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SHORT COMMENTARY

Effects of dopaminergic therapy on sleep quality in fluctuating Parkinson's disease patients

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Abstract

Background Sleep disorders negatively impact quality of life in Parkinson's disease (PD), yet the role of antiparkinsonian drugs on sleep quality is still unclear. We aimed to explore the correlation between sleep dysfunction and dopaminergic therapy in a large cohort of advanced PD patients.

Methods Patients consecutively evaluated for device-aided therapies eligibility were evaluated by means of the PD Sleep Scale (PDSS-2; score ≥ 18 indicates poor sleep quality), and the Epworth Sleepiness Scale (ESS score ≥ 10 indicates excessive daytime sleepiness—EDS).

Binary logistic regression analysis, adjusting for age, sex, disease duration, motor impairment, and sleep drugs, was employed to evaluate the association between dopaminergic therapy and PDSS-2 and ESS scores. Analysis of covariance assessed differences in PDSS-2 and ESS scores between patients without DA, and between patients treated with low or high doses of DA (cut-off: DA-LEDD = 180 mg).

Results In a cohort of 281 patients, 66.2% reported poor sleep quality, and 34.5% reported EDS. DA treatment demonstrated twofold lower odds of reporting relevant sleep disturbances (OR 0.498; p = 0.035), while DA-LEDD, levodopa-LEDD, total LEDD, and extended-release levodopa were not associated with disturbed sleep. EDS was not influenced by dopaminergic therapy. Patients with DA intake reported significant lower PDSS-2 total score (p = 0.027) and "motor symptoms at night" domain score (p = 0.044). Patients with higher doses of DA showed lower PDSS-2 total score (p = 0.043).

Conclusion Our study highlights the positive influence of DA add-on treatment on sleep quality in this group of advanced fluctuating PD patients.

Keywords Parkinson disease · Sleep · Dopamine agonists · Levodopa

Introduction

Parkinson's disease (PD) is a chronic progressive neurological disorder which affects up to 1–2% of the population over 65 years of age and is the second most common neurodegenerative disorder after Alzheimer's disease [1, 2]. It is characterized by cardinal motor symptoms (bradykinesia, rest tremor, rigidity), and several nonmotor symptoms [3]. Among these, sleep dysfunction is highly prevalent, occurring in 60–98% of PD patients across all disease stages [4, 5]. Sleep dysfunction in PD includes excessive daytime sleepiness (EDS), rapid eye movement sleep behavior disorder (RBD), insomnia (including difficulties in sleep initiation and sleep maintenance), sleep fragmentation with increased periods of wakefulness during the night, periodic limb movements of sleep, restless leg syndrome, obstructive sleep apnea, nocturia, and night akinesia [2, 4, 5]. These nonmotor symptoms greatly impact quality of life [4, 6]. Also, poor sleep quality has been associated with faster neurodegeneration and cognitive decline [4, 7].

Different hypotheses have been proposed to explain sleep dysfunction in PD, including the damage to key regions involved in sleep architecture (e.g., locus coeruleus,

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hypothalamus, pedunculopontine nucleus), and alterations in hormonal balance (e.g., melatonin, hypocretin and cortisol) [2].

Several antiparkinsonian drugs have demonstrated to influence sleep quality. However, while high levodopa intake seems to correlate with nocturnal akinesia [4] and higher sleep disturbances [8], data on the role of dopamine agonists (DA) are less univocal. Indeed, while dopamine agonists (DA) have been linked to excessive daytime sleepiness [2], they have also shown subjective improvement in sleep quality compared to placebo and fewer sleep disturbances compared to levodopa [8]. Moreover, other medications, such as selective serotonin reuptake inhibitors (SSRIs), might trigger or exacerbate specific sleep-related symptoms [2].

In this context, the aim of our study was to analyze the association between sleep dysfunction and dopaminergic therapy in a large cohort of advanced PD patients. Additionally, we analyzed the correlation of reduced sleep quality and excessive daytime sleepiness with the intake of nocturnal extended-release levodopa and with low or high doses of DA.

Methods

In this retrospective study, we enrolled advanced PD patients consecutively evaluated for eligibility for device-aided therapies from January 2016 to December 2021 at the Movement Disorder Clinic of the University of Turin. We collected the following data: age, sex, disease duration, motor impairment assessed by means of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, and motor complications assessed by means of the MDS-UPDRS part IV score. Dopaminergic treatment was also collected, and levodopa equivalent daily dose (LEDD) was calculated as per a validated conversion table [9]; in absence of a validated cut-off, low dose DA treatment was arbitrarily defined as a DA LEDD ≤ 180 mg. Moreover, we also considered the intake of other drugs potentially influencing sleepiness and sleep quality, such as SSRIs, benzodiazepines, melatonine, trazodone, neuroleptics.

Sleep quality was assessed with the Parkinson's disease sleep scale-2 (PDSS-2), a validated self-administered questionnaire evaluating the complexity of sleep disturbances in PD patients, exploring three different domains: PD-specific nocturnal motor symptoms (akinesia, early morning dystonia, tremor during waking period at night, periodic limb movements, restlessness, motor symptoms due to RBD), PD-specific nocturnal nonmotor symptoms (hallucinations, confusional states, pain, muscle cramps, difficulties in breathing and snoring), and sleep-specific disturbances (insomnia, sleep maintenance, unrestored sleep, nocturia and the overall quality of sleep in the patient's rating) [5].

The overall score ranges from 0 (no disturbance) to 60 (maximum nocturnal disturbance). Scores ≥ 18 are considered suggestive of relevant PD-related sleep disturbances [10].

Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS), which evaluates the chance of "dozing" in different daily situations. Scores range from 0 to 24; scores ≥ 10 are indicative of excessive daytime sleepiness [11].

Statistical analysis

Demographical and clinical data are presented as mean ± standard deviation, or as percentages, depending on their continuous or categorical nature. The correlation between dopaminergic treatments, namely DA, nocturnal extended-release levodopa, DA LEDD, levodopa LEDD and total LEDD (independent variables), and disturbed sleep or excessive daytime sleepiness (dependent variables) were evaluated by means of a binary logistic regression analysis, correcting for patient's age, sex, disease duration, motor impairment (MDS-UPDRS III in the Off state), and treatment influencing sleep (including benzodiazepines, melatonine, zolpidem, neuroleptics, SSRIs, and trazodone). A sub-analysis, comparing the effect of the different DAs on disturbed sleep or excessive daytime sleepiness was also run. Furthermore, analysis of covariance (ANCOVA) was used to evaluate differences in PDSS-2 score (both total and each domain scores) and ESS score (dependent variables) between patients with or without DA treatment, and for patients with low or high doses of DA (fixed terms), correcting for age, sex, disease duration, MDS-UPDRS III in the Off state score, and treatment influencing sleep (covariates). Based on our clinical practice, we considered high doses of DA to be > 180 mg of DA LEDD. All the analyses were performed with Statistical Package for the Social Sciences (SPSS 27.0 for Macintosh, Chicago, IL), using two-tailed p-values with a level of significance of 0.05.

Results

We enrolled 281 consecutive advanced PD patients (187 males; 66.5%), with a mean age of 60.3 ± 7.9 years and disease duration of 11.6 ± 3.7 years. Two-thirds of patients (n = 186; 66.2%) reported poor sleep quality, as per a PDSS-2 score ≥ 18, and one-third (n = 97; 34.5%) reported an ESS score consistent with excessive daytime sleepiness (ESS score ≥ 10). Mean MDS-UPDRS part III and IV scores showed a moderate level of motor impairment [12]. All but one patient were treated with levodopa (mean levodopa LEDD = 968.3 ± 438.4). Three-fourths (74.4%) of patients were treated with DA (i.e., pramipexole, ropinirole,

rotigotine), including five patients with subcutaneous apomorphine treatment, while half of the patients (49.5%) took nocturnal extended-release levodopa. All patients took DA in the morning, except for three patients, which took it in the evening. Among patients with DA intake, 71 out of 209 (34.0%) were on low-dose treatment. The mean total LEDD was 1236.9 ± 432.9 mg. All clinical and demographical data are reported in Table 1.

After adjusting for sex, age, disease duration, motor impairment, and treatment influencing sleep, patients treated with DA showed a reduced risk of presenting relevant sleep disturbances, with an odds ratio (OR) of 0.498 (95% CI 0.260–0.954; p = 0.035), meaning that patients without DA treatment had a twofold higher odds of reporting significant sleep disturbances. When considering the influence of the different DAs, patients treated with rotigotine or pramipexole showed a lower risk of disturbed sleep (OR = 0.349, 95% CI 0.129–0.947, p = 0.039; and OR = 0.455, 95% CI 0.223–0.927, p = 0.030, respectively), while no significant influence of ropinirole was observed (OR = 0.703, 95% CI 0.318–1.553, p = 0.383). On the other hand, there was no statistically significant association between disturbed sleep and DA LEDD, levodopa LEDD, total LEDD and nocturnal extended-release levodopa (Table 2). Excessive daytime sleepiness was not significantly influenced by the dopaminergic regimen (Table 2).

DA treatment was associated with better sleep quality, as showed by the lower PDSS-2 scores in DA treated patients compared with those not treated with DA (corrected mean ± standard error: 21.7 ± 0.7 vs. 24.9 ± 1.3; p = 0.027). In patients with DA intake, we observed lower scores in all the three PDSS-2 domains, with the "motor symptoms at night" domain showing a significant difference (6.4 ± 0.3 vs. 8.1 ± 0.6; p = 0.044) (Table 3). Although patients taking high DA doses showed lower PDSS-2 total and domains scores, compared to those taking low DA doses, no significant differences were reported between the two groups; however, patients with high dose DA demonstrated lower PDSS-2 total scores compared to patients without DA treatment (p = 0.043) (Table 3).

No significant differences were observed on daytime sleepiness when comparing patients with and without DA treatment (ESS corrected mean ± standard error: 8.7 ± 0.3 vs 8.1 ± 0.6; p = 0.416) and patients with high and low DA doses intake (8.7 ± 0.4 vs 8.6 ± 0.6; p = 0.999).

Table 1 Demographic and clinical variables

Age, y	60.3 ± 7.9 (35–77)
Men/women	187/94 (66.5%/33.5%)
Disease duration, y	11.6 ± 3.7 (4–32)
MDS-UPDRS III on	20.3 ± 9.9 (3–55)
MDS-UPDRS III off	48.4 ± 14.9 (11–92)
MDS-UPDRS IV	7.7 ± 3.9 (0–17)
Dopamine agonist treatment, yes/no	209/72 (74.4%/25.6%)
Rotigotine	26/209 (12.4%)
Pramipexole ER/IR	108/209 (51.7%)
Ropinirole	68/209 (32.5%)
Apomorphine	5/209 (2.4%)
Cabergoline	2/209 (0.9%)
Nocturnal extended-release levodopa treatment, yes/no	139/142 (49.5%/50.5%)
Total LEDD, mg	1236.9 ± 432.9 (200–2865)
Dopamine agonist LEDD, mg	206.9 ± 189.5 (0–1150)
Levodopa LEDD, mg	968.3 ± 438.4 (0–2100)
Epworth Sleepiness Scale	8.5 ± 4.7 (0–23)
Excessive Daytime Sleepiness, yes/no	97/184 (34.5%/65.5%)
Parkinson's Disease Sleep Scale	22.7 ± 10.8 (0–55)
PDSS-2 disturbed sleep	9.7 ± 4.3 (0–20)
PDSS-2 motor symptoms at night	7.4 ± 4.9 (0–25)
PDSS-2 PD symptoms at night	6.3 ± 4.8 (0–25)
Disturbed sleep, yes/no	186/95 (66.2%/33.8%)
Sleep treatment, yes/no	118/163 (42.0%/58.0%)

All data are reported as means ± standard deviation and (range), or absolute numbers (percentage)

MDS-UPDRS Movement Disorder Society-Unified Parkinson's Disease Rating Scale, *ER* extended release, *IR* immediate release, *LEDD* Levodopa equivalent daily dose

Table 2 Association between treatment, disturbed sleep, and daytime sleepiness

Treatment	OR (95% CI)	P value
Disturbed sleep		
Dopamine agonist	0.498 (0.260–0.954)	***0.035***
Nocturnal extended-release Levodopa	0.981 (0.581–1.657)	*0.944*
Dopamine agonist LEDD	0.999 (0.998–1.001)	*0.182*
Levodopa LEDD	1.001 (0.999–1.001)	*0.133*
Total LEDD	1.000 (1.000–1.001)	*0.484*
Excessive daytime sleepiness		
Dopamine agonist	1.098 (0.605–1.993)	*0.758*
Nocturnal extended-release Levodopa	1.019 (0.503–1.613)	*0.925*
Dopamine agonist LEDD	1.001 (0.999–1.002)	*0.365*
Levodopa LEDD	1.000 (0.999–1.000)	*0.481*
Total LEDD	1.000 (0.999–1.001)	*0.932*

Results are reported as odds ratio (OR); 95% confidence interval is reported in brackets. P value: statistical significance

Disturbed sleep was defined as a Parkinson's Disease Sleep Scale-2 score ≥ 18; Excessive daytime sleepiness was defined as a Epworth Sleepiness Scale score ≥ 10. Analyses are corrected for sex, age, disease duration, motor impairment (UPDRS-III Off), sleep treatment

Table 3 Difference on total and domains scores of Parkinson's Disease Sleep Scale between patients with or without dopamine agonist intake (low- or high-dose)

	DA no, N = 72	DA yes, N = 209	P value	DA no, N = 72	Low-dose DA, N = 71	High-dose DA, N = 138	P value
Parkinson's Disease Sleep Scale	24.9 ± 1.3	21.7 ± 0.7	***0.027***	24.9 ± 1.3	22.6 ± 1.3	21.1 ± 0.7*	***0.043***
PDSS-2 disturbed sleep	10.1 ± 0.5	9.5 ± 0.3	*0.280*	10.1 ± 0.5	10.0 ± 0.5	9.2 ± 0.4	*0.257*
PDSS-2 motor symptoms at night	8.1 ± 0.6	6.4 ± 0.3	***0.044***	8.1 ± 0.6	7.4 ± 0.6	6.7 ± 0.4	*0.122*
PDSS-2 PD symptoms at night	6.5 ± 0.6	6.1 ± 0.3	*0.540*	6.5 ± 0.6	6.3 ± 0.6	5.9 ± 0.4	*0.742*

Results are reported as adjusted mean ± standard error. P value: statistical significance

PDSS Parkinson's Disease Sleep Scale

*Significant difference vs. "DA no"

Low-dose DA was defined as dopamine agonist LEDD < 180 mg

Analyses are corrected for sex, age, disease duration, motor impairment (MDS-UPDRS-III Off), sleep treatment

Discussion

In this retrospective study, we evaluated on a large cohort of advanced PD patients the role of dopaminergic treatment in influencing sleep disturbances. While levodopa intake and total dopaminergic treatment did not affect sleep quality and daytime sleepiness, DA treatment was associated with a reduced risk of presenting relevant nocturnal sleep disturbances. We observed a significantly better sleep quality in patients treated with DA compared to those not treated with DA, with lower PDSS-2 total score and lower "nocturnal motor symptoms" domain score. Moreover, patients with high doses of DA showed lower, though not significant, PDSS-2 scores. When comparing different DAs, rotigotine and pramipexole showed a lower risk of disturbed sleep, while no significant influence of ropinirole was observed.

Previous research has explored the impact of specific dopamine agonists, such as ropinirole, pramipexole, rotigotine, and subcutaneous apomorphine, on sleep quality. For instance, Chaudhuri and colleagues performed post hoc analyses of the EASE-PD Adjunct study, to investigate the effect of ropinirole prolonged release (PR) on nocturnal symptoms (measured with the PDSS) in advanced PD patients [13]. Patients reporting insomnia at baseline and randomized to ropinirole PR showed greater improvements in the PDSS scale at follow-up compared to those taking placebo, in particular in "global sleep quality" and in "motor symptoms on waking" [13]. Another study observed similar results in 119 advanced PD patients with insomnia taking pramipexole sustained release (SR) or immediate release (IR) [14]. A recent meta-analysis of randomized controlled trials, evaluating the efficacy and safety of rotigotine transdermal patch in the treatment of sleep disorder in PD, demonstrated that patients receiving rotigotine reported significant improvement in their sleep symptoms (measured by means of PDSS or PDSS-2); moreover, the magnitude of sleep amelioration was similar between rotigotine and other DA [15]. A prospective study comparing 87 patients receiving subcutaneous apomorphine or intrajejunal levodopa gel infusion showed that both treatments significantly improved the sleep/fatigue domain of the NonMotor Symptom Scale [16]. Furthermore, the APOMORPHEE study [17] showed that subcutaneous night-time-only apomorphine infusion reduced sleep disturbances in 46 patients with advanced PD with moderate to severe insomnia, improving items on the PDSS score related to overall quality of night sleep, sleep onset, maintenance insomnia and nocturnal restlessness.

On the other hand, there are also studies reporting no statistically significant, or even detrimental, effect [8, 18] on sleep quality associated to DA intake [19–22]. Pramipexole has been associated with significantly higher rates of insomnia in 144 PD patients of African, Asian, or Hispanic heritage [22], while pergolide worsened actigraphy measures of sleep efficiency and sleep fragmentation [21]. Apomorphine at high doses has shown to worsen quality of sleep [19]. Another study conducted on 62 PD patients reported that high doses of dopaminergic therapy prior to sleep were associated with poor sleep quality and less REM sleep [20]. On the contrary, our study seems to indicate that high doses of DA are associated with better sleep quality.

Our results confirm the positive effect of DAs on sleep quality on a large cohort of advanced PD patients. A possible explanation of this improvement lies in the significant efficacy of DAs on the nocturnal motor symptoms, as demonstrated by their greater effect on the "motor symptoms at night" domain of the PDSS-2, that includes akinesia, early morning dystonia, tremor during waking period at night, periodic limb movements, restlessness, and motor symptoms due to RBD [5, 17, 23].

In our study levodopa treatment was not associated with the PDSS-2 scale, while some data concerning worsening of sleep related to levodopa has been previously reported [6, 8]. Continuous dopaminergic stimulation provided by LCIG on the other hand seems to improve subjective

sleep quality and leads to a less fragmented sleep pattern, probably by means of its stabilizing effect on motor and nonmotor fluctuations, which can probably be extended overnight even if LCIG infusion is halted [24].

Regarding EDS, we did not find an association with dopaminergic therapy, aligning with some previous research [13, 14, 17]. However, conflicting results exist in the literature, suggesting a complex relationship between DA, levodopa, and EDS in PD patients [18, 19, 25–27]. Some studies propose EDS as a potential "class effect" of any dopaminergic treatment [18, 19], particularly with DA, and a dose-related relationship with sleepiness has been suggested [18, 25, 26]. However, the causes of EDS in PD are still unknown, with different pathogenetic mechanisms probably involved, and without agreement between subjective and objective measurements of daytime sleepiness [26, 27]. Moreover, some studies hypothesize that EDS may not be a side effect of dopaminergic therapy but may be an integral part of PD pathophysiology [28, 29].

Our study has some limitations. Firstly, sleep quality and daytime sleepiness was evaluated only by means of the PDSS-2 and the ESS, a patient's self-reported questionnaire, without objective measurements. However, different studies demonstrated that self-reported improvement in sleep disturbances did not necessarily reflect objective sleep parameters [8, 17], and previous interventional studies targeting sleep disturbances in PD patients have used such questionnaire-based clinical scales as a primary outcome. Additionally, we must acknowledge that we included only patients evaluated for eligibility for device-aided therapies, which may not be representative of the entire late-stage PD population. Finally, the cut-off value for definition of high and low doses of DA was arbitrarily based on our clinical practice and the retrospective nature of the study should be considered as additional limitations. These limitations notwithstanding, our study adds relevant information on a large cohort of advanced PD patients regarding dopaminergic therapy and sleep, a still controversial and debated issue.

In conclusion, based on the results of our study, we suggest that DA add-on treatment can improve overall sleep quality in advanced fluctuating PD patients, especially by improving motor symptoms at night. The recent increasing attention on PD nonmotor symptoms may enforce the need to better understand the role of dopaminergic treatment in sleep quality.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The authors confirm that they have received the approval of an institutional review board of the University of Turin for this work and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from the patients.

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