF. Circadian Rhythm Sleep Disorders. *J Clin Outcomes Manag*. 2013;20(11):513–528.
59. Lee EK. Introduction to Circadian Rhythm Disorders. In: Auger RR, editor. *Circadian Rhythm Sleep-Wake Disorders: An Evidence-Based Guide for Clinicians and Investigators*. Vol. 37. Springer; 2020:chap3.
60. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol*. 2019;18(3):307–318. doi:10.1016/s1474-4422(18)30461-7
61. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373–377. doi:10.1126/science.1241224
62. Bae YJ, Kim JM, Choi BS, et al. Glymphatic function assessment in Parkinson's disease using diffusion tensor image analysis along the perivascular space. *Parkinsonism Relat Disord*. 2023;114:105767. doi:10.1016/j.parkreldis.2023.105767
63. Chen H, Schernhammer E, Schwarzschild MA, Ascherio A. A prospective study of night shift work, sleep duration, and risk of Parkinson's disease. *Am J Epidemiol*. 2006;163(8):726–730. doi:10.1093/aje/kwj096
64. Leng Y, Blackwell T, Cawthon PM, Ancoli-Israel S, Stone KL, Yaffe K. Association of circadian abnormalities in older adults with an increased risk of developing Parkinson disease. *JAMA Neurol*. 2020;77(10):1270–1278. doi:10.1001/jamaneurol.2020.1623
65. Asadpoordezaki Z, Coogan AN, Henley BM. Chronobiology of Parkinson's disease: past, present and future. *Eur J Neurosci*. 2023;57(1):178–200. doi:10.1111/ejn.15859
66. Wu JQ, Li P, Stavitsky Gilbert K, Hu K, Cronin-Golomb A. Circadian rest-activity rhythms predict cognitive function in early Parkinson's disease independently of sleep. *Mov Disord Clin Pract*. 2018;5(6):614–619. doi:10.1002/mdc3.12692
67. Ashbrook LH, Krystal AD, Fu YH, Ptáček LJ. Genetics of the human circadian clock and sleep homeostat. *Neuropsychopharmacology*. 2020;45(1):45–54. doi:10.1038/s41386-019-0476-7
68. Lou F, Li M, Luo X, Ren Y. CLOCK 3111T/C variant correlates with motor fluctuation and sleep disorders in Chinese patients with Parkinson's disease. *Parkinson's Dis*. 2018;2018:4670380. doi:10.1155/2018/4670380
69. Li T, Cheng C, Jia C, et al. Peripheral clock system abnormalities in patients with Parkinson's disease. *Front Aging Neurosci*. 2021;13:736026. doi:10.3389/fnagi.2021.736026
70. Smilowska K, van Wamelen DJ, Bloem BR. The multimodal effect of circadian interventions in Parkinson's disease: a narrative review. *Parkinsonism Relat Disord*. 2023;110:105309. doi:10.1016/j.parkreldis.2023.105309
71. Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. *J Thorac Dis*. 2012;4(6):608–616. doi:10.3978/j.issn.2072-1439.2012.10.07
72. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540–545. doi:10.1093/sleep/14.6.540
73. Thorpy MJ. The clinical use of the multiple sleep latency test. the standards of practice committee of the American sleep disorders association. *Sleep*. 1992;15(3):268–276. doi:10.1093/sleep/15.3.268
74. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. *J Sleep Res*. 2000;9(1):5–11. doi:10.1046/j.1365-2869.2000.00177.x

75. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology*. 2005;65(9):1442–1446. doi:10.1212/01.wnl.0000183056.89590.0d
76. Rissling I, Körner Y, Geller F, Stiasny-Kolster K, Oertel WH, Möller JC. Preprohypocretin polymorphisms in Parkinson disease patients reporting "sleep attacks". *Sleep*. 2005;28(7):871–875. doi:10.1093/sleep/28.7.871
77. Happe S, Berger K. The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease. *J Neurol*. 2001;248:1062–1067. doi:10.1007/s004150170026
78. Stefansdottir S, Gjerstad MD, Tysnes OB, Larsen JP. Subjective sleep problems in patients with early Parkinson's disease. *Eur J Neurol*. 2012;19(12):1575–1581. doi:10.1111/j.1468-1331.2012.03791.x
79. Rodrigues TM, Castro Caldas A, Ferreira JJ. Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson's disease: systematic review and meta-analysis. *Parkinsonism Relat Disord*. 2016;27:25–34. doi:10.1016/j.parkreldis.2016.03.002
80. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med*. 2019;380(15):1442–1449. doi:10.1056/NEJMcp1816152
81. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687–698. doi:10.1016/s2213-2600(19)30198-5
82. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev*. 2017;34:70–81. doi:10.1016/j.smrv.2016.07.002
83. Lavie L. Intermittent hypoxia: the culprit of oxidative stress, vascular inflammation and dyslipidemia in obstructive sleep apnea. *Expert Rev Respir Med*. 2008;2(1):75–84. doi:10.1586/17476348.2.1.75
84. Chou PS, Lai CL, Chou YH, Chang WP. Sleep apnea and the subsequent risk of Parkinson's disease: a 3-year nationwide population-based study. *Neuropsychiatr Dis Treat*. 2017;13:959–965. doi:10.2147/ndt.S134311
85. Yeh NC, Tien KJ, Yang CM, Wang JJ, Weng SF. Increased risk of Parkinson's disease in patients with obstructive sleep apnea: a population-based, propensity score-matched, longitudinal follow-up study. *Medicine*. 2016;95(2):e2293. doi:10.1097/md.0000000000002293
86. Sheu JJ, Lee HC, Lin HC, Kao LT, Chung SD. A 5-year follow-up study on the relationship between obstructive sleep apnea and Parkinson disease. *J Clin Sleep Med*. 2015;11(12):1403–1408. doi:10.5664/jcsm.5274
87. Chen JC, Tsai TY, Li CY, Hwang JH. Obstructive sleep apnea and risk of Parkinson's disease: a population-based cohort study. *J Sleep Res*. 2015;24(4):432–437. doi:10.1111/jsr.12289
88. Maggi G, Giacobbe C, Iannotta F, Santangelo G, Vitale C. Prevalence and clinical aspects of obstructive sleep apnea in Parkinson disease: a meta-analysis. *Eur J Neurol*. 2024;31(2):e16109. doi:10.1111/ene.16109
89. Kerner NA, Roose SP. Obstructive sleep apnea is linked to depression and cognitive impairment: evidence and potential mechanisms. *Am J Geriatr Psychiatry*. 2016;24(6):496–508. doi:10.1016/j.jagp.2016.01.134
90. Coman AC, Borzan C, Vesa CS, Todea DA. Obstructive sleep apnea syndrome and the quality of life. *Clujul Med*. 2016;89(3):390–395. doi:10.15386/cjmed-593
91. Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. *Sleep*. 2013;36(2):203–220. doi:10.5665/sleep.2374
92. Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. *Chest*. 2012;141(6):1601–1610. doi:10.1378/chest.11-2214
93. Yu Q, Hu X, Zheng T, et al. Obstructive sleep apnea in Parkinson's disease: a prevalent, clinically relevant and treatable feature. *Parkinsonism Relat Disord*. 2023;115:105790. doi:10.1016/j.parkreldis.2023.105790
94. Mukherjee S, Saxena R, Palmer LJ. The genetics of obstructive sleep apnoea. *Respirology*. 2018;23(1):18–27. doi:10.1111/resp.13212
95. Daneman R, Zhou L, Kebede AA, Barres BA. Pericytes are required for blood-brain barrier integrity during embryogenesis. *Nature*. 2010;468(7323):562–566. doi:10.1038/nature09513
96. Huang J, Liu L, Qin L, Huang H, Li X. Single-cell transcriptomics uncovers cellular heterogeneity, mechanisms, and therapeutic targets for Parkinson's disease. *Front Genet*. 2022;13:686739. doi:10.3389/fgene.2022.686739
97. Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in Parkinson's disease. *J Cereb Blood Flow Metab*. 2015;35(5):747–750. doi:10.1038/jcbfm.2015.32
98. Knox EG, Aburto MR, Clarke G, Cryan JF, O'Driscoll CM. The blood-brain barrier in aging and neurodegeneration. *Mol Psychiatry*. 2022;27(6):2659–2673. doi:10.1038/s41380-022-01511-z
99. Cavuoto MG, Robinson SR, O'Donoghue FJ, et al. Associations between amyloid burden, hypoxemia, sleep architecture, and cognition in obstructive sleep apnea. *J Alzheimers Dis*. 2023;96(1):149–159. doi:10.3233/jad-221049
100. Lal C, Ayappa I, Ayas N, et al. The link between obstructive sleep apnea and neurocognitive impairment: an official American thoracic society workshop report. *Ann Am Thorac Soc*. 2022;19(8):1245–1256. doi:10.1513/AnnalsATS.202205-380ST
101. Meng L, Benedetti A, Lafontaine A-L, et al. Obstructive sleep apnea, CPAP therapy and Parkinson's disease motor function: a longitudinal study. *Parkinsonism Relat Disord*. 2020;70:45–50. doi:10.1016/j.parkreldis.2019.12.001
102. Barone DA, Henchcliffe C. Rapid eye movement sleep behavior disorder and the link to alpha-synucleinopathies. *Clin Neurophysiol*. 2018;129(8):1551–1564. doi:10.1016/j.clinph.2018.05.003
103. Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. *Sleep*. 2018;41(2). doi:10.1093/sleep/zsx197
104. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep*. 1986;9(2):293–308. doi:10.1093/sleep/9.2.293
105. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*. 2019;142(3):744–759. doi:10.1093/brain/awz030
106. Bramich S, Noyce AJ, King AE, et al. Isolated rapid eye movement sleep behaviour disorder (iRBD) in the Island study linking ageing and neurodegenerative disease (ISLAND) sleep study: protocol and baseline characteristics. *J Sleep Res*. 2024;33(3):e14109. doi:10.1111/jsr.14109
107. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med*. 2013;14(8):744–748. doi:10.1016/j.sleep.2012.10.009
108. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology*. 2009;72(15):1296–1300. doi:10.1212/01.wnl.0000340980.19702.6e

109. Iranzo A, Molinuevo JL, Santamaría J, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol*. 2006;5(7):572–577. doi:10.1016/s1474-4422(06)70476-8
110. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology*. 1996;46(2):388–393. doi:10.1212/wnl.46.2.388
111. Knudsen K, Fedorova TD, Hansen AK, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. *Lancet Neurol*. 2018;17(7):618–628. doi:10.1016/s1474-4422(18)30162-5
112. Krohn L, Heilbron K, Blauwendraat C, et al. Genome-wide association study of REM sleep behavior disorder identifies polygenic risk and brain expression effects. *Nat Commun*. 2022;13(1):7496. doi:10.1038/s41467-022-34732-5
113. Gan-Or Z, Mirelman A, Postuma RB, et al. GBA mutations are associated with rapid eye movement sleep behavior disorder. *Ann Clin Transl Neurol*. 2015;2(9):941–945. doi:10.1002/acn3.228
114. Thaler A, Bregman N, Gurevich T, et al. Parkinson's disease phenotype is influenced by the severity of the mutations in the GBA gene. *Parkinsonism Relat Disord*. 2018;55:45–49. doi:10.1016/j.parkreldis.2018.05.009
115. Perez-Lloret S, Chevalier G, Bordet S, et al. The genetic basis of probable REM sleep behavior disorder in Parkinson's disease. *Brain Sci*. 2023;13(8). doi:10.3390/brainsci13081146
116. Simitsi AM, Koros C, Stamelou M, et al. REM sleep behavior disorder and other sleep abnormalities in p. A53T SNCA mutation carriers. *Sleep*. 2021;44(5). doi:10.1093/sleep/zsaa248
117. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. *Mov Disord*. 2007;22(16):2386–2393. doi:10.1002/mds.21740
118. Bjørnarå KA, Dietrichs E, Toft M. Longitudinal assessment of probable rapid eye movement sleep behaviour disorder in Parkinson's disease. *Eur J Neurol*. 2015;22(8):1242–1244. doi:10.1111/ene.12723
119. Bugalho P, Viana-Baptista M. REM sleep behavior disorder and motor dysfunction in Parkinson's disease–a longitudinal study. *Parkinsonism Relat Disord*. 2013;19(12):1084–1087. doi:10.1016/j.parkreldis.2013.07.017
120. Zhang J, Xu CY, Liu J. Meta-analysis on the prevalence of REM sleep behavior disorder symptoms in Parkinson's disease. *BMC Neurol*. 2017;17(1):23. doi:10.1186/s12883-017-0795-4
121. Sixel-Döring F, Zimmermann J, Wegener A, Mollenhauer B, Trenkwalder C. The evolution of REM sleep behavior disorder in early Parkinson disease. *Sleep*. 2016;39(9):1737–1742. doi:10.5665/sleep.6102
122. Zimansky L, Muntean ML, Leha A, Mollenhauer B, Trenkwalder C, Sixel-Döring F. Incidence and progression of rapid eye movement behavior disorder in early Parkinson's disease. *Mov Disord Clin Pract*. 2021;8(4):534–540. doi:10.1002/mdc3.13168
123. Sringean J, Stefani A, Marini K, et al. Rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia are more frequent in advanced versus early Parkinson's disease. *Sleep*. 2021;44(9). doi:10.1093/sleep/zsab067
124. Barasa A, Wang J, Dewey RB Jr. Probable REM sleep behavior disorder is a risk factor for symptom progression in Parkinson disease. *Front Neurol*. 2021;12:651157. doi:10.3389/fneur.2021.651157
125. Berry RB, Brooks R, Gamaldo CE, et al; for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2.2. *Ame Acad Sleep Med*. 2012;176(2012):7.
126. Cesari M, Heidbreder A, St Louis EK, et al. Video-polysomnography procedures for diagnosis of rapid eye movement sleep behavior disorder (RBD) and the identification of its prodromal stages: guidelines from the International RBD Study Group. *Sleep*. 2022;45(3). doi:10.1093/sleep/zsab257
127. Sixel-Döring F, Schweitzer M, Mollenhauer B, Trenkwalder C. Intraindividual variability of REM sleep behavior disorder in Parkinson's disease: a comparative assessment using a new REM sleep behavior disorder severity scale (RBDSS) for clinical routine. *J Clin Sleep Med*. 2011;7(1):75–80.
128. Zhang J, Lam SP, Ho CK, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? *Sleep*. 2008;31(8):1179–1185.
129. Cesari M, Portscher A, Stefani A, et al. Machine learning predicts phenoconversion from polysomnography in isolated REM sleep behavior disorder. *Brain Sci*. 2024;14(9). doi:10.3390/brainsci14090871
130. Cardinali DP. Melatonin: clinical perspectives in neurodegeneration. *Front Endocrinol*. 2019;10:480. doi:10.3389/fendo.2019.00480
131. Postuma RB, Gagnon JF, Bertrand JA, Génier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. *Neurology*. 2015;84(11):1104–1113. doi:10.1212/wnl.0000000000001364
132. Xu Z, Anderson KN, Saffari SE, et al. Progression of sleep disturbances in Parkinson's disease: a 5-year longitudinal study. *J Neurol*. 2021;268(1):312–320. doi:10.1007/s00415-020-10140-x
133. Stefani A, Gabelia D, Mitterling T, Poewe W, Högl B, Frauscher B. A prospective video-polysomnographic analysis of movements during physiological sleep in 100 healthy sleepers. *Sleep*. 2015;38(9):1479–1487. doi:10.5665/sleep.4994
134. Postuma RB, Bertrand JA, Montplaisir J, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. *Mov Disord*. 2012;27(6):720–726. doi:10.1002/mds.24939
135. Bugalho P, Ladeira F, Barbosa R, et al. Polysomnographic predictors of sleep, motor and cognitive dysfunction progression in Parkinson's disease: a longitudinal study. *Sleep Med*. 2021;77:205–208. doi:10.1016/j.sleep.2020.06.020
136. Bugalho P, Magriço M, Alves L, Borbinha C. Objective sleep data as predictors of cognitive decline in dementia with Lewy Bodies and Parkinson's disease. *Sleep Med*. 2021;80:273–278. doi:10.1016/j.sleep.2021.01.042
137. Latreille V, Carrier J, Lafortune M, et al. Sleep spindles in Parkinson's disease may predict the development of dementia. *Neurobiol Aging*. 2015;36(2):1083–1090. doi:10.1016/j.neurobiolaging.2014.09.009
138. Kristjánsson T, Stone KL, Sorensen HBD, Brink-Kjaer A, Mignot E, Jennum P. Mortality risk assessment using deep learning-based frequency analysis of EEG and EOG in sleep. *Sleep*. 2024. doi:10.1093/sleep/zsae219