



NEUROPSYCHOPHARMACOLOGY REVIEWS

Sleep in Parkinson's disease

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Sleep disturbances are common in Parkinson's disease and comprise the entire spectrum of sleep disorders. On the one hand regulation of sleep and wakefulness is affected in Parkinson's disease, leading to the development of disorders, such as insomnia and daytime sleepiness. While on the other hand control of motor activity during sleep is impaired, with subsequent manifestation of parasomnias (mainly REM sleep behavior disorders, but also, albeit more rarely, sleepwalking, and overlap parasomnia). Restless legs syndrome has been reported to be frequent in patients with Parkinson's disease, although there is no consensus on whether it is more frequent in Parkinson's disease than in the general population. The same is true for sleep-related breathing disorders. Regarding the diagnosis of sleep disorders in patients with Parkinson's disease, one of the main challenges is correctly identifying excessive daytime sleepiness as there are many potential confounding factors, for example it is necessary to distinguish sleep-related breathing disorders from medication effects, and to distinguish restless legs syndrome from the concomitant presence of potential mimics specific to Parkinson's disease, such as akathisia, nocturnal leg cramps, nocturnal hypokinesia, early morning dystonia, etc. The correct diagnosis of REM sleep behavior disorder is also not always easy, and video-polysomnography should be performed in order to exclude mimic-like movements at the end of sleep apneas or violent periodic leg movements of sleep. These aspects and specific considerations about diagnosis and treatment of sleep disorders in patients with Parkinson's disease will be reviewed.

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INTRODUCTION

Sleep and wakefulness regulation rely on a highly complex and integrated function of multiple brain areas and neurotransmitters, many of which have also been shown to be affected in patients with Parkinson disease (PD) [1–7]. With this pathophysiological background, it is not surprising that disturbances of sleep and wakefulness are almost ubiquitous in patients with PD. An oft-cited survey performed in 1988 found that among PD patients, 98% had experienced disabilities at night or on waking since the onset of their disease [8], and disturbed wakefulness regulation was shown to be a prominent feature in up to 30% of patients with PD [1, 2, 9–11].

Beyond the PD-related impairments of brain and neurotransmitter function there are other major contributing factors to disturbances of sleep and wakefulness in patients with PD, these include dopaminergic drugs, which are known to influence regulation of sleep and wakefulness, as well as other medications used in this elderly and often multimorbid population, comorbidities, PD symptoms that impair patients' sleep, such as nocturnal akinesia, and genetic factors that predispose to certain disturbances of sleep and wakefulness [2, 9, 12–14]. Moreover, lifestyle factors and impulse control disorders, a frequent side effect of dopaminergic drugs, can also play a role in the development and continuation of sleep disturbances in patients with PD.

An interesting, yet often neglected feature of PD concerns the interaction of sleep and motor function, with sleep benefit, i.e. some patients experience an improvement of motor function upon awakening [15–19], while others experience positive effects of sleep deprivation on motor function [20–22].

In patients with PD, both the sleep macrostructure (manifesting for instance as sleep fragmentation and a relative increase in superficial sleep) [23, 24] and sleep microstructure, manifesting as disturbed integrity of certain sleep stages (e.g. disturbed sleep spindles and K-complexes, or insufficient muscle atonia during REM sleep) [25–32] are affected.

The range of sleep disturbances in PD comprises the full spectrum of sleep disorder categories as outlined in the International classification of sleep disorders 3rd edition (ICSD-3) [33]. The categories of sleep disturbances apparent in patients with PD thus comprise insomnia, disorders of daytime somnolence, sleep-related breathing disorders, circadian disorders, and sleep-related movement disorders, namely restless legs syndrome (RLS), and parasomnias. This heterogeneity of sleep phenotypes might reflect the well-known heterogeneity of PD motor phenotypes as well as the biologic (biomarker) heterogeneity of PD.

Insomnia and daytime sleepiness in patients with Parkinson's disease

As outlined above, patients with PD frequently experience insomnia, most often as a disorder of sleep maintenance, but also as a disorder of sleep onset or early morning awakening. The diagnosis of insomnia is always based on subjective symptoms. Patients report difficulties falling asleep or maintaining sleep, early awakening or non-restorative sleep, associated with subjective concern or daytime impairment [1, 2, 9–11, 23]. Notably, there is sometimes a discrepancy between subjective complaints of insomnia and only subtle disturbances of sleep structure in otherwise healthy people, whereas in patients with PD, in addition

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to the subjective complaints of insomnia, there is often a significant manifest disruption of the integrity of sleep macro and microstructure.

Multiple studies have reported high prevalences of insomnia in patients with PD [10]. Gjerstad and co-workers investigated sleep in a prospective longitudinal cohort of 231 patients with PD, and performed an 8-year follow-up in 89 of them. The authors reported a large intraindividual variation in insomnia symptoms as evaluated by questionnaires, but found that in the population-averaged logistic regression model the presence of insomnia was related to female sex ($p=0.001$, OR 2.21, 95% CI 1.36–3.59), disease duration ($p=0.009$, OR 1.07, 95% CI 1.02–1.13) and to depression as measured by the Montgomery and Aasberg Depression Rating Scale ($p=0.03$, OR 1.06, 95% CI 1.01–1.11) [34]. However, PD-specific treatment, namely dopaminergic drugs, can be responsible for these symptoms. Therefore, in another study the same group examined the frequency, development, and associated covariates for different types of insomnia complaints in a cohort of originally drug-naïve patients with incident PD during the first 5 years of treatment after diagnosis of PD. Overall, in this study they found that the prevalence of insomnia did not increase at the 5-year follow-up in these early PD patients, but, after the initiation of dopaminergic medication, disorders of sleep maintenance significantly increased over time, whereas disorders of sleep onset decreased [35].

In a Dutch 5-year, longitudinal cohort study of 421 PD patients who were examined annually, Marinus and co-workers used a prospective cohort design to evaluate frequency, course, longitudinal associations, and risk factors of insomnia. Linear mixed models were used to identify factors associated with longitudinal changes in the SCOPA sleep scales. Presence of insomnia (defined as a nighttime sleep section of the SCOPA-SLEEP questionnaire score ≥ 7) was reported at baseline in 27% of the total of 412 PD patients evaluated, and insomnia symptoms developed at some point during the annual follow-up examinations in an additional 33% of patients who did not have insomnia at baseline ($n=302$). Once again female sex was associated with higher SCOPA sleep disturbance scores as were depressive symptoms, more severe motor complications (dyskinesias and motor fluctuations), higher antiparkinsonian medication doses and sleep medication use. In addition there was an association with higher disability, higher autonomic dysfunction, presence of hallucinations, and postural instability gait difficulty phenotype [36].

Joy and co-workers evaluated newly diagnosed levodopa-naïve patients with PD and reported frequent and variable alteration of sleep macro-architecture in these patients [37]. However, Ferreira and co-workers reported poor sleep quality and sleep architecture changes in PD patients, which improved with levodopa following improvement of motor symptoms (reduction of rigidity and tremor), but dopamine did not reverse sleep architecture changes [38].

In a very large epidemiological dataset comprising 220,934 participants, Gao and colleagues evaluated daytime napping and nighttime sleeping durations in subsets of patients with established PD ($n=267$), recent diagnosis of PD ($n=396$), and in those who were in the prediagnostic PD stage ($n=770$) and who only later converted. They reported that longer daytime napping was associated with higher odds of PD in all three clinical stages. This association was strongest for established PD (long nappers, i.e. ≥ 1 h, versus non-nappers OR 3.9; 95% CI: 2.8, 5.6; $p < 0.0001$) but also significant in the other cases (recent cases OR 2.2; 95% CI: 1.7, 3.0; $p < 0.0001$; prediagnostic cases OR 1.5; 95% CI: 1.2, 1.9; $p=0.0003$). However, in nighttime sleep duration analysis, a U-shaped relation between hours of nighttime sleep and diagnosis of PD was observed for established cases, but was less apparent for recent cases and disappeared for prediagnostic cases. The authors therefore showed that daytime sleepiness—as expressed by daytime napping duration, but not nighttime sleep duration—is one of the early nonmotor symptoms of PD [39].

Daytime sleepiness in PD was first described many decades ago [1, 17, 40, 41], nonetheless it still remains an underappreciated feature despite its relevance, especially, for example, following reports of PD patients (taking dopamine agonists) falling asleep while driving [42]. Driving safety in patients with PD has been evaluated through driving simulators with studies reporting more total collisions in PD patients compared to controls [43, 44]. Studies using the Epworth sleepiness scale to evaluate daytime sleepiness in PD found varying abnormal scores (9.3% [45], 33% [1], or 43.2%) [46], with 28.4% noting somnolence with dopaminergic drug intake and 6.8% describing unintended sleep episodes [46].

However, the relationship between PD and daytime sleepiness is controversial, and a large study using the Epworth sleepiness scale conducted by the Parkinson's Progression Markers Initiative (PPMI) group on 423 PD patients, reported no difference in prevalence of excessive sleepiness in de novo untreated PD patients compared with healthy controls [47]. A 3-year follow-up in this cohort showed that daytime sleepiness increases significantly over time in early PD, with a dose-dependent effect of dopaminergic therapy, suggesting a relevant role of PD-specific therapy more than underlying pathophysiological mechanisms for excessive daytime sleepiness in PD [48].

Sleep-related breathing disorders

Early reports showed large variability of sleep-related breathing disorders in PD, with some studies showing more central, others more obstructive, or no sleep-related breathing disorder at all, but in early studies these differences may have been due to less established methods of respiratory event recording during polysomnography (PSG) and small sample sizes.

Even in patients without a confirmed diagnosis of manifest sleep apnea a significant correlation between heavy snoring and daytime sleepiness has been reported for PD [1, 49]. One study showed that manifest or subclinical sleep breathing disorders are present in up to 50% of PD patients, but in contrast to non-PD patients sleep structure in PD is not normalized with CPAP treatment [50].

However, other studies have reported variable prevalence and severity of sleep-related breathing disorders in PD. Diederich and colleagues reported a 43% prevalence of sleep apnea syndrome in PD, which was, however, mostly mild or moderate with little decline of the minimal or mean oxygen saturation levels compared to an apnea-hypopnea index (AHI)-matched control group [51]. Arnulf and co-workers found sleep apnea (defined according to established criteria for moderate or severe obstructive sleep apnea) in 20% of 54 PD patients treated with levodopa or a combination of levodopa and dopamine agonists referred for sleepiness [52]. In another study the same group reported that sleep apnea in PD was less frequent than in controls, when this latter group was BMI-matched with hospitalized controls (27% vs. 40%), and only 10% of PD patients had severe sleep apnea [53]. Similarly, Trotti and Bliwise reported no increased risk of obstructive sleep apnea in PD compared to normative population-based data from the Sleep Heart Health Study. In this cohort, Epworth Sleepiness Scales scores, BMI, and snoring did not correlate with the AHI [54].

Further adding to the complexity of sleep disturbances in PD, these patients spend more time in the supine position and the presence of severe obstructive sleep apnea syndrome in PD is associated with a major reduction in position changes [55].

At least one study has shown that PD patients with obstructive sleep apnea have worse cognitive functioning on cognitive screening measures than those without, but again, CPAP-treatment may not result in overall cognitive improvement in patients with PD [56].

Based on these data, there is some discussion about whether obstructive sleep apnea is a problem in patients with PD,

especially as common symptoms associated with sleep apnea, e.g. sleepiness, cognitive impairment, nocturia, and snoring have been reported to not be related with AHI in PD patients [53, 54]. These observations lead to questions about whether sleep apnea is a cause of sleepiness in PD patients and when is it clinically relevant [53, 57]. These concerns highlight the importance of a detailed sleep history and the need to perform adequate sleep studies in PD in order to account for all sleep disturbances. Nevertheless, even symptoms commonly associated with sleep apnea may not relate to AHI in PD; PD patients with relevant sleep apnea should be treated as a general rule due to probable long-term negative cardiovascular outcomes, although long-term comparative follow-up studies investigating cardiovascular outcomes in PD patients with treated and untreated sleep-related breathing disorders, are lacking [57].

Circadian disturbances

Regulation of sleep and wakefulness is a highly complex and integrated function involving multiple brain areas and neurotransmitters, many of which are impaired in PD [1–7]. Dopamine for example plays a key role in the circadian system, but its metabolism and activity are also strongly influenced by the circadian clock [6]. On this pathophysiological background it is not surprising that disturbances of sleep and wakefulness are almost ubiquitous in patients with PD. Moreover, impairment of circadian function in PD is relevant not only for sleep–wake cycles but also for motor, autonomic, cognitive, and psychiatric symptoms in PD patients [6].

Interestingly, some components of the circadian system seem to be preserved in PD. In a rat PD model with unilateral 6-hydroxy-dopamine lesions, it was shown that circadian distribution of motor activity is intact [58]. Circadian distribution of temperature rhythms is also maintained in PD, which is not the case in multiple system atrophy (MSA) [59]. However, increased sleepiness under treatment with dopamine agonists may also relate to an effect on body temperature (as described in 1999) [60, 61].

Despite these reports of preserved circadian distribution of motor activity pattern and temperature, on a clinical basis circadian disturbances are frequent in patients with PD [6, 7, 10, 62], and were noted as early as 1817 by James Parkinson [63]. It was later shown that circadian melatonin secretion rhythms are blunted in PD, and amplitude of melatonin rhythm is reduced [64]. These alterations in PD patients may also relate to both insufficient exposure to bright light [65–67] and phase advance of the sleep–wake cycle due to treatment with dopaminergic drugs [68, 69]. Moreover, it is conceivable that impulse control disorders, such as gambling, compulsive shopping, binge eating, compulsive sexual behavior, and punding, take place mainly during the nighttime or favor losing track of time and therefore accompany circadian disruption or contribute to precipitating and perpetuating sleep–wake cycle disturbances. In clinical cases, this may lead to the inversion of the day- and nighttime rhythm, with insomnia after midnight and increased daytime sleepiness [70].

Interestingly, in a large case control study of Han Chinese patients, an association of single nucleotide polymorphisms in the clock genes *ARNTL* and *PER1* was found in patients with PD, thus supporting the notion that genetic polymorphisms are present in these two circadian regulation genes [71].

Published evidence highlights the complexity and multifactorial nature of circadian rhythm disturbances in PD, which implies that an accurate clinical and instrumental (using e.g. actigraphy and polysomnography) evaluation is needed in these patients to identify the main cause or main problem in sleep–wake cycle impairment and provide individualized treatment.

Sleep-related movement disorders

Among sleep-related movement disorders, RLS and periodic leg movements of sleep (PLMS) have been particularly investigated in

patients with PD and this aspect was recently reviewed by Högl and Stefani [72].

In the past three decades, multiple studies have attempted to evaluate the frequency of RLS in patients with PD producing very discrepant results ranging from 0% to 52.3% [12, 13, 72–76]. Together with these discrepancies, some authors noted early on that RLS diagnosis may be confounded in patients with PD due to potential overlap of RLS symptoms with early morning dystonia, akathisia, painful neuropathy, nocturnal hypokinesia (which may be associated with a reported urge to move), biphasic dyskinesia, and nocturnal legs cramps [12, 75, 76].

Interestingly, augmentation of RLS is present very rarely in patients with PD, probably because of a different underlying alteration in dopaminergic circuits in RLS (dopamine dysfunction) and PD (dopamine deficit), and different responses of these altered circuits to dopamine/dopaminergic therapy.

Frequency and causes of RLS in PD are still unclear. Angelini and co-workers investigated a series of 109 cognitively unimpaired de novo PD and compared them to age-matched and sex-matched controls. They found that there was no significant difference in overall lifetime and current primary RLS between PD patients and controls, but discussed whether the frequent onset of RLS symptoms after diagnosis of PD could be related to dopaminergic therapy for PD [77]. This hypothesis is supported by the reports that even in subjects with PLMS the use of dopaminergic agents might lead to the development of RLS [78].

Verbaan and co-workers evaluated the frequency and clinical profile of RLS in 269 non-demented PD patients and also reported a similar prevalence of RLS as in the general population [79].

Gjerstad and co-workers performed a study in 200 drug-naïve patients with early, untreated PD and 173 age-matched and gender-matched control subjects. They clearly reported that there was a three-fold higher risk of leg motor restlessness, but not of true RLS, in patients with early PD. 40.5% of PD patients and 17.9% of controls reported leg restlessness ($p < 0.001$), but only 15.5% of patients with PD and 9.2% of controls met criteria for full RLS ($p = 0.07$) [80]. Similar results were also reported by another group in a large sample of PD patients [81]. These data highlight the need for an accurate assessment of symptoms when suspecting RLS in PD patients in order to exclude potential mimics.

Only Cochen De Cock and colleagues evaluated the suggested immobilization test (SIT) in PD and reported that it is useful for making a diagnosis of RLS in patients with PD in whom the diagnosis of RLS based on expert interview alone may be difficult. The most sensitive instrument was the sensory part of the SIT that clearly showed an increase of sensory leg discomfort over time [82]. The PLM index was increased in patients with primary RLS compared to controls, but did not differ between patients with PD, with and without RLS [82].

Nocturnal akinesia, a well-known motor manifestation of PD, significantly diminishes the capacity to make comfort moves and can lead to sleep disruption [12]. Moreover, patients may report an urge to move due to nocturnal akinesia/hypokinesia. Lakke and colleagues have shown that axial rotation is even more disturbed in the recumbent position than while standing, which may lead to increase of symptoms due to hypokinesia at rest or during the night, mimicking RLS symptoms [83].

Impaired turning ability in bed has been associated with sleep disturbances [84]. Louter and co-workers evaluated a PD cohort prospectively and found that patients who subjectively reported impaired bed mobility (i.e., nocturnal hypokinesia), indeed showed fewer sleep-related body position changes than controls, and that polysomnographically evaluated sleep efficiency was diminished in these patients [85]. This should be taken into account when treating motor symptoms in PD patients, as a study from Thailand has shown that in PD patients with nocturnal hypokinesia/akinesia, nighttime apomorphine infusion improves the number of

turns in bed, turning velocity, and the extension of turning as measured by actigraphy [86].

RBD and other parasomnias

In patients with PD, beyond the well-known and peculiar occurrence of REM sleep behavior disorder (RBD), non-REM-sleep parasomnias (e.g. sleepwalking) and parasomnia overlap disorder have also been described.

Bassetti and co-workers systematically investigated the presence of sleepwalking in 165 consecutive PD patients. 3.6% ($n = 6$) reported adult-onset sleepwalking. In 4 out of 6 patients, RBD was detected on video-polysomnography [87]. In another study, video-polysomnography (vPSG) was used to assess 30 patients with PD (10 of them with a history of sleepwalking, 10 with a history of RBD and 10 without a history of parasomnia). Again, 8 out of 10 patients with a history of sleepwalking presented RBD on vPSG. Sleepwalking in this cohort was associated with depression, higher disease severity, and functional disability. Due to the frequent occurrence of overlap parasomnia, the authors suggested that a common underlying disturbance of motor control during sleep exists in PD [88].

The diagnostic criteria for RBD comprise repeated episodes of sleep-related vocalization and/or complex motor behaviors, and these behaviors need to be documented by PSG as occurring during REM sleep, or, based on a clinical history of dreaming, are presumed to occur during REM sleep. In addition, it is obligatory that polysomnographic recording demonstrates REM sleep without atonia [89]. Other sleep-related movement disorders that are frequent in PD (e.g. PLMS, sleep apnea) might produce similar symptoms mimicking RBD by history and need to be excluded.

RBD affects up to 47% of patients with PD [90–93]. In the past RBD has received much attention due to the fact that it may precede PD by more than a decade [93–99], but there is also the possibility that RBD onset is more or less simultaneous with PD onset or that RBD follows PD onset by several years [91, 100].

In fact, the remarkably high rate of conversion from isolated RBD into alpha synuclein disease, namely PD, dementia with Lewy bodies, or rarely MSA, has led several authors to suggest here that RBD itself needs to be considered more than a REM-parasomnia, as it represents an alpha synuclein disease or an early manifestation of alpha synuclein disease [94, 97, 101]. For clinical studies, combinations of isolated RBD with other Parkinson/alpha-synuclein-related neurodegeneration risk markers is probably the most useful approach. Multiple biomarkers of alpha synuclein-related neurodegeneration have been described [93], and may serve to evaluate different aspects of neurodegeneration, and while some, such as olfactory dysfunction, are stable markers indicating a higher risk of short-term conversion, others such as DAT-SPECT are progressive markers useful for monitoring disease progression over time [93].

The International Parkinson and Movement Disorder Society has calculated that the PSG-confirmed likelihood ratio of more than 80% probability of suffering of prodromal PD is 130 in patients with isolated (previously called "idiopathic") RBD [102]. However, this is true and has been extensively confirmed only for vPSG confirmed RBD. In fact, likelihood ratio declines to 2.3 in case of positive response to a screening test for RBD with documented specificity of 80–99% [102]. These is even more relevant considering that an increasing amount of studies reported lower specificity of validated questionnaires for RBD outside the context of validation studies [103–107].

Interestingly, there is increasing evidence that there may be prodromal stages of RBD, which manifest as minor jerks [91, 100, 108, 109] or REM sleep without atonia [101]. Mollenhauer and co-workers found that even PD patients who did not yet meet the criteria for RBD had more movement during REM sleep [91], and Sixel-Döring and Trenkwalder denominated these seemingly purposeful movements "REM sleep behavioral events" (RBE) and

demonstrated that they could represent another prodromal sign of RBD [100, 108].

Dream content was investigated in PD as early as 1992 [110]. Later on, Borek and colleagues investigated dream content in PD with and without RBD, showing that violent and aggressive dreams were more common in RBD patients, and that men with PD had more aggressive dreams than women with PD [111]. The same group further evaluated aggressive dream content in men with PD and searched for a correlation with testosterone levels, which was not found [112].

Bugalho and Paiva characterized dream content in PD in detail using the Hall and van de Castle system. They found more dreams with animals, aggression/friendliness, physical aggression, befriender in PD compared to controls, and less aggressor and bodily misfortunes features [113]. Valli and colleagues further analyzed dreams in patients with PD and RBD systematically, using spontaneous free-worded dream reports and a structured dream questionnaire during vPSG. Those data could be linked to motor behaviors on vPSG above chance level [114]. Interestingly, another study by the same group assessed dream content analysis in PD with and without RBD and reported no major differences between these two groups regarding action-filledness, vividness, or threat content. However, negative dreams were more frequent in PD with RBD compared to PD without RBD [115].

Dream content has also been investigated in the prodromal phase of RBD. Most patients with RBE can recall dream content, and report nonviolent, non-threatening dreams. RBE subjects who at follow-up developed RBD reported more vivid and elaborate dreams [109].

Sleep benefit and positive effect of sleep deprivation in patients with PD

The complex interaction of sleep and motor function is reflected in two interesting phenomena: sleep benefit, i.e. the experience of an improvement of motor function upon awakening [15–19], and a positive effect of sleep deprivation on motor function [20–22].

Sleep benefit was first described based on patients' reports, and systematically evaluated in large cohorts of patients with PD with contrasting results. Some groups reported this phenomenon to be common in a subgroup of PD patients with specific clinical characteristics, e.g. with longer disease duration [17] and younger age at onset of disease [19, 116]. This phenomenon has been reported to be so relevant to allow PD patients with sleep benefit to skip or delay medication [18]. A study systematic evaluating motor state a night before sleep and in the morning upon awakening reported a slight motor improvement in the morning in patients with sleep benefit, without polysomnographic differences between the two groups [15]. Another study using PSG reported shorter total sleep times and longer sleep latencies in PD patients reporting sleep benefit [117].

However, other groups found no actual improvement in motor functioning in PD patients reporting sleep benefit [118, 119], or only in a small percentage of them [120, 121], or reported in those patients with PD experiencing sleep benefit no association with the previously reported clinical variables [122], maybe because of methodological issues.

Interestingly, in patients with PD it has also been described, for the first time as early as 1987 [22], a motor improvement after sleep deprivation. These observations have been later on replicated [20], but could not be confirmed in a controlled study. These latter results suggested that only a subgroup of PD patients could benefit from partial sleep deprivation [21].

Assessment of sleep disturbances in patients with PD

In general, a comprehensive sleep history is often a very useful first step to narrow down the type of sleep disorders in patients with PD. It should start with the time when the patient goes to bed and gets up and also include planned daytime naps. It should

involve the perceived sleep latency, perceived awakenings (including prolonged wake phases during the nighttime and daytime dosing of/or fighting against sleepiness). The Epworth sleepiness scale or other scales can be used [123].

Specifically, the evaluation of insomnia should rule out sleep hygiene or circadian disorders. Patients should be questioned specifically about the presence of impulse control disorders and nighttime activities, particularly in case of suspected circadian rhythm disturbances. If a circadian disorder, such as delayed or advanced sleep phase syndrome or non-24-h sleep-wake disorder is suspected, assessments with actigraphy or dim light melatonin onset may prove useful [124].

For patients with prominent daytime sleepiness, polysomnography should be used in every case (to rule out sleep disordered breathing), but a multiple sleep latency test (for instance to demonstrate a narcolepsy-like phenotype and to quantify the amount of daytime sleepiness) is also warranted [124].

Respiration questioning should at least include snoring and witness apneas, positional dependence, breathing pauses, intensity of snoring, nocturnal hypertranspiration or nocturia. In specific cases stridor (which is for patients relatively difficult to distinguish from simple snoring) should also be assessed. If underlying sleep disordered breathing is suspected, cardiorespiratory polygraphy or polysomnography should be performed [124].

Every attempt should be made to assess the presence of RLS, and distinguish it from other types of restlessness, specifically investigating possible mimics or confounders. Patients should be asked about the ability to turn in bed. Polysomnography is not needed to make a diagnosis of RLS, and in patients with PD PLM are very frequent [72, 125]. In case of suspected RLS, an extensive clinical history is fundamental to rule out possible mimics which are very common in PD patients, these include nocturnal hypokinesia/akinesia (sometimes associated with an urge to move), akathisia, nocturnal leg cramps, early morning dystonia, and painful neuropathy. In addition, medication-induced dyskinesias could be mistaken for RLS-related PLM.

For patients with suspected RBD, vPSG is required, also if the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [126], in contrast to the ICSD-3 [33], does not require polysomnographic demonstration of REM sleep without atonia if there is a history suggestive of RBD in patients with an established synucleinopathy diagnosis. However, it is likely that performance of vPSG would diagnose more patients with RBD, in whom history taking alone was not sensitive [93, 127, 128] or also rule out mimics in subjects with an apparently "clear" history of RBD, such as obstructive sleep apnea which may go along with violent behavioral releases [129] and violent PLM [130].

Patients should be specifically investigated for altered dream content, dream enactment with movements or jerks, and vocalizations, specifically highly variable vocalizations for RBD [124]. In general, current treatment should be assessed due to potential side effects or influence on sleep disorders.

Several questionnaires have been developed and validated for patients with PD [123]. The International Movement Disorder Society (MDS) task force recommends, for overall sleep disturbance, both the Parkinson's Disease Sleep Scale (PDSS) [131] and Scales for Outcomes in PD Sleep (SCOPA sleep), as well as two generic scales, namely the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale [123, 132].

Specific questionnaires for specific sleep disorders, such as for RBD, have also been developed [93]. In general, they have the advantage of being used to screen the general population or large samples of study populations without performing a vPSG. However, they cannot usually be used as diagnostic instruments and e.g. for RBD questionnaires several limitations have been demonstrated [93, 103–107, 127]. Actigraphy is also useful as a first screening method to potentially indicate suspected RBD [133].

However, in the evaluation of patients with abnormal daytime sleepiness, and with suspected RBD, vPSG evaluation is indispensable. Also, if there is some treatment-refractory sleep disturbance, or if one suspects multiple contributors and comorbid sleep disorders, vPSG will help to narrow down the differential diagnostic possibilities.

Due to the multifactorial aspects of sleep disorders in patients with PD, vPSG will often provide much more detailed, objective, and quantifiable information about the underlying aspects of the sleep disorder in an individual patient, and at the same time provide information about sleep integrity or fragmentation, the number of arousals or awakenings, the total sleep efficiency, respiration during sleep and respiratory events, and the quantification of motor activity during sleep, ranging from REM sleep without atonia (RWA)/RBD to PLM, fragmentary myoclonus [72, 134] and others. vPSG in patients with PD should in every case include not only the usual EMG channels of mental/submental muscles and tibial anterior muscles, but also of upper extremity muscles (flexor digitorum superficialis from both arms). This is not only recommended based on normative values provided by the SINBAR group [135] but also provides more sensitivity and specificity than using EMG alone [136].

Treatment of sleep disorders in patients with Parkinson's disease From the manifold clinical manifestations and underlying pathomechanisms of sleep disorders in patients with PD outlined above, it is obvious that treatment needs to be tailored individually according to the predominant clinical symptomatology and underlying specific sleep-related diagnosis. However, a major problem is the sparsity of randomized, controlled trials for sleep disorders in PD.

For treatment of insomnia in patients with PD, hypnotics are sometimes indicated, but the caveats of potential worsening of daytime sleepiness or sleep-related breathing disorders should be kept in mind. Clinically, quetiapine is sometimes used, and in cases of very severe insomnia clozapine—with the usual treatment caveats—have been used. Melatonin treatment is not specifically indicated for insomnia in PD, but is often used for RBD (see below). Rotigotine has been reported to improve sleep quality and continuity in PD patients by promoting sleep stability and increasing REM [137]. However, in general, there is insufficient evidence on drugs to treat insomnia in PD patients, although eszopiclone and melatonin are considered "possibly useful". Some authors maintain that cognitive behavioral treatment for insomnia, as in patients without PD, may be useful [138]. To treat daytime sleepiness in PD, caffeine [139, 140], and modafinil can be used.

Regarding treatment of sleep-related breathing disorders, there is some controversy. If sleep apnea is moderate or severe, positive airway pressure therapy for PD patients can be indicated [141]. However, the response to this treatment regarding improvement of sleep structure or daytime sleepiness is less clear than in patients without PD [50]. Motor impairment often makes handling of the CPAP device difficult for patients with PD. Intraoral devices as an alternative treatment for certain patients with obstructive sleep apnea may also be limited in those with abnormal salivation or oro-facial dyskinesias.

For treatment of circadian disorders, light therapy shows promising outcomes on sleep and alertness in PD, with beneficial effects on sleep, mood, and other non-motor symptoms in PD [66, 142–144].

As prospective treatment studies for RLS co-existing with PD are missing, most commonly used medications in the PD population are the same as in the general RLS population, namely dopamine agonists, calcium channel alpha-2-delta ligands, clonazepam, and opioids [145–147]. As dopamine agonists and levodopa are already used to treat motor symptoms in PD, adjustments in timing of intake depending on time of appearance of RLS

symptoms may be beneficial. Iron supplementation should be considered if ferritin levels are low [148]. Medication known to exacerbate RLS (e.g. dopamine blockers, anti-cholinergic, and anti-histaminic agents) should be discontinued if possible.

Treatment of REM sleep behavior disorder should first include safety measures to ensure maximum safety in the sleeping environment. Such measures may include removing any objects close to the bed that may cause injuries during dream enactment, or making adjustments by moving furniture or using pillows to cover furniture, walls, and the floor. Bed partners should be advised to sleep separately. Medications which potentially aggravate RBD (e.g. antidepressants) should be eliminated if possible [149]. A bed alarm has been shown to be beneficial for RBD in preliminary studies [150]. Rotigotine was also shown to improve RBD in a vPSG study [151]. A double-blind, crossover pilot trial in 12 patients reported a reduction in frequency of RBD episodes (as reported by diaries of bed partners) with rivastigmine [152]. Effective pharmacological treatment based on case reports and series include clonazepam and melatonin, but double-blind, placebo-controlled trials are missing [93, 142, 147].

FUTURE RESEARCH DIRECTIONS

Sleep and regulation of sleep and wakefulness are relevant aspects in patients with Parkinson's disease. Disorders of sleep and wakefulness in Parkinson's disease are often reported, and comprise the full spectrum of sleep disorder categories. However, for most of them there are discordant data in the literature and treatment studies specifically conducted on patients with Parkinson's disease are mostly missing. Therefore, these aspects should be further clarified in future studies. Specifically, open issues with discordant data such as relevance of restless legs syndrome and sleep apnea in Parkinson's disease should be disentangled. Moreover, disturbances of circadian rhythm are very relevant in those patients and deserve more attention and investigations as their recognition and treatment might relevantly improve quality of life of patients with Parkinson's disease. Other less understood aspects like sleep benefit and effect of sleep deprivation need to be further investigated.

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