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REVIEW

The Park Sleep subtype in Parkinson's disease: from concept to clinic

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ABSTRACT

Introduction: The heterogeneity of Parkinson's disease (PD) is evident from descriptions of non-motor (NMS) subtypes and Park Sleep, originally identified by Sauerbier et al. 2016, is one such clinical subtype associated with the predominant clinical presentation of sleep dysfunctions including excessive daytime sleepiness (EDS), along with insomnia.

Areas covered: A literature search was conducted using the PubMed, Medline, Embase, and Web of Science databases, accessed between 1 February 2023 and 28 March 2023. In this review, we describe the clinical subtype of Park Sleep and related 'tests' ranging from polysomnography to investigational neuromelanin MRI brain scans and some tissue-based biological markers.

Expert Opinion: Cholinergic, noradrenergic, and serotonergic systems are dominantly affected in PD. Park Sleep subtype is hypothesized to be associated primarily with serotonergic deficit, clinically manifesting as somnolence and narcoleptic events (sleep attacks), with or without rapid eye movement behavior disorder (RBD). In clinic, Park Sleep recognition may drive lifestyle changes (e.g. driving) along with therapy adjustments as Park Sleep patients may be sensitive to dopamine D3 active agonists, such as ropinirole and pramipexole. Specific dashboard scores based personalized management options need to be implemented and include pharmacological, non-pharmacological, and lifestyle linked advice.

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KEYWORDS
Non-motor; Parkinson's, excessive daytime sleepiness; narcolepsy; insomnia; rapid eye movement behavior disorder; sleep apnea; Park Sleep; non-motor phenotype

1. Introduction

1.1. Prevalence of sleep dysfunction as related to the Park Sleep subtype in PD

Non-motor symptoms (NMS) in Parkinson's disease (PD) have been shown to have a high prevalence and huge burden on the quality of life (QoL) and clinical expression of symptoms in PD [1,2]. A survey by Parkinson's UK reported that NMS such as pain, anxiety, and sleep disorders were listed ahead of motor problems in clinical practice, and another study reported that seven out of 10 symptoms reported as most bothersome by patients with advanced PD were non-motor in nature, with sleep featuring as the fourth most bothersome symptom out of 10 in PD of 6 years or more duration [1,3]. While the motor subtypes of PD are well established, the non-motor subtyping concept is relatively new, and several recent papers have focused on the clinical differentiation of the non-motor subtypes, in addition to subtype-specific personalized treatment [1,4–7]. This approach is supported by animal model studies as well as clinical data-driven and cluster analysis-based studies [8,9].

Sleep dysfunction in Parkinson's includes a wide range of symptoms and exploring each potential symptom is outside the scope of this review, however this has been widely published before [10–14]. The focus of this review is on the sleep-related symptoms associated with the Park Sleep subtype, as well as the supportive investigations that can be used to clinically define this subtype. Sleep-related symptoms that occur in the Park Sleep subtype have their main anchors, which principally include excessive daytime somnolence (EDS) along with insomnia as a secondary phenomenon. Many such cases may also have co-morbid rapid eye movement (REM) behavior disorder (RBD) [4].

1.2. The non-motor phenotypes and Park Sleep subtype

Cluster analysis studies have identified four specific clusters of Parkinson's: mild, non-motor dominant, motor-dominant, and severe [15]. Further analysis has outlined seven main NMS dominant subtypes: Park Sleep, Park Autonomic, Park Fatigue, Park Pain, Park Cognitive, Park Apathy, and Park

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Article highlights

- The Park Sleep subtype is characterized by excessive daytime somnolence (EDS), along with insomnia as a secondary phenomenon, which may co-exist with RBD.
- Tests such as polysomnography and the Multiple Sleep Latency Test (MSLT) may be useful in the recognition of anormal sleepiness and RBD, alongside simple screening scales including the non-motor symptoms questionnaire and the ESS.
- Clinical recognition of the Park Sleep subtype is critical, particularly in cases with a propensity to sudden onset of sleep, where Dopamine D3 agonists should be avoided
- The treatment of sleep disorders in PD is challenging, due to their complex nature, and management involving both pharmacological and non-pharmacological strategies may be the most efficacious
- Further research will enhance our clinical phenotyping of PD in the clinic, and as such, will enrich our understanding of the Park Sleep subtype, its biomarkers and management.

Depression/Anxiety [4,16], based on varying neuropathology and neurotransmitter involvement. These non-motor subtypes are exhibited clinically, where specific NMS is predominantly expressed over other, NMS with a background of varying motor involvement, which may be minor [4]. The Park-Sleep subtype is typically characterized by the expression of somnolence of varying degree, with or without associated insomnia. RBD, as mentioned before, may co-exist, and it is worth noting that, from a pathophysiological point of view, RBD has recently been proposed as a core feature of the noradrenergic subtype of PD [17].

EDS is the inability to stay alert and awake during the day waking hours, resulting in periods of uncontrollable need for sleep or unintended lapses into drowsiness or sleep [18]. EDS can be present in as high as 50% of People with Parkinson's [19], with the frequency rising in line with disease severity [20,21] as measured by Hoehn & Yahr (H&Y) staging, disease duration, and the Unified PD Rating Scale (UPDRS) Part III scores [22,23].

RBD is defined as parasomnia demonstrated by vivid dreams allied with simple or complex motor behaviors during REM sleep [24]. Often the bed partner is the first to notice these behaviors during sleep, whilst the individual themselves may very well be unaware. The general population prevalence of RBD is less than 1%, but this rises to 50% in PD populations [25]. Furthermore, RBD can be a prodromal NMS of PD manifesting for 10 years or more, prior to the motor features of PD itself [26,27]. More recently, RBD has been described as a component of the noradrenergic subtype for PD and is also considered a part of the cholinergic subtype [28].

Secondary symptoms include insomnia, which may also co-exist with Park Sleep. Insomnia is defined as the difficulty in initiating, maintaining, and awakening from sleep on at least 3 days per week for 3 months [29] and is reported in over 80% of the people with PD [30]. Insomnia of Park Sleep could be multifactorial and in part could be secondary to EDS and manifest as 'sleep onset insomnia' the latter being associated with comorbidities such as mood disturbances [31,32].

Another important secondary cause of EDS to consider includes Obstructive Sleep Apnea (OSA), the repetitive pharyngeal collapse during sleep causing reduced airflow leading to periodic arrest in breathing [33,34]. Complication of OSA can lead to EDS, fatigue, cognitive changes, limb restlessness, among others. The prevalence and frequency of OSA in the PD population varies across different studies [35–41]. Arguably, OSA-driven hypercapnic acidosis may additionally precipitate sleep fragmentation, and it can also lead to non-REM (NREM) parasomnia events via stimulation of serotonergic neurons, resulting in an increased excitability of motor neurons [42–45].

Several lines of evidence suggest that circadian dysfunction may play an important role in somnolence and that it may present co-morbidity with other sleep disorders in patients with PD [46]. For instance, dopaminergic therapy in PD is linked to a circadian phase advance and decrease in nighttime levels of melatonin [47]. Melatonin is a pineal hormone thought to play a crucial role in enhancing the robustness of suprachiasmatic circadian function, which is also an indirect but practical indicator of suprachiasmatic function [48]. Also, it has been shown that neurodegeneration affects the retina in PD, and frequently leads to impairment of retinal ganglion cells (RGCs), some of which are involved in circadian entrainment to light – dark cycles [49].

2. Potential biomarkers

2.1. Polysomnography and electroencephalogram biomarkers

Polysomnography (PSG) is the gold standard for the diagnosis of RBD [50] and is therefore an important existing diagnostic biomarker, although with limited availability in many countries, and at a high cost [51]. A large study, with 2770 subjects without PD, was conducted using PSG, and those with longer total sleep time, lower REM sleep time, and higher minimum oxygen saturation during REM sleep had a higher risk of developing PD [51,52]* suggesting PSG could be a prodromal biomarker for PD. Whether this could apply as a prodromal biomarker for park-sleep phenotype needs investigation. Several studies suggest that RBD remains the gold standard for RBD diagnosis as well as an important prognostic biomarker and is currently the only instrument to objectively assess RBD severity [53–55]. Alongside RBD, PSG is used for the diagnosis of NREM parasomnia, periodic limb movement disorder (PLMD), and sleep apnea, making it an important biomarker tool for Park Sleep subtypes of somnolence and RBD [38–41].

Electroencephalogram (EEG), part of the PSG, has been shown to be an independent biomarker whereby studies report showing macro- and micro-structural sleep abnormalities prior to formal PD diagnosis, implying a neurodegeneration biomarker capability [56–58]. Further supporting the notion PSG would provide good supporting evidence for confirmation of the Park Sleep subtype, specifically RBD.

2.2. Neuroimaging biomarkers

Several neuroimaging markers could be considered as potential tests to support the Park Sleep subtype; however, at this time, none have a proven evidence base. Dopamine transporter (DaT) single-photon emission computed tomography (DaTScan) using tracers such as *99mTc-TRODAT-1* and

123I–2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane (123I-FP-CIT) in iRBD patients shows that those with decreased update have a higher relative risk of developing synucleinopathies, primarily PD [59–61]. Wasserman and colleagues 2021 have shown iRBD patients having a strong positive association between the reduced dopaminergic availability and poor quality of sleep, as shown with reduced uptake in the left caudate ($r = -0.630$, $p = 0.028$) on DaTScan [10], thus postulating those with reduced dopaminergic availability and poorer sleep quality, tend to have higher risk of phenoconversion to synucleinopathies. This has led many studies to be consistent with their findings in reporting DaTScans ability to be 75% sensitive, 51% specific, 44% positive predictive value, and 80% negative predictive value, with a likelihood ratio of 1.54 to predict the phenoconversion of iRBD [60]. DaTScans in those with somnolence and PD shows there to be an inverse correlation between Epworth Sleepiness Scale (ESS) score and the mean DaT binding in the striatum ($r = -0.627$, $p = 0.03$); however, this is only seen with subjective somnolence reporting [62]. Mirroring these findings, others have found abnormal caudate dopaminergic uptake ($p = 0.030$) and disease duration ($p = 0.018$), were both predictors for the development of EDS in PD [63]. DaTScan has been proposed as a biomarker for other sleep dysfunction, such as narcolepsy with limited supportive results [64].

Cerebral glucose metabolism in iRBD patients, as analyzed with 18F-fluorodeoxyglucose (18F-FDG)-PET, whereby studies have shown involvement in the amygdala, cerebellum, frontal cortical areas, and basal ganglia, corresponding to phenoconversion to PD [65,66]. A recent study by Diaz-Glavan and colleagues 2023 has shown that iRBD patients at higher risk of phenoconversion to PD have lower FDG uptake in the substantia nigra, thalamus, and angular gyrus [67].

Magnetic resonance imaging (MRI) can be used to assess regional volume changes by applying voxel-based morphometry. Studies show significant reduction of gray matter volume, especially in the right superior temporal gyrus, right thalamus, and the posterior regions of PD-RBD patients compared to PD populations without RBD [68–71]. Likewise, neuromelanin (NM) MRI has been reported to reveal changes in the locus coeruleus, sub-coeruleus complex, and substantia nigra of patients with iRBD, indicating their value as potential biomarkers [72,73].

Serotonergic (SERT) transporter activity (DASB) position emission tomography (PET) scans have shown lower activity in Park Sleep subtype in a small study and relate to excessive somnolence, which needs to be further investigated to establish whether central SERT deficit in the graph could underpin the Park Sleep subtype, at least in part [74,75]. Abnormal sensitivity to dopamine D3 receptors in the ventral striatum has been implicated and may explain the susceptibility of Park Sleep patients to highly dopamine D3 receptor selective dopamine agonists such as pramipexole and ropinirole [76,77].

123I-labeled meta-iodobenzylguanidine (MIBG) cardiac uptake has been shown to be reduced in clinical iRBD at similar levels to those developing PD and dementia with Lewy bodies (DLB), and therefore needs to be investigated as a potential biomarker [78].

Sommerauer and colleagues 2018, conduct a study with 30 non-demented PD patients (16 of whom had PSG-confirmed RBD) undergoing cognitive function assessments using a neuropsychological battery of tests and assessment of blood pressure changes on tilting. They report PD-RBD patients had decreased locus coeruleus NM-MRI signaling ($p < 0.001$), and extensive reduction of 11C-MeNER update that correlated with the amount of REM sleep without atonia they had [73].

Combining several imaging modalities together, as discussed above, a study by Knudsen and colleagues 2018 find that compared to controls, iRBD patients had decreased colonic ^{11}C-donepezil uptake ($p = 0.0020$), 123I-MIBG heart:mediastinum ratio ($p < 0.0001$), NM-MRI locus coeruleus:pons ratio ($p = 0.0028$), and putaminal 18F-DOPA uptake ($p = 0.0013$). The iRBD patients had pathology of that observed in PD, yet mostly had normal putaminal dopaminergic storage but had noradrenergic thalamic denervation pathology [79], thus suggesting, in part, a noradrenergic basis of iRBD.

2.3. Biofluid and tissue biomarkers

To date, no single tissue or blood-based biomarker has an evidence base to support a clinical subtype, and specifically for Park Sleep. Despite this, circulating microRNA alterations, specifically downregulated in iRBD, have been demonstrated in several neurodegenerative studies [80], suggesting this downregulation in iRBD could be a biomarker for PD. Furthermore, systemic inflammatory markers, specifically C-reactive protein (CRP) and interleukin-6 (IL6), have been found to be consistently associated with sleep disturbances including insomnia although no specific link with somnolence of Park Sleep has been described [81].

Likewise, plasma melatonin levels have been shown to be significantly higher in PD populations than in controls (mean $19.40 \pm$ SEM 4.23 vs. 12.82 ± 4.85, $p < 0.001$) with a significantly negative correlation between plasma melatonin levels and daytime somnolence (Spearman rank $= -0.308$, $p < 0.05$) and general sleep quality as assessed by PD sleep scale (spearman $= 0.336$, $p < 0.05$) [82]. These findings have been echoed by others finding somnolence in PD as having a more significant negative correlation with plasma melatonin than other NMS [83].

Cerebrospinal fluid (CSF)-based biomarkers have enabled the identification of real-time quaking-induced conversion, which detects pathogenic alpha-synuclein in CSF of iRBD patients with a high specificity and sensitivity implying an increased risk of phenoconversion of iRBD to PD [84,85]. Furthermore, low alpha-synuclein CSF levels have been associated with EDS, insomnia, and narcolepsy, however, levels were also found to be influenced by other external factors, limiting its potential as a stand-alone biomarker [86,87].

PD-related narcolepsy, EDS, sleep attacks, and cataplexy have loss of hypocretin (orexin) neurons with lower orexin levels in CSF observed in some studies, however these findings remain controversial [88–92]. Glial fibrillary acidic protein (GFAP) from CSF has been shown to be elevated in PD populations with narcolepsy, potentiating it as a biomarker, but studies on GFAP remain limited at present [93].

Furthermore, gut microbiome in PD has gained significant momentum in recent decades given our understanding on the guts impact [94–100]* on PD progression and prognosis, but further evidence is now coming to light for the similarity of iRBD gut microbiome to that of people with PD, suggesting evaluating gut microbiome of iRBD as a biomarker for phenoconversion risk to PD [101,102].

2.4. Biomarkers in Park Sleep summary

Recognition of Park Sleep is important not just for research into the natural history of this subtype but also for delivery of bespoke personalized treatment (Figure 1). Much work still needs to be done regarding tests and potential biomarkers, but at this time PSG, if available, remains a useful surrogate to ascertain the diagnosis of RBD, while Multiple Sleep Latency Test (MSLT) may be a useful test for abnormal sleepiness along with simple clinical screening tests such as sleep items in NMS questionnaire (NMSQuest) (items 22–26) as well as the ESS. RBD in particular also appears to predict parkinsonian phenotypes which have faster progression, alongside cognitive and autonomic deficits [17,103]. In the future, serotonin PET studies using DASB as a ligand may be useful based on preliminary proof of concept data.

3. Importance of clinical recognition

As a result of the wide range and complex combinations of sleep disorders in PD, the recognition and diagnosis of sleep dysfunction, and as such the Park Sleep subtype, remains a challenge [104]. However, there are several clinical implications of the diagnosis of the Park Sleep subtype in our routine clinical practice. The narcoleptic subtype, or indeed a propensity to sudden onset of sleep, in PD can be triggered by Dopamine D3 receptor sensitivity in the ventral striatum [105]. There are also studies suggesting that specific dopamine D3 receptor agonists, such as pramipexole and ropinirole, which have a high D3 receptor affinity, may precipitate 'sleep attacks' in PD. In fact, this has been described originally by Frucht and colleagues (1999) who first described a phenomenon of falling asleep at the wheel in patients taking pramipexole or ropinirole [106]. Road traffic accidents in such patients have serious functional consequences. Therefore, clinical recognition of this subtype would mean that subtype-specific treatment [107] needs to be considered including specifically avoiding dopamine D3 receptor agonists, as well as lifestyle advice such as avoiding driving, swimming alone, and operating heavy machinery. Figure 1 1shows an algorithm to consider a pathway to screen patients in the clinic for early clinical recognition and subsequent bespoke personalized management of Park sleep.

In the future, objective quantification tools, as shown in Figure 1, may provide a better evaluation of the causes of daytime somnolence in PD. The standard objective tests of daytime sleepiness are the MSLT and the maintenance of wakefulness test (MWT) [108]. MSLT and MWT provide quantitative measures of daytime sleepiness and ability to maintain vigilance. Both tests are based on latency to electroencephalographic sleep onset. However, both investigations are labor intensive, and they require technician attendance for daytime EEG monitoring. Some centers and studies have similarly argued for the utility of a behavioral test, called the Oxford sleep resistance (OSLER) test, which utilizes a computerized, non-assisted method for monitoring wakefulness and detecting sleep onset [109].

4. Management

Detailed management strategies for all the components of the Park Sleep subtype are beyond the scope of this review. Clinical management of Park sleep should focus on two fundamental principles, one being pharmacotherapy and the

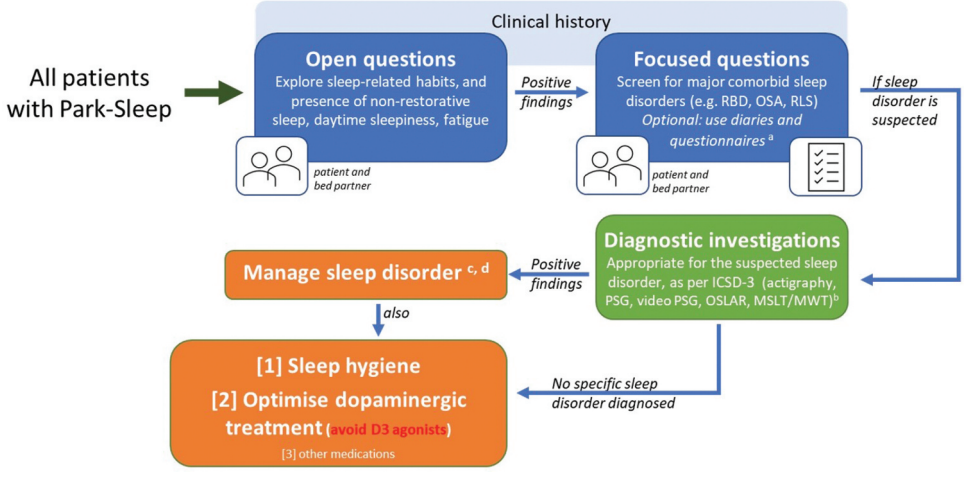

Figure 1. A proposed algorithm for identifying causes and establishing pathway for personalized management of somnolence in people with Park Sleep.

[a]Diaries can help to record clinical details in a standardized way. Formal screening tools may be useful, but note that few questionnaires for sleep disorders have been validated for use in people with PD.

[b]Clinical practice guidelines define the indications for diagnostic tests when sleep disorders are suspected; the same indications apply for patients with PD.

[c]Manage sleep disorder as per relevant guidelines for that sleep disorder.

[d]Management of the most complex cases should be transferred to specialized sleep centers.

ICSD-3 *International Classification of Sleep Disorders version-3*; MSLT *multiple sleep-latency test*; MWT *multiple wakefulness test*, OSA *obstructive sleep apnea*; OSLAR o*xford sleep resistance test*; PSG *polysomnography*; RBD *rapid eye movement behavior disorder;* RSL *restless leg syndrome*.

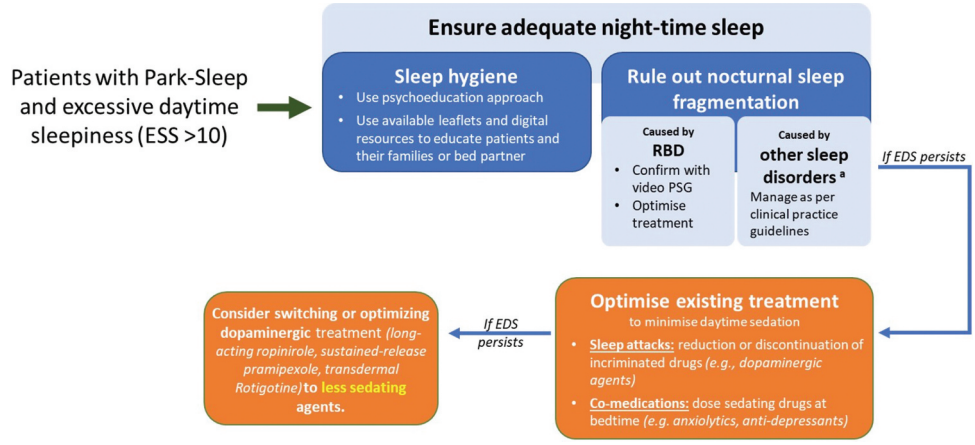

Figure 2. Algorithm of managing poor nighttime sleep in Park Sleep subtype.

Note: [a]Such as sleep apnea, circadian rhythm sleep disorders, non-REM parasomnia, central hypersomnia, periodic limb movement disorder.

PSG polysomnography; SSRI *selective serotonin reuptake inhibitors;* REM *rapid eye movement;* RBD *REM behavior disorder.*

Table 1. Interventions, alongside pharmacological and non-pharmacological management strategies for the treatment of several sleep disorders in PD.

	Interventions	Pharmacological	Non-pharmacological
Insomnia	• Management of contributing factors (irregular sleep patterns, 'bad' habits prior sleep, side effects of medication, undertreated motor symptoms, association of non-motor symptoms) • Optimization of dopaminergic treatment (long-acting ropinirole, sustained-release pramipexole, or transdermal rotigotine)	• Eszopiclone • Doxepin (low doses) • Benzodiazepines/ Benzodiazepine receptor agonists* • Mirabegron (nocturia)	• Sleep hygiene • CBT for insomnia • If co-morbid with circadian rhythm disorder consider melatonin supplements, light therapy and/or chronotherapy. • Physical exercise programs • DBS • Behavioral changes-nocturia (reduced fluid intake before night) • Botulinum-toxin injections in detrusor muscle (nocturia)
Rapid eye movement (REM) sleep behavior disorder (RBD)	• Reduction/discontinuation of drugs that exacerbate symptoms (selective serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants)	• Clonazepam • Melatonin • Dopaminergic agonists (pramipexole, rotigotine) • Melatonin receptor agonists (Agomelatine, ramelteon) • Rivastigmine patch • Calcium alpha-2-delta ligands (pregabalin)** • Sodium oxybate***	• Sleep hygiene (regular sleep routine, safe sleep environment) • DBS
Excessive Daytime Sleepiness Sleep attacks (sudden onset of sleep)	• Improvement of nocturnal sleep duration & quality (e.g. treatment of primary sleep disorders) • Medication adjustments (hypnotics, antidepressants, PD drugs) • Reduction/discontinuation of incriminated drugs (e.g. dopaminergic agents)	Wake-promoting agents: • Modafinil • Caffeine • Memantine • Istradefylline • Methylphenidate • Atomoxetine • Pitolisant/ Solriamfetol	• Sleep hygiene • Adequate exposure to daytime light • If co-morbid with circadian rhythm disorder consider melatonin supplements, light therapy, and/or chronotherapy. • Bright light therapy • Physical activity (not recommended 3–4 h prior to sleep)

*Careful consideration: risk of cognitive decline and risk of pneumonia in elderly PD patients.
**Not widely used for this indication, careful consideration might aid sleep continuity and prevent sleep fragmentation.
***Careful consideration: risk of central nervous system & respiratory depression and risk of addiction.
CBT cognitive behavioral therapy; CPAP continuous positive airway pressure; DBS deep brain stimulation.

second being non-pharmacological interventions, such as regular exercise during the day. Figures 1 and Figure 2 provide a recommended algorithm to consider when approaching management strategies in Park Sleep subtype patients with somnolence, insomnia, and RBD.

Pharmacotherapy needs to be addressed based on dominant clinical features, which could range from RBD, EDS, and insomnia. Table 1 outlines the interventions, alongside pharmacological and non-pharmacological management strategies for the treatment of several sleep disorders in PD. Specific

management strategies for these symptoms are already available as part of the Movement Disorder Society's evidence-based review of management of NMS [110].

Modafinil, a wake-promoting agent, is approved for treatment of EDS in narcolepsy having been shown to provide modest improvement of EDS in PD [111,112], however much of the data shows modafinil's improvement is rather subjective than objective [111–115]. Modafinil has been proposed to have additional anti-parkinsonian actions and, intriguingly, possible neuroprotective action [116–120], giving it more potential for usefulness in Park Sleep subtype, theoretically when combined with non-pharmacological therapy too.

Pitolisant, a novel stimulant drug, with potential for use in Park Sleep subtype. It is a histamine-3 receptor competitive antagonist and inverse agonist promoting histamine release in the brain, which given that in PD histamine neurons are spared suggests the potential use of this drug in treating EDS in PD patients, especially in Park Sleep subtype or in those with comorbid narcolepsy [121]. One of the possible caveats could be related to the caution in potentiating the histaminergic system, since the local release of histamine in the substantia nigra may accelerate neurodegeneration. However, so far, there are no indications that the pitolisant mechanism of action compromises the effect of the anti-parkinsonian drugs.

Solriamfetol, an emerging drug that has dual action of both dopaminergic and noradrenergic reuptake inhibitor, used for EDS in narcolepsy [122]. Solriamfetol has been shown to be safe and effective in maintaining wakefulness, but as a phase II Proof of Concept trial found, it does not show any significant improvement for ESS in PD [123]. Unlike Pitolisant, Solriamfetol remains controversial in its effectiveness for cataplexy and similar sleep disturbances [124]. Nonetheless, both Solriamfetol and Pitolisant are new drugs with the potential to be effective in Park Sleep subtype, given there is evidence for their role in EDS management.

Dual orexin receptor antagonists, including suvorexant and Lemborexant, may be recommended for the management of insomnia and EDS in many neurodegenerative and psychiatric diseases [125]. Such drugs have not yet been investigated in PD specifically, but demonstrate a good safety profile for non-PD patients [126,127].

As mentioned, specific attention needs to be given to avoiding dopamine D3 agonists, such as ropinirole and pramipexole, in the Park Sleep group with a narcoleptic subtype, which can be identified by a high ESS score of 10 or above (Figure 3) [6,106]. Alerting agents such as modafinil may be specifically required and is rated as 'possibly useful' in addition to caffeine, which is currently considered 'investigational' [110].

A specific point should be made about those who declare snoring, as these patients should have ESS performed and subsequently PSG, if required. Such patients have a high risk of developing OSA with there being effective treatment available [128,129]. These patients left untreated are at high risk of sleep attacks during the day impacting their work and QoL.

Special mention should be given to continuous delivery therapies in PD, with current focus for advanced stages of PD, given sleep disturbance is significantly more bothersome and an independent predictor of disease progression [130,131]. Notably, levodopa-carbidopa intestinal gel (LCIG) and continuous subcutaneous apomorphine infusion (CSAi) have shown in clinical trials to have significantly improved sleep disturbances, such as improved nighttime control of motor symptoms, improvement in daytime sleepiness, and reduced RBD features [132–135]. Rotigotine (RTG) transdermal patch, a non-ergot dopamine agonist, provides continuous delivery, and has been shown in open-label studies to improve RBD and may be specifically indicated [136,137].

Lifestyle modification, such as advice on driving, swimming, and other occupations would need to be provided as part of the holistic management strategies [138]. In addition, there is emerging evidence of the use of non-pharmacological therapies in the Park Sleep subtype group, as are depicted in Figure 4 Such therapies include sleep hygiene education, exercise, and interestingly, cognitive behavior therapy (CBT) for insomnia, parasomnia, or affective symptoms [139–141]. In clinical trials, CBT for insomnia in PD has

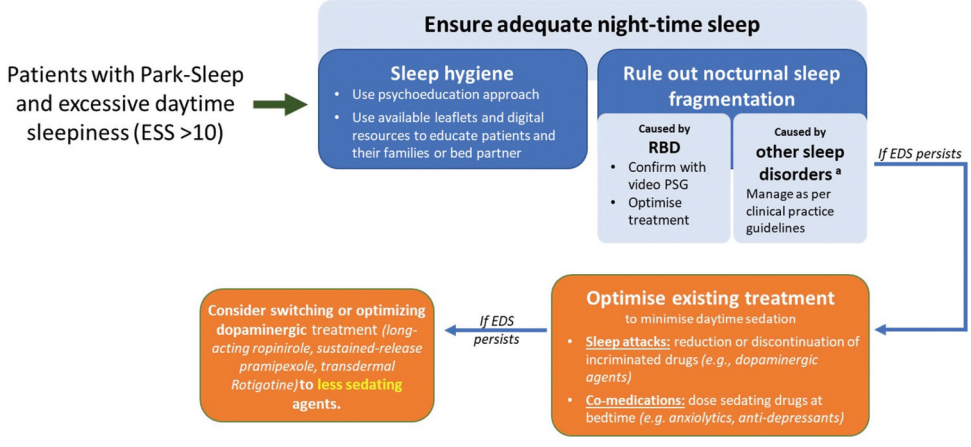

Figure 3. Algorithm for managing excessive daytime sleepiness in Park Sleep subtype.

Note: [a]Such as sleep apnea, circadian rhythm sleep disorders, non-REM parasomnia, Restless Leg Syndrome, Periodic Limb Movement Disorders

EDS excessive daytime sleepiness; ESS Epworth Sleepiness Scale; PSG polysomnography; REM rapid eye movement; RBD REM behavior disorder.

Figure 4. A pictorial summary of potential mind-body approaches to address sleep dysfunction as observed in Park Sleep…
CBT cognitive-behavioral therapy.

shown significant improvement in sleep efficiency, reducing nocturnal wakefulness, and even improving some functional performance [142–145].

Other non-pharmacological strategies include approaches using mind-body interventions, such as mindfulness meditation [146], exercise [147], and hypnotherapy [148] and are further potential routes being investigated. Of note, clinical hypnosis is a possible mental strategy with the ability to better sleep efficiency, being administered either from a trained hypnotherapist, applying post-hypnotic suggestions for a better sleep whenever patient goes to bed or by using an audio recording [148,149]. These mind-body interventions continue to be explored further in the field of PD treatment.

5. Conclusion

In conclusion, the Park Sleep subtype is a clinically relevant concept underpinning the clinical and pathological heterogeneities of PD. Its recognition, as part of the dashboard described by previously [150], highlights the critical need to tailor treatment for the relevant PD populations, and the avoidance of medications such as pramipexole and ropinirole is practical in this subgroup to protect the safety and wellbeing of the patient. Much work needs to be done regarding tests and potential biomarkers, however at this time PSG, if available, remains a useful surrogate, alongside clinical assessments, to ascertain the diagnosis of certain features of this subtype. The treatment of sleep disorders in PD remains a challenge faced by clinicians, due to their complex and often intricate nature; however, a wide range of both pharmacological and non-pharmacological interventions exist. Further research is now important to enrich our clinical phenotyping of PD in the clinic so that clinical practice as well as research is enabled to address the natural history of this important non-motor subtype of PD.

6. Expert opinion

PD is a pathologically and phenotypically heterogeneous, multi-system disorder affecting the central and peripheral nervous system and is not a single ‘disease’ as traditionally viewed. Multiple neurotransmitters are involved, and apart from dopaminergic neurotransmission, the other key involvement is seen in the cholinergic, noradrenergic, and serotonergic systems. Clinically, preferentially greater pathological involvement of these non-dopaminergic systems may give rise to non-motor symptom-predominant presentations at diagnosis, termed non-motor subtypes of PD.

Non-motor subtypes segregate into several clinical categories, and Park Sleep has been postulated to be a clinical subtype often

associated with a dominant underlying serotonergic deficit, which can be imaged in vivo and may become a potential biomarker. Such patients may also have significant orexin cell loss in the arousal area of the raphe in the brainstem and clinically may develop 'sleep attacks' like narcolepsy without cataplexy in addition to generalized excessive somnolence.

Clinical characterization can be aided by assessments with scales such as NMSQuest and ESS in the clinic and can be confirmed by using PSG. Awareness is important as such patients may be very sensitive to dopamine D3 agonists, such as ropinirole and pramipexole, and should mostly be advised not to drive or not undertake activities such as swimming alone. In addition, alerting agents such as modafinil are often required for tailored subtype-specific therapy. In our advanced PD subgroup, Park Sleep subtype tends to be more problematic, so infusion therapies such as CSAi and LCIG are shown to be promising therapeutics in advanced PD populations with sleep disturbances. As further options for advanced therapies in PD are explored, it is essential to ensure that the impact of sleep disturbances in people with PD is assessed, given the high burden as the disease progresses. Other potential treatments including Opicapone, a Catechol-O-methyl transferase (COMT) inhibitor, which is emerging on the market with the potential to provide benefit in Park Sleep manifestations in PD, are showing increasing recognition of Park Sleep subtype in PD treatment.

Non-pharmacological therapy in Park Sleep subtype is shown to be a useful agent to adopt in the clinical management of these subtypes of patients. Therapies that follow a body-mind wellness route, such as mindfulness meditation and exercise, are a growing area of management in these groups.

Abbreviations

PD	Parkinson's disease
NMS	Non-motor symptoms
QoL	Quality of Life
EDS	Excessive daytime sleepiness
REM	Rapid eye movement
RBD	REM sleep behavior disorder
OSA	Obstructive sleep apnea
H&Y	Hoehn & Yahr
UPDRS	Unified PD Rating Scale
NREM	Non-REM
PLMD	Periodic limb movement disorder
RGC	Retinal ganglion cells
PSG	Polysomnography
EEG	Electrophysiology
DaT	Dopamine transporter
DaTScan	Dopamine transporter single photon emission computed tomography
123I-FP-CIT	123I–2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane
iRBD	Idiopathic RBD
ESS	Epworth sleepiness scale
PET	Positron emission tomography
MRI	Magnetic Resonance Imaging
NM	Neuromelanin
SERT	Serotonergic
CRP	C-reactive protein
IL-6	Interleukin-6
CSF	Cerebral spinal fluid
GFAP	Glial fibrillary acidic protein
SNP	Single nucleotide polymorphism
MSLT	Multiple sleep latency test
NMSQuest	Non-motor symptom questionnaire
FDG	[$^{1\ 8}$ F] Fluorodeoxyglucose
GM	Grey matter
MIBG	123I-labeled meta-iodobenzylguanidine
DLB	Dementia with Lewy Bodies
RNA	Ribonucleic acid
SERT	DASB serotonergic transporter activity.
MWT	Maintenance of wakefulness test
OSLER	Oxford sleep resistance
ICSD-3	International Classification of Sleep Disorders version-3
LCIG	Levodopa-carbidopa intestinal gel (LCIG)
CSAi	Continuous subcutaneous Apomorphine infusion
RTG	Rotigotine
CBT	Cognitive behavioral therapy
CPAP	Continuous positive airway pressure

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