





# Co-Existent Probable RBD and PD: Disease Progression, Medication Response, and Clinical Trial Implications

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Rapid eye movement (REM) sleep behavior disorder (RBD) often precedes Parkinson’s disease (PD) motor signs and may serve as a risk factor for impairment progression.<sup>1</sup> The Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part 3 sum score has been primarily used to measure PD motor severity. To address regulatory calls for outcomes to include the “patient voice”<sup>2</sup> we have previously combined part 2 (patient-reported) and part 3 (clinician-reported) item information for two distinct and validated clinical motor domains: non-tremor and tremor.<sup>3</sup> We investigated the association of probable RBD (pRBD) with landmarks of PD motor disease progression in early PD using this novel approach.

Among 721 untreated early PD patients from the Parkinson’s Progression Markers Initiative (PPMI) and Oxford studies at

baseline, there were 264 subjects with pRBD (termed as PD +pRBD) and 457 subjects without pRBD (PD–pRBD). We first applied Cox modeling to evaluate the association of concomitant pRBD with time to start of dopaminergic treatment, adjusting for age and PD duration. Because the initiation of dopaminergic treatment greatly changes MDS-UPDRS scores, we created a pre-medication dataset with 721 participants (1593 visits) and a post-medication dataset with 512 participants (2424 visits). The non-tremor domain included 35 non-tremor items (2.1–2.9, 2.11–2.13, and 3.1–3.14, with a total score range of 0–140) and the tremor domain included 11 tremor items (2.10 and 3.15a–3.18, with a total score range of 0–44), respectively, in MDS-UPDRS parts 2/3. To investigate the progression in non-tremor and tremor domains and its association with the presence of

**TABLE 1** Parameter estimates and 95% credible intervals from the Multidim longitudinal IRT model on MDS-UPDRS parts 2/3, based on (1) 721 PD patients in the pre-medication dataset with time zero being the study onset (upper table); and (2) 512 PD patients in the post-medication dataset (lower table)

Model	Time	pRBD	pRBD*Time
Pre-medication analysis			
MDS-UPDRS parts 2/3 Multidim–non-tremor	<b>0.451 (0.367, 0.539)</b>	<b>0.218 (0.064, 0.371)</b>	–0.003 (–0.121, 0.120)
MDS-UPDRS parts 2/3 Multidim–tremor	<b>0.205 (0.144, 0.271)</b>	–0.026 (–0.203, 0.142)	–0.026 (–0.118, 0.064)
Post-medication analysis			
MDS-UPDRS parts 2/3 Multidim –non-tremor	<b>0.118 (0.087, 0.153)</b>	<b>0.222 (0.157, 0.284)</b>	<b>0.058 (0.035, 0.082)</b>
MDS-UPDRS parts 2/3 Multidim –tremor	–0.028 (–0.061, 0.007)	0.090 (–0.014, 0.195)	0.000 (–0.038, 0.036)

Note: Statistically significant parameters are boldface.

Abbreviations: Multidim, multidimensional; IRT, item response theory; MDS-UPDRS, Movement Disorder Society Unified Parkinson’s Disease Rating Scale; PD, Parkinson’s disease; pRBD, probable rapid eye movement sleep behavior disorder.

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pRBD, we applied the multidimensional longitudinal item response theory (IRT) models<sup>4</sup> on both pre- and post-medication datasets.

PD+pRBD subjects needed dopaminergic treatment earlier than those with PD-pRBD (adjusted hazard ratio, 1.204; 95% confidence interval, 1.010–1.436;  $P = 0.039$ ). Before dopaminergic treatment, both the non-tremor and tremor domains worsened with time. The PD+pRBD group exhibited worse severity of non-tremor motor symptoms compared to the PD-pRBD group. This pattern occurred at study baselines and persisted longitudinally. However, the presence of pRBD did not show any significant association with tremor severity, or with a distinct progression in either the non-tremor or tremor domains. After the start of dopaminergic treatment, the non-tremor domain score continued to worsen with time, but not the tremor domain. PD+pRBD subjects were more impaired and progressed faster in the non-tremor domain than those with PD-pRBD, and pRBD status was not associated with the tremor domain progression over time. However, the datasets were insufficient to analyze the medication effects in the form of levodopa equivalent daily dose or specific sleep treatments (see Table 1).

The presence or absence of pRBD is an important prognostic factor of clinical progression before and after dopaminergic treatment in early PD. Whereas prior studies have linked RBD with more severe long-term clinical progression,<sup>5</sup> our data and IRT approach that incorporate objective assessment and patient voice specifically identify that this progression focuses primarily on the non-tremor domain. We recommend incorporating baseline pRBD status as a stratification factor or considering it as a covariate in early PD studies that focus on natural disease progression and therapeutic response.

## Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

H.Z.: 1B, 1C, 2A, 2B, 2C, 3A, 3B

Y.G.: 1B, 1C, 2A, 2B, 2C, 3A, 3B

C.G.G.: 1A, 1B, 2C, 3B

T.A.M.: 1A, 1B, 2C, 3B

G.T.S.: 1A, 1B, 2C, 3B

F.A.H.: 3B

M.L.: 3B

M.H.: 3B

S.L.: 1A, 1B, 2A, 2C, 3A, 3B

## Disclosures

**Ethical Compliance Statement:** The current study has been approved by the Duke Institutional Review Board (Protocol Identification: Pro00107266). Informed consent was obtained

from all patients in the original PPMI and Oxford studies. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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