

Sleep and daytime sleepiness in Parkinson's disease

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Summary

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Disturbances of sleep and wakefulness in patients with Parkinson's disease (PD) have multiple contributing factors and multiple clinical manifestations. The causes, however, are incompletely understood. Although several of these disturbances have first been described decades ago, awareness for their clinical implications has only increased in recent years, which also prompted new research into the underlying pathomechanisms. The spectrum of sleep and wakefulness disorders in Parkinson's disease comprises sleep fragmentation, microstructural changes, REM-sleep behaviour disorder, periodic limb movements in sleep, respiratory disturbances, autonomic disturbances and daytime sleepiness, which are discussed in detail. Among the contributing factors, dopamine deficiency, motor impairment, the influence of age and comorbid depression, possible genetic influences and the effect of dopaminergic therapy on night sleep and daytime sleepiness are reviewed. Interactions between sleep or sleep deprivation and motor states are discussed (e.g. sleep benefit). One chapter is dedicated to the issue of driving in patients with Parkinson's disease. The final chapter reviews the evaluation of PD patients with sleep disorders and treatment, namely treatment of daytime sleepiness.

Keywords: daytime sleepiness; Parkinson's disease; polysomnography; REM-sleep behaviour disorder; sleep benefit; dopamine agonists; sleep attacks

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Background

Although mentioned by James Parkinson in his “essay on the shaking palsy” [1], sleep disorders in patients with Parkinson's disease (PD) received little attention in past decades, and disorders of wakefulness have been neglected even longer. Sleep and wakefulness problems are a potentially disabling symptom of Parkinson's disease, due to their possible consequences on quality of life, social functioning and the risk of injury to oneself and others due to disturbed night sleep or daytime sleepiness.

Sleep disorders are reported in nearly two-thirds of the PD patients, and half of them consider this symptom to be moderate or severe [2]. In one of the first questionnaire surveys of sleep problems in Parkinson's disease, 98% reported at least one sleep-disturbing symptom since the onset of their disease [3]. Daytime sleepiness is often not adequately perceived, but present in about one-third of the patients (e.g. [4]).

It is important to specifically question PD patients for sleep and wakefulness disorders. Precise identification of the underlying sleep disorder is the prerequisite for specific treatment.

The spectrum of sleep and wakefulness disorders in Parkinson's disease

Sleep fragmentation

One of the most prominent characteristics of sleep in PD patients is the “pattern of light and fragmented sleep” [5]. Sleep fragmentation manifests itself in increased arousals or awakenings and a deficiency in consolidated sleep, mostly also a reduced amount of REM sleep. The principal subjective complaint caused by sleep fragmentation is frequent awakening throughout the night leading to prolonged periods of wakefulness in bed. Sleep fragmentation in Parkinson's disease is probably the final consequence of distinct sleep-disturbing factors, such as nocturnal akinesia, dopamine

deficiency, dopaminergic therapy and associated symptoms such as periodic limb movements in sleep, nocturia and respiratory disorders.

Sleep microstructure

A decrease in hallmark elements of stage-2 sleep, especially sleep spindles and in part also K-komplexes, has been observed since the early studies of Parkinson's disease and sleep (reviewed in [6]). Frequency analysis was only rarely used in earlier studies [7]. Recent studies, however, using Fast Fourier Transformation of EEG data, point to discrete but distinct changes in sleep EEG in Parkinson's disease [8, 9]. These studies have shown an increase in the alpha frequency range during REM sleep. Alterations of non-REM sleep are reversible with levodopa treatment [9].

REM-sleep behaviour disorder

An absence or deficiency of physiological muscular atonia during REM sleep of Parkinson's disease patients has been described in early studies [10, 11]. The term REM-sleep behaviour disorder (RBD) was coined by Schenck and Mahowald only in 1986 [12]. This disorder is characterised by jerking, sometimes complex and potentially violent movements during REM sleep, which seem to be congruent with dream content [11]. Polysomnography shows excessive tonic and phasic muscle activity during REM sleep [13]. Both REM sleep without atonia and REM-sleep behaviour disorder are frequent in Parkinson's disease (e.g. [14]). Pathophysiologically, degeneration of various brainstem nuclei (e.g. [15]) and reduced striatal dopamine transporter activity [16] seem to play a role. Lewy bodies and alpha-synuclein are found in brainstem nuclei in Parkinson's disease and REM-sleep behaviour disorder, and the diagnosis of the latter may herald or follow the diagnosis of Parkinson's disease in an individual patient [15, 17]. The clinical relevance of REM-sleep behaviour disorder is based on the potential harm to the patient and others, which may be inflicted through violent movements associated with this condition [14, 17].

Periodic limb movements in sleep

The relationship between Parkinson's disease, periodic limb movements in sleep (PLMS) and dopaminergic therapy is still not fully understood. Wetter and coworkers found increased periodic

movements during sleep, even in untreated patients with Parkinson's disease [18], a finding which is not shared by all authors [19].

A significant negative correlation between reduced striatal dopamine transporter binding in SPECT and the number of PLMS in Parkinson's disease patients has also been reported [20]. PLMS significantly decreased after onset of de novo or add-on cabergoline therapy in PD patients [21].

Respiratory disturbances

Previous studies of respiration in PD patients have produced inconsistent results. Some found no abnormalities [22, 23] while others found exclusively central [24] or mainly obstructive events [25]. More recent studies demonstrate that obstructive sleep apnoeas are more prevalent in PD patients [26, 19] which is probably due to abnormal tone of the muscles surrounding the upper airways [27]. One preliminary anecdotal report [28] and a polysomnographic study [26] have suggested that abnormal muscle tone-induced partial upper airway obstruction during sleep might be levodopa-responsive. However, the initiation of nasal continuous airway pressure (nCAP) treatment in PD patients does not have the same beneficial effects on sleep structure as in patients with obstructive sleep apnoea syndrome alone [26].

In a recent questionnaire survey a significant correlation between heavy snoring and daytime sleepiness has been found in PD patients, which is in line with the well-established relation in subjects without Parkinson's disease and points to the importance of comorbidity as contributor to daytime sleepiness in Parkinson's disease [4].

Autonomic disturbance in sleep

Autonomic disturbances are not only found in multiple-system atrophy but also in idiopathic Parkinson's disease, especially during sleep: Ferini-Strambi and coworkers describe in untreated PD patients with less than 5-year disease duration that turning in bed leads to the expected heart rate increase but subsequent parasympathetic heart rate deceleration was impaired. It is interesting to note that all patients had unremarkable findings in autonomic testing during wakefulness [23]. An absence of the parasympathetic deceleration component of heart rate was described with a static charge sensitive bed [29].

Table 1 Epworth sleepiness scale (ESS) scores in patients with Parkinson's disease.

ESS	n	PD duration	age	study group
7 (0–23)	638	8.1 y	65.7 ± 10.4	Hobson et al. 2002 [56]
7.5 ± 4.6	99	7.4 y	67.7 ± 10.3	Högl et al. 2003 [4]
11.1 ± 5.9	303	9 y	67.1 ± 10.7	Ondo et al. 2002 [57]
10.8 ± 5.3	368	7.9 y	66.8 ± 10	O'Suilleabhain and Dewey 2002 [60]
9.1 ± 6.1	101	n.i.	64.4 ± 11	Paus et al. 2003 [93]
5.6 ± 4.5	201	5.5 y	63.2 ± 10	Tan et al. 2002 [62]

n.i. = not indicated

Daytime sleepiness

Excessive daytime sleepiness (EDS) was noted in patients with parkinsonian syndromes in early descriptions [30] and spontaneous dozing during the daytime occurred in nearly half of the PD patients in one study [31]. However, excessive daytime sleepiness has only received increasing attention since the controversially discussed reports of “sleep attacks” in PD patients on dopaminergic therapy. These case reports first involved patients taking non-ergoline dopamine agonists [32] and were subsequently supplemented by case reports for virtually all other dopamine agonists and levodopa (see below).

Previous studies reported sleepiness with greatly varying frequencies between 17% [33], 42% [34] and 49% [31]. This is most probably due to the fact that the authors used different, non-standardised definitions of sleepiness and that sleepiness was not quantified. More recent studies have applied the Epworth Sleepiness Scale (ESS) (see table 1). ESS scores ranged between 5.6 and 11.1 and seemed to relate in part to duration of Parkinson's disease (table 1).

To our knowledge only one polysomnographic study dealt with excessive daytime sleepiness before the “sleep attack” report was published [35]. This study unexpectedly found a negative correlation between night sleep efficiency and daytime sleep latency in PD patients. Polysomnographic studies including assessment of daytime sleepiness with multiple sleep latency test (MSLT) or maintenance of wakefulness tests are still limited in number [19, 36, 37]. Rye found a markedly reduced sleep latency ≤ 5 min in nearly one third of 27 PD patients. Ten per cent of the nap opportunities contained sleep onset (SO) REM periods. Arnulf performed MSLT in 54 treated PD patients, who were referred for daytime sleepiness and had a mean ESS Score of 14.3. These patients had a reduced sleep latency of 6.3 minutes and 39% showed 2 or more sleep-onset REM periods.

Patients with ≥ 2 SOREM periods had a shorter sleep latency than patients without [19].

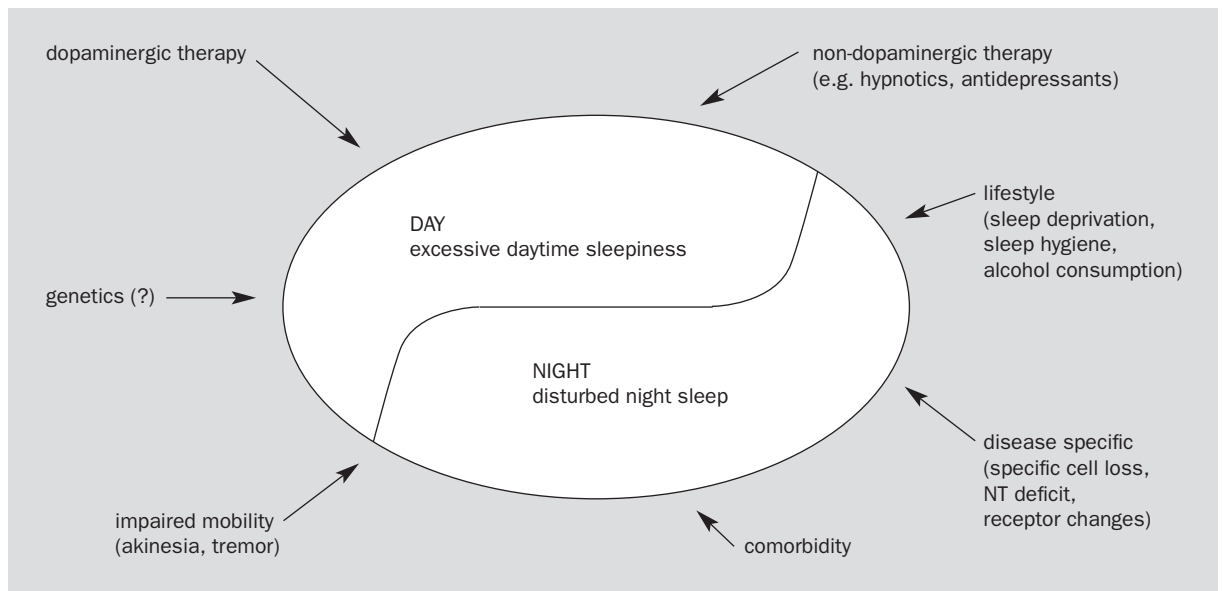
Sleep experts have criticised that the term “sleep attacks” is inappropriate as sleepiness is not adequately perceived, specifically in chronically sleepy patients, and electrophysiological signs of sleepiness precede sleep onset even in patients who are not aware of it (e.g. [38, 39]). This has been confirmed recently. Forty-seven somnolent PD patients underwent MSLT. After each nap, they were asked whether they had slept or dozed. Thirty-eight per cent of the PD patients did not perceive at least one PSG-confirmed nap. These patients also showed a lower score on the subjective Epworth Sleepiness Scale. Patients with sleep-state misperception tended to have more car accidents [40]. However, sleep-state misperception was not more frequent than in the control subjects who had other hypersomnias or sleep apnoea [40]. These findings demonstrate that sleep misperception is a factum in Parkinson's disease as it is in individuals with chronic sleepiness due to other conditions [38].

Sleep disorders in Parkinson's disease – contributing factors

Several major factors contribute to the multiple manifestations of sleep disorders in Parkinson's disease: the disease-specific dopamine deficiency, motor impairment, antiparkinsonian and other drug therapies, comorbidity, age and lifestyle factors and possibly genetic influences [39]. These factors are shown in figure 1.

Dopamine deficiency: Apart from the well-known role of dopamine in motor function, an “active and passive role” in sleep wakefulness regulation has been described and reviewed by Wauquier [41]. Whereas motor function relates to the nigro-striatal dopamine system, the meso-corticolimbic dopamine system has been involved in sleep-wakefulness control. Moreover, in the

Figure 1 Sleep and daytime sleepiness in Parkinson's disease – contributing factors (from: Poewe and Högl, 2000 [39]).



pathophysiology of Parkinson's disease the secondary involvement of other neurotransmitter systems, such as the serotonergic raphe nucleus, the noradrenergic locus coeruleus, the cholinergic nucleus basalis Meynert and pedunculopontine nuclei (e.g. [42]), all known to modulate sleep-wakefulness regulation, must be taken into account. Recent studies have shown that nigrostriatal dopaminergic cells send collaterals to the thalamus, which plays an important role in sleep-wake regulation, and these collaterals also degenerate in Parkinson's disease [43].

Motor impairment: Axial rotations in the recumbent position are impaired, even in awake patients with Parkinson's disease, a symptom not well responsive to levodopa [44]. Moreover, the interval between the night and morning drug doses is prolonged. Therefore, nocturnal akinesia involving difficulties in turning in bed and adjusting the sheets is frequently reported [3]. Laihinen and coworkers showed that PD patients take longer than control persons to turn over in bed and that attempts to turn over are frequently followed by awakening (possibly due to discomfort and paraesthesias) [29]. Painful dystonias, especially early morning dystonias, also may impair sleep.

Effects of dopaminergic therapy on night sleep: Only a minority of polysomnographic studies have been performed in untreated or drug-free patients [9, 18, 23]. In most other studies treatment-induced effects on sleep structure are superimposed on disease-related alterations and few prospective studies have been performed.

In healthy volunteers, levodopa infusions during non-REM sleep have been found to prolong REM-sleep latency and during REM sleep to shorten the ongoing REM-sleep episode. PD patients on levodopa (without decarboxylase inhibitors) showed reduction of REM sleep and prolonged REM-sleep latency. Despite these influences on sleep and despite a sleep-disrupting effect of levodopa at higher dosages, the initiation of levodopa therapy in previously untreated patients was reported to improve sleep. This has been associated with the improvement of nocturnal akinesia. These studies, mostly from the 1970s, are reviewed elsewhere [6].

For dopamine agonists a biphasic effect on sleep and wakefulness has been well documented in animal studies. Low-dose apomorphine or pergolide, for instance, induced sleepiness or sleep whereas high doses reduced sleep and increased wakefulness (reviewed in [41]). A biphasic effect on sleep in rats has also been found with the dopamine agonist pramipexole [45].

A recent study has investigated the effect of cabergoline on night sleep in Parkinson's disease patients. Although no significant effects of cabergoline treatment on sleep efficiency were found, and sleep latency even tended to decrease, a significant increase in short awakenings and stage shifts was found in the treatment condition, indicating a sleep-fragmenting effect of dopaminergic therapy in PD patients. The clinical significance of this finding is uncertain [21].

Selegiline has been found to activate a REM-sleep behaviour disorder [46]. Insomnia has also

been reported with selegiline and amantadine [47, 48], but the findings are controversial (reviewed in [6]).

Several studies have emphasised the significance of increasing sleep disruption and vivid dreams as an indication of an evolving dopaminergic psychosis [49, 50]. Patients with hallucinations showed markedly more sleep disturbances than did controls in clinical [51] and polysomnographic studies [52].

Effects of dopaminergic therapy on daytime sleepiness

Yawning, sleepiness or sleep induction after levodopa intake have been observed earlier (e.g. [53]). The initial notion that the so-called "sleep attacks" might be a specific novel side effect of non-ergoline dopamine agonists [32] was quickly replaced by the recognition that increased sleepiness or sleep onset is observed with a steadily increasing list of dopaminergic agents including levodopa [54, 55] irrespective of their receptor subtype preference, although the specific risk of the various dopamine agonists to induce sleep has not prospectively been assessed until now.

In her population-based survey, Tandberg reported a relation between excessive daytime sleepiness and PD stage, cognitive decline, longer L-dopa use, but not sleeping problems or hypnotics [33]. In the large survey by Hobson et al. ESS scores did not differ between dopamine agonists, but the levodopa dose correlated with ESS score and the inappropriate sleep composite score (ISCS), which was introduced by Hobson et al. [56]. Ondo et al. reported a correlation between PD duration and stage, male gender and use of any dopamine agonist. However, ESS did not differ between the specific agonists pramipexole, ropinirole and pergolide [57]. ESS scores were similar in PD patients on levodopa monotherapy or a combination of levodopa and dopamine agonists. Neither was there a difference between patients who received ergoline or non-ergoline dopamine agonists [4]. Sanjiv et al. found similar ESS scores between PD patients who were treated with L-dopa alone or a combination of L-dopa plus pramocriptine, ropinirole or pramipexole [58]. In further studies daytime sleepiness was associated with the Hoehn and Yahr stage, levodopa dose [59, 60] and additionally dopamine agonist use [60]. No significant difference for the occurrence of daytime sleepiness between PD patients treated with ergoline, non-ergoline or no dopamine agonists was found [61], but PD duration predicted ESS which again

correlated with LD dose [62]. Fabbrini et al. reported higher ESS scores in treated PD patients than in controls, but de novo PD patients and controls had similar ESS scores in this study [63].

Polysomnographic studies reporting on the effect of dopaminergic therapies on daytime sleepiness in PD patients have been published as single case reports. Ulivelli et al. performed polysomnography in a PD patient on a combination therapy with levodopa and pergolide and reported four diurnal sleep episodes during a 24-hour recording with clear improvement after pergolide withdrawal [64]. Tracik and Ebersbach studied a patient with irresistible sleep attacks during the daytime while on medication with levodopa, entacapone, budipine and cabergoline. They highlight the abrupt transition from wakefulness to stage-II sleep, which occurred in this patient [65]. Schäfer and Greulich demonstrated a shift of EEG power spectra towards slower frequencies 60 to 90 minutes after medication intake in a patient on treatment with levodopa plus ropinirole [66]. Högl and coworkers reported placebo-controlled and polysomnography-confirmed sleep induction by L-dopa single-dose challenges in one patient with multiple-system atrophy [55]. Sedation or sleepiness induced by levodopa or dopamine agonists has also been reported in healthy persons [67–69].

Depression and age

Two studies that applied the DSM criteria of the American Psychiatric Association for diagnosis of major depression found a significant impact of depression on sleep [2, 70]. Another study not applying these criteria did not demonstrate any influence [71]. Kostic and coworkers described reduced REM-sleep latency in depressed as compared to non-depressed PD patients [72]. It is probable that in the majority of PD patients age-related changes in sleep structure also play a role. However, whereas a loss of slow-wave sleep and an increase in awakenings are also observed in healthy elderly persons, major alterations in the amount of REM sleep and in REM-sleep microstructure (such as those seen in Parkinson's disease) are not a phenomenon of normal ageing [73]. One study showed that age indeed has a significant influence on sleep in parkinsonian patients [71]. However, these changes are also related to disease duration [74].

Genetics

A possible contribution of genetics to daytime sleepiness in sleep disorders or daytime sleepiness in Parkinson's disease has been proposed [39]. Genetic influences on sleep and the clinical presentations of sleep disorders are increasingly recognised [75]. In a recent study an association between COMT polymorphism and ESS scores has been reported, suggesting that COMT genotype could modulate daytime sleepiness in Parkinson's disease [76]. It is not known, how far the notable variation between ESS scores of Chinese [62] and Caucasian populations (e.g. [4, 56, 57]) might be related to genetic causes.

Interaction between sleep and motor function

A modulation of Parkinson's disease symptoms by sleep was first described by J. Parkinson and later by other authors [1, 5, 77]. The extended positive effect of sleep on waking motor function in some PD patients has first been observed by C.D. Marsden who coined the term "sleep benefit" for a subgroup of PD patients who experience improved motor function upon awakening before the intake of their daily medication [78]. Whereas several studies demonstrated the existence of sleep benefit or its clinical correlates and relation to therapy (e.g. [79]), one single study included polysomnography which did not show any difference between the sleep architecture in PD patients with and without sleep benefit [80].

On the basis of animal studies showing an increased response to dopaminergic treatment by sleep deprivation and imaging studies in depressed subjects showing an effect of therapeutic sleep deprivation on dopaminergic neurotransmission (reviewed in [81]), the question arises whether sleep deprivation might be able to improve motor function in PD patients. A positive effect had been reported by several previous studies [82–84] but was not confirmed in a controlled protocol using standard methodology [81].

Driving in Parkinson's disease

Since the report of PD patients falling asleep at the wheel [32], the driving capacity of PD patients has been discussed extensively, mostly with regard to treatment effects on daytime sleepiness (see also: Mathis, this issue). As a response to the Frucht report, in the respective drug information, PD patients on treatment with pramipexole and ropi-

nireole were warned not to drive a car; this was subsequently replaced by the alert that sleepiness may occur. Along with the ever-growing lists of other dopaminergic agents inducing sleepiness and similar ESS scores with different dopamine agonists (see above), subsequent editorials focussed on the importance of patient education to recognise sleepiness and not to drive when excessive daytime sleepiness occurred or at least take the appropriate reactions (pulling off immediately) when minimal signs of sleepiness occur [85, 86].

Perception of sleepiness has been shown to be deficient in Parkinson's disease but this does not differ from what has been reported in patient populations with chronic sleepiness due to other reasons (e.g. [38]). A misperception of sleepiness seems also reflected in the relatively low ESS scores of PD patients in many surveys (see above) and the high frequency of dozing during the day [31]. Despite this, the overall rate of falling asleep while driving in PD patients is still controversial and might be lower than expected on the basis of the above data, ranging from an annual incidence rate of 2% [87] to a frequency of 3.8% [56]. However, a recent study has reported that 20.8% of 101 patients had experienced a sleep episode while driving [88], which is still similar to data obtained from Finnish truck drivers [89].

Independent of Parkinson's disease intrinsic and drug-induced sleepiness, the issue of driving in PD patients is critical because impaired mobility makes them more dependent on driving on the one hand, and akinesia and motor fluctuations may impair driving capacities on the other hand. Reduced visual perception, prolonged reaction times and cognitive decline play an additional role [86]. Whereas PD patients make more errors in specific driving simulations [90], the accident rate of PD patients was not increased compared to a control population [91]. This might relate to patients at risk stopping driving [91] or a compensatory or disease-related increased carefulness as has been shown for elderly drivers with narcolepsy. In this context it needs to be taken into account that there is an ongoing and lively debate on the transferability results obtained with driving simulators to real-life driving performance, specifically regarding daytime sleepiness, and data providing a rationale for the use of costly and highly complex devices compared to simple software programs are not conclusive [92].

Although this is a matter of debate, recent studies have shown that ESS or the inappropriate sleep composite score predict an increased risk of falling asleep while driving (e.g. [56, 93]), thus pro-

viding a rationale for the systematic use of these scales in the driving PD population.

In addition to careful patient education, it might make sense to provide selected PD patients with a stimulant when they need to drive longer.

Assessment and treatment of sleep disturbances and daytime sleepiness in Parkinson's disease

A complete sleep history is an essential prerequisite in PD patients with complaints or disturbances of sleep or wakefulness. The self-applied PDSS (Parkinson's disease sleep scale), a validated VAS (visual analogue scale), is a useful tool [94]. A German-language sleep questionnaire specific for PD patients, which includes remarks on differential diagnosis and treatment, is also available [6]. The sleep history needs to be complemented by polysomnography in selected cases.

The treatment of night-sleep disturbances in PD patients has been reviewed elsewhere (e.g. [6, 95]).

Recent reviews deal with the treatment of daytime sleepiness in PD patients (e.g. [96, 97]). First, a possible relation of daytime sleepiness and dopaminergic therapy should be checked and whenever possible addressed by substance change, dose reduction or dose splitting [39]. Sedative and hypnotic medications should be eliminated whenever possible. The specific treatment of coexistent sleep-related disorders such as sleep-disordered breathing, REM-sleep behaviour disorder, PLMS or nocturia may improve daytime sleepiness, although this has not been specifically studied and may not apply to every patient.

Symptomatic treatment of daytime sleepiness is achieved with wake-enhancing or stimulant drugs. A positive effect of modafinil on daytime sleepiness in PD patients has been reported in single case reports and one open study earlier. Two double-blind placebo-controlled studies found small improvements in the Epworth sleepiness scale [37, 98]. Objective polysomnographic measures of daytime sleepiness were included in only one study and did not show significant improvement [37]. The mode of action of modafinil is at least in part due to its effect on dopaminergic neurotransmission, and modafinil response is reduced in dopamine transporter knock-out mice [99]. It is not clear whether the modest improvement of daytime sleepiness in PD patients with modafinil is due to the submaximal doses used in these studies or reflects a decreased responsiveness to modafinil in PD patients. Stimulants such as methylphenidate or amphetamines have also been proposed for the treatment of daytime sleepiness

in Parkinson's disease (e.g. [96, 100]), but no studies are available. Due to the many side effects of stimulants, the complications of prescription under narcotic law in most countries and possible interaction with antiparkinsonian therapy (such as hypertensive crisis with MAO inhibitors and stimulant cotreatment, or increased dyskinesias in levodopa and methylphenidate cotreated PD patients), the use of stimulants in this patient group should only be considered after a careful sleep laboratory evaluation.

The severity of sleep and wakefulness disorders in Parkinson's disease and its multiple contributors and manifestations shed light on the fascinating relationship between neurologic disease and sleep and wakefulness disorders. An efficient evaluation and treatment provide a challenge for neurologists and sleep disorder specialists.

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