



# Association between dopaminergic medications and REM sleep behavior disorder in Parkinson's disease: a preliminary cohort study

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## Abstract

**Background** Rapid eye movement sleep behavior disorder (RBD) is highly comorbid with Parkinson's disease (PD). Emerging evidence suggests that dopamine-replacement therapies (DRTs) for PD may modify the course of RBD, yet the nature of the association between DRTs and RBD remains unclear. To begin addressing this issue, we conducted a preliminary retrospective study to document whether DRTs are associated with the occurrence of RBD symptoms in PD patients.

**Methods** The study included 250 PD patients who were screened for probable RBD via the RBD Screening Questionnaire (RBDSQ). For each patient, disease severity data were collected, in addition to their therapy and the associated levodopa equivalent daily dose (LEDD). The association between DRTs and RBDSQ scores was analyzed using logistic regression and correlation models.

**Results** RBD scores were found to be associated with the LEDD of levodopa alone, but not of dopaminergic agonists (mainly D2/D3 receptor agonists) or their combination with levodopa. This association was not accounted for patient age or Hoehn and Yahr (H&Y) severity scores.

**Conclusions** Our study detected a significant association between doses of levodopa and RBD symptoms in PD patients. Future longitudinal studies are needed to establish what causal nexus may link these variables.

**Keywords** Parkinson's disease · REM sleep behavior disorder · Dopamine-replacement therapies · Levodopa equivalency daily dose

## Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by the loss of skeletal muscle atonia during REM sleep, resulting in increased phasic motor activity and dream enactment [1, 2]. Accordingly, when RBD patients experience vivid, violent, frightening dreams, they typically respond by flailing their arms or legs, often inflicting physical harm to themselves or their bed partners [3]. RBD is generally associated with neurodegenerative problems, such as multiple system atrophy, Lewy body dementia, and, particularly, Parkinson's disease (PD) [4]. The comorbidity of RBD and PD has become a theme of growing interest, given that the onset of RBD often precedes that of PD and is a risk factor for a more rapid decline in motor and cognitive function, as well as more severe symptom fluctuations in PD [5]. While this background points to RBD as a long-term predictor of PD, the influence of PD on the clinical course of RBD remains less well-understood.

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Previous studies have shown that basal ganglia structures, such as the substantia nigra pars reticulata and the internal segment of the globus pallidus, have caudal connections to regions that modulate REM sleep atonia [6]. In a nonhuman primate study, the dopaminergic neuronal death caused by a neurotoxin determined an increase in the number of sleep epochs with high-amplitude EMG bouts during REM suggesting that the presence of REM sleep without atonia might reflect the early involvement of dopaminergic neurotransmission on medullary and pontine REM sleep-related structures [7]. In particular, emerging evidence on the role of dopamine in RBD pathophysiology [8] raises the question as to whether the use of dopamine-replacement therapies (DRTs) for PD may modify the course of RBD. While initial surveys suggested that DRTs do not generally affect the quality and structure of sleep in PD patients [8], recent findings have shown that the comorbidity of PD and RBD is associated with higher levodopa equivalent daily dose (LEDD) [9]; conversely, several studies have pointed to a beneficial effect of dopaminergic agonists in the management of RBD in PD patients [10]. Based on this background, we conducted a preliminary retrospective study to investigate the association between DRTs and the occurrence of RBD symptoms in PD patients.

## Materials and methods

The present study included 250 PD patients recruited from the Movement Disorders Clinic of University Hospital of Cagliari, Italy. PD diagnosis was based on the United Kingdom Parkinson's Disease Brain Bank criteria [11]. Exclusion criteria were: (1) vascular parkinsonism; (2) drug-induced parkinsonism; (3) features suggestive of atypical parkinsonism and severe dementia (MMSE values < 18); (4) inability to provide informed consent. The study was approved by the Hospital Institutional Review Board (IRB). All participants gave informed consent in accordance with the declaration of Helsinki.

Demographic and clinical variables were collected for each patient, including age, gender, PD severity based on the Hoehn and Yahr (H&Y) stage, as well as dopaminergic and non-dopaminergic therapy. PD subjects were subdivided into four groups based on therapy category: (1) no dopamine-replacement therapies (no-DRTs); (2) only levodopa; (3) exclusively dopamine agonists (DA); (4) combined levodopa + DA therapy. The LEDD was calculated for each patient [12].

All patients and their bed partners were asked to complete the RBD Screening Questionnaire (RBDSQ) [13] and systematically interviewed regarding sleep problems by board-certified neurologists with expertise in sleep disorders. The RBDSQ consists of 10-item patient self-rating questionnaire

covering the clinical features of RBD. The maximum total score of the RBDSQ is 13 points. A cut-off score of 6 for PD patients has been suggested [14].

## Statistical analysis

Differences in variables of interest among the four therapy categories were evaluated. Because of a non-parametric distribution, Kruskal–Wallis H test was used to evaluate differences relating to median values of age, H&Y stage, total LEDD, and RBD scores. Pearson's chi-squared test was instead used to test differences relating to gender distribution and the presence or absence of RBD scores  $\leq 6$ . Differences among subjects with RBD scores  $\leq 6$  (no-RBD) or  $> 6$  (probable-RBD) relating to age, H&Y stage, and total LEDD were evaluated by Mann–Whitney *U* test. Pearson's chi-squared was used to evaluate differences relating to gender and therapy category distribution. Spearman's correlation coefficient was used to evaluate correlations between age, H&Y stage, total LEDD, and RBD scores. Correlation between total LEDD and RBD scores was also evaluated by categories of therapy (only DA, only levodopa, combined levodopa + DA).

Unconditional logistic regression models with RBD score  $> 6$  versus  $\leq 6$  as alternative outcomes were used to calculate the Odds Ratio (OR) and its 95% confidence intervals (95% CI) associated with categories of therapy (no-DRTs category was used as reference). Models included age (continuous), gender (males as reference) H&Y stage (continuous) and total LEDD (continuous). To reject the null hypothesis, two-tailed  $\alpha$  error threshold was set at  $p < 0.05$ . Analyses were conducted using SPSS® version 20.0 (IBM Corporation, Armonk, NY, USA).

## Results

Table 1 shows demographic and clinical data for the overall study population and by categories of therapy. Patients in therapy with only levodopa showed a significantly higher median age (74.0—IQR 67.0, 78.0) as compared to patients with no-DRTs, DA and combined therapy (71.0—IQR 61.0, 76.0; 65.0—IQR 60.0, 73.0; 71.0—IQR 63.0, 75.0, respectively) ( $p = 0.004$ ). Total LEDD values were significantly higher in subjects with combined levodopa + DA therapy (742.8—IQR 464.5, 1000.0) than in those with DA therapy or levodopa therapy alone (175.5—IQR 140.7; 400.0—IQR 337.5, 540.0, respectively) ( $p < 0.001$ ). No differences across groups were found with respect to gender distribution ( $p = 0.61$ ), H&Y stage scores ( $p = 0.73$ ), and RBD scores ( $p = 0.14$ ).

**Table 1** Demographic and clinical data for overall study population and by categories of therapy

	Overall study population	No-DRTs	Dopamine agonist	Levodopa	Combined therapy	P value
N (%)	250 (100)	62 (24.8)	31.0 (12.4)	87.0 (34.8)	70 (28.0)	nc
Age (median–IQR)	71.0–63.0, 76.0	71.0–61.0, 76.0	65.0–60.0, 73.0	74.0–67.0, 78.0	71.0–63.0, 75.0	0.004 <sup>a</sup>
Gender (M/F)	133/117	37/25	15/16	43/44	38/32	0.61 <sup>b</sup>
H&Y stage (median–IQR)	2.5–2.0, 3.0	2.5–2.0, 3.0	2.5–1.8, 3.0	2.5–1.5, 3.0	2.5–2.0, 3.0	0.73 <sup>a</sup>
Total LEDD (median–IQR)	400.0–27.13, 600.0	na	175.5–140.7, 400.0	400.0–337.5, 540.0	742.8–464.5, 1000.0	<0.001 <sup>a</sup>
RBD (median–IQR)	6.0–3.0, 8.0	5.0–3.0, 7.0	5.0–2.0, 8.0	6.0–3.5, 8.0	6.0–3.0, 8.0	0.14 <sup>a</sup>
RBD > 6 (N–%)	133–53.2	29–46.8	12–38.7	53–60.9	39–55.7	0.12 <sup>b</sup>

IQR interquartile range, H&Y Hoehn & Yahr, LEDD levodopa equivalent daily dose, RBD REM behaviour disorder, no-DRTs no dopamine-replacement therapies, na not applicable, nc not calculated

<sup>a</sup>Kruskal–Wallis H test

<sup>b</sup>Pearson’s chi-squared test

**Table 2** Distribution of subjects without (RBD scores ≤ 6) and with (RBD scores > 6) probable RBD by selected variables

	No RBD RBD ≤ 6	Probable RBD RBD > 6	P value
Study population (N–%)	117 (46.8)	133 (53.2)	
Age (Median–IQR)	71.0–63.0, 77.0	71.0–64.0, 75.0	0.30 <sup>a</sup>
Gender (M/F)	55/62	78/55	0.076 <sup>b</sup>
H&Y stage (median–IQR)	2.5–2.0, 3.0	2.5–1.8, 3.0	0.66 <sup>a</sup>
Total LEDD (median–IQR)	300.0–0.0, 600.0	400.0–115.1, 642.2	0.072 <sup>a</sup>
No-DRTs (N–%)	33–53.2	29–46.8	0.12 <sup>b</sup>
Dopamine agonist (N–%)	19–61.3	12–38.7	
Levodopa (N–%)	34–39.1	53–60.9	
Combined therapy (N–%)	31–44.3	39–55.7	

IQR Interquartile Range, H&Y Hoehn & Yahr, LEDD levodopa equivalent daily dose, RBD REM behaviour disorder, no-DRTs no dopamine-replacement therapies

<sup>a</sup>Mann–Whitney U test

<sup>b</sup>Pearson’s chi-squared test

No significant differences were found for H&Y stages, Total LEDD, and other variables such as gender distribution, age, DRTs, and no-DRTs between no-RBD and probable-RBD (Table 2).

Since RBD can also arise as a side effect of medications such as selective serotonin reuptake inhibitors (SSRI) and beta blockers we looked at the frequency of these drugs in probable-RBD and no-RBD subjects that was no different. We also looked at the frequency of SSRI and beta blockers in DRT and no-DRT subgroups without finding any significant difference.

In the matrix of correlation between variables (age, H&Y stage, Total LEDD, and RBD), Total LEDD was directly, although weakly, correlated with RBD score (Spearman’s correlation coefficient = 0.157;  $p = 0.013$ ). No other correlation was detected (Table 3).

Correlation analyses were then run to identify single-therapy (only levodopa; only DA; combined levodopa + DA)

**Table 3** Correlation matrix between covariates, overall study population. Spearman correlation coefficients (\* $p < 0.05$ ; \*\* $p < 0.01$ )

Covariates	Age	H&Y stage	Total LEDD	RBD
Age	1.000	–0.100	0.020	–0.086
H&Y stage		1.000	0.001	–0.013
Total LEDD			1.000	0.157*
RBD				1.000

H&Y Hoehn & Yahr, LEDD levodopa equivalent daily dose, RBD REM behaviour disorder

effects on RBD scores. A positive and moderate direct correlation was detected in levodopa category (Spearman’s correlation coefficient = 0.288;  $p = 0.007$ ) (Table 4).

In a logistic regression model adjusted for age, gender and H&Y stage, the odds for the condition = RBD score > 6

**Table 4** Correlation matrix between covariates RBD and Total LEDD mg/day by categories of therapy

Covariates	Total LEDD <sup>a</sup>	Total LEDD <sup>b</sup>	Total LEDD <sup>c</sup>
RBD <sup>a</sup>	0.101		
RBD <sup>b</sup>		0.288**	
RBD <sup>c</sup>			−0.092

Spearman correlation coefficients (\* $p < 0.05$ ; \*\* $p < 0.01$ )

LEDD levodopa equivalent daily dose, RBD REM behaviour disorder

<sup>a</sup>Dopamine agonist

<sup>b</sup>Levodopa

<sup>c</sup>Combined therapy

(probable-RBD) among subject with levodopa therapy was 2.01 folds in respect to subjects with no-DRTs (95% CI 1.02–3.96;  $p = 0.04$ ) (Table 5). When the estimates were also adjusted for Total LEDD, a non-significant association was observed, although a suggestive association was again detected in the levodopa therapy's category (OR = 2.08; 95% CI 0.94–4.61) (Table 6).

## Conclusions and discussion

Sleep disturbances are features of PD that may be influenced by DRT. A recently published study base on polysomnography recordings showed an association between the increased levodopa doses and the reduction of total sleep time in PD patients [15]. More in general, levodopa treatment has been documented to exacerbate sleep disorders in PD patients [16]. Among sleep disturbances, the natural history of RBD and its response to antiparkinsonian treatment has not been

**Table 5** Results of the logistic regression model predicting RBD scores > 6 as a function of therapy type adjusted by age, gender and H&Y stage

Covariates	Probable-RBD (RBD > 6)	
	OR	CI
Age	0.98	0.95, 1.01
Gender		
Male (reference)	1.0	
Female	0.63	0.37, 1.05
H&Y stage	0.85	0.60, 1.19
Therapy type		
No-DRTs (reference)	1.0	
Dopamine agonist	0.69	0.28, 1.69
Levodopa	2.01	1.02, 3.96
Combined therapy	1.50	0.74, 3.01

CI confidence interval, OR Odds Ratio, RBD REM behaviour disorder, no-DRTs no dopamine-replacement therapies

**Table 6** Results of the logistic regression model predicting RBD scores > 6 as a function of therapy type adjusted by age, gender, Hoehn & Yahr stage and Total LEDD

Covariates	RBD > 6	
	OR	CI
Age	0.98	0.95, 1.01
Gender		
Male (reference)	1.0	
Female	0.63	0.37, 1.05
H&Y stage	0.85	0.60, 1.19
Total LEDD	1.00	0.99, 1.00
Therapy type		
No-DRTs (reference)	1.0	
Dopamine agonist	0.70	0.28, 1.78
Levodopa	2.08	0.94, 4.61
Combined therapy	1.59	0.60, 4.22

CI confidence interval, H&Y Hoehn & Yahr, LEDD levodopa equivalent daily dose, OR odds ratio, RBD REM behaviour disorder, no-DRTs no dopamine-replacement therapies

clarified. Although RBD has been considered as a prodromal non-motor symptom in PD, some patients showed RBD symptoms after the onset of PD, and the effects of dopaminergic treatment on RBD symptoms are still controversial.

The main result of our study shows that, in a population of 250 PD patients, RBD scores were significantly correlated ( $p = 0.013$ ) with total LEDD. In particular, we found a positive and direct correlation between levodopa therapy and higher RBD scores. This association, which was confirmed by regression analyses, was not affected by either patient age or PD severity (as assessed via H&Y stage scores). This finding is in alignment with previous reports documenting an association between RBD and higher LEDD in advanced PD stages [9]. The association between levodopa-LEDD and RBD lends itself to different interpretations of its pathophysiological meaning. On the one hand, the comorbidity of RBD and PD has been shown to predict for a greater severity of motor symptoms; from this perspective, it is possible to conjecture that higher PD severity would require greater doses of levodopa, and the higher PD severity may reflect a faster, more severe course of the underlying synucleinopathy, rather than untoward effects of levodopa. This interpretation is significantly challenged by our finding that the association between LEDD and RBD scores was not affected by H&Y severity scores; however, it should be recognized that, compared with other assessment tools, such as the UPDRS, the H&Y scale is less adequate to capture the severity of specific motor problems in PD in a research setting. On the other hand, our results may indicate that levodopa therapy results in a greater incidence of RBD symptoms. The fact that RBDSQ scores were associated with the

LEDD of levodopa alone, but not dopaminergic agonists points to a role of D1 receptors activation in shaping RBD pathophysiology. Indeed, unlike levodopa, most current dopaminergic agonists selectively activate D2 and D3, but not D1 receptors. The possibility that chronic stimulation of D1 receptors may facilitate the pathogenesis of RBD is in line with previous findings indicating dopaminergic alterations in idiopathic RBD patients [17]. Previous evidence has shown that D1 receptor agonists modulate REM sleep and increase wakefulness [18]. Moreover, DRTs in PD may modulate EMG activity during REM sleep. Zoetmulder and colleagues recently documented that the increased EMG activity during REM sleep is linked with DRTs in PD [19]. In particular, an increase in both phasic twitching and tonic EMG activity was demonstrated in PD patients under levodopa in comparison to treatment-naïve PD patients [20].

Several limitations should be acknowledged in this study. First, since RBD diagnoses were based on RBDSQ scores instead of polysomnography, the sensitivity of our assessments may have been limited, as RBD symptoms may have been under-reported by some patients. Recent studies, for example, have shown that RBDSQ might not be well-suited for the detection of subtle RBD forms among “de novo PD” patients [21]. In addition, the RBDSQ questionnaire does not measure the severity of RBD or account for asymptomatic cases (i.e., REM sleep without atonia cases). While we recognize these limitations, it is worth noting that, while polysomnography remains the gold standard for severity analyses, the RBDSQ has been consistently shown to serve as a useful, sensitive, and inexpensive diagnostic tool [14, 22]. Furthermore, our cohort was mainly comprised of patients with relatively high PD severity (as qualified by their average H&Y stage and LEDD values); thus, the risk of underestimation of RBD among our patients was likely limited. Second, our analyses did not include some potentially relevant data, such as disease duration (which was only available for ~25% of the population) and DAT scan data. Future studies incorporating these crucial parameters are needed to confirm and validate our findings.

These limitations notwithstanding, our report documents a robust relationship between RBDSQ scores and levodopa treatment; while the pathophysiological direction of this link remains partially unclear, our findings strongly advocate for the need of future longitudinal studies aimed at further examining the possibility that different classes of DRTs may shape and influence the course and severity of RBD.

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**Author contributions** Conceptualization, MM, MP, MB and AC; methodology, MM, MP and MB; software, MM; validation, MM, MP, MB; formal analysis, MM, FM; investigation, MM, MP; resources, MP, AC MF and IL; data curation, MM, MP, FM and IL; writing-original draft preparation, MM; writing-review and editing, MM, MP, MB;

visualization, GD, AC, MF and PC; supervision, GD, MP, MM and MB; project administration, MP and GD; funding acquisition, MP.

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## Compliance with ethical standards

**Conflicts of interest** The authors declare no conflict of interest.

**Ethics approval** The study was approved by the "Comitato Etico Indipendente; Azienda Ospedaliero—Universitaria; Cagliari".

**Consent to participate** All participants gave informed consent in accordance with the declaration of Helsinki.

**Availability of data and material** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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