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Is RBD a risk factor for impulse control disorder in Parkinson's disease?

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Running head: ICB RISK IN PD WITH RBD

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Abstract

Objective: To assess the association between REM sleep behavior disorder (RBD) and other determinants and incident impulse control disorder behaviors (ICBs) in patients with early Parkinson's disease (PD) using longitudinal data from the Parkinson's Progression Markers Initiative (PPMI).

Methods: 401 newly-diagnosed PD patients were prospectively evaluated at baseline (BL), month 6, and annually for 5 years. Probable RBD (pRBD) was assessed with the RBD Screening Questionnaire and dichotomized using a cut-off value ≥ 6 . The association of BL and time-dependent (TD) pRBD and other covariates with the development of ICB symptoms, was evaluated using Cox proportional hazards regression and general estimating equations logistic regression. Models considered adjustment for age, sex, MDS-UPDRS III, Geriatric Depression Scale (GDS-15), RBD medication use, total levodopa equivalent daily dose (LEDD), and dopamine agonist (DA) and antidepressant medication use.

Results: Both baseline pRBD and TD pRBD were not associated with an increased risk for incident ICB symptoms after adjustment for covariates (adjusted HR=1.17, $p=0.458$ and HR=1.27, $p=0.257$ respectively). In a modified-TD pRBD model (i.e., considering subjects as pRBD onward from the first time point with RBDSQ score ≥ 6), the risk for incident ICB symptoms was higher in pRBD in unadjusted (HR=1.48, $p=0.038$), but not adjusted (HR=1.29, $p=0.202$) models. TD DA use (HR=1.64, $p=0.039$), TD GDS-15 score (HR=1.12, $p<0.001$), and male sex (year 3: HR=2.10, $p=0.009$; year 4: HR=3.04, $p=0.006$; year 5: HR=4.40, $p=0.007$) were associated with increased ICB symptom risk.

Interpretation: pRBD is not clearly associated with ICB symptom development in early PD, in contrast to DA use, depression, and male sex.

Introduction

A variable proportion of Parkinson's disease (PD) patients, ranging from 14% to 60% may develop impulse control disorder behaviors (ICBs) during the course of the disease.¹ These include impulse control disorders (ICDs), such as pathological gambling, hypersexuality, compulsive shopping and compulsive eating, as well as related behaviors, such as punding, hobbyism, walkabout and dopamine dysregulation syndrome. ICBs in drug-naïve PD patients have the same prevalence than in the general population,² thus ICBs appear to be related to PD treatment, and specifically strongly associated with dopamine agonist (DA) use, with a dose-effect relationship.³

Other non-motor symptoms (NMS) in PD are also frequent and often disabling. About 33% to 60% of PD patients have REM sleep behavior disorder (RBD),⁴ a parasomnia characterized by elaborate and violent motor behaviors during sleep, often associated with vivid aggressive dreams.⁵ RBD is a premotor, or prodromal, symptom of PD, has a prevalence estimated up to 25% in *de novo* parkinsonian patients,⁶ and tends to increase over the initial years of the disease.⁶⁻⁹ PD comorbid with RBD predicts a more severe course of the disease, with earlier axial symptoms and greater cognitive decline.^{10,11}

Six cross-sectional studies have examined the relationship between ICBs and RBD in PD patients. We found that patients with probable RBD assessed by questionnaire (pRBD, not confirmed by video-polysomnography) have an increased prevalence of ICB symptoms compared with PD patients without pRBD.¹² A similar study replicated the finding.¹³ An increased prevalence of video polysomnographic (vPSG)-confirmed RBD was also observed in PD patients with ICBs compared to those without.¹⁴ However, three other studies, using either a questionnaire or standard criteria to diagnose both RBD and ICBs, did not find this association.¹⁵⁻¹⁷ A recent meta-analysis, including 10 observational cross-sectional studies and involving a total of 2781 PD patients, found that RBD was associated with a more than twofold higher risk of having ICBs, and the same result was obtained after stratifying subgroups based on methods for diagnosing RBD and ICBs.¹⁸

Although one study assessed longitudinal severity of ICBs and its predictors in PD using multiple imputation analysis,¹⁷ to date only one longitudinal study has assessed whether RBD is a possible risk factor for the development of incident ICBs.¹⁹ This study, using Parkinson's Progression Markers Initiative (PPMI) cohort data, found that pRBD at baseline, defined by a score ≥ 5 on the RBD Screening Questionnaire (RBDSQ), was an independent predictor of ICD development over time, after adjusting for some covariates (sex, age of disease onset, disease severity and duration, cognitive abilities, anxiety, and depression). However, this study did not control for total levodopa equivalent daily dose (LEDD), only for DA use by stratifying the sample. Furthermore, the study did not look at the clinical longitudinal variability in pRBD and other time-varying covariates.

Using the PPMI database, we aimed to evaluate the association between both pRBD and other predictors and the development of ICB symptoms in PD using validated longitudinal assessments.

Material and Methods

PPMI is an ongoing observational, international, multicenter study aimed at identifying biomarkers of PD progression in a large cohort of participants with early untreated (*de novo*) PD at enrollment, compared with healthy controls (HC). The aims and methodology of the study have been published elsewhere (www.ppmi-info.org/study-design).²⁰ The study is conducted in accordance with Good Clinical Practice and any applicable national and local regulations. Although PPMI mainly aims the study of biological markers of PD progression, it provides clinical information, including some focus on neuropsychiatric symptoms. Validated screening questionnaires for both RBD (RBDSQ)²¹ and ICB symptoms (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, QUIP) are among the longitudinal assessments administered.²² Both the baseline and longitudinal RBD and ICBs data from the PPMI cohort have already been used to demonstrate longitudinal course of these and other key NMS of PD.²³ Data downloaded on April 1, 2019 were used for this analysis.

Participants

Four hundred twenty-three newly diagnosed, untreated (at baseline, BL) patients with PD were enrolled in PPMI. Inclusion and exclusion criteria have been described elsewhere.²⁰

Data for this analysis was limited to subjects that had no missing baseline RBDSQ or baseline QUIP, and had at least one additional follow-up RBDSQ and QUIP at year one or later (n=401). Data up through year 5 was used.

Clinical assessment

Demographical and clinical data (sex, age, age of disease onset, duration of PD, current treatment) were collected for all participants. The severity of PD was assessed by means of the Hoehn and Yahr Stage²⁴ and MDS-UPDRS part III²⁵ at each visit.

All patients completed the RBDSQ at BL, 6 months, and annually starting at year 1. The RBDSQ is a 10-item patient self-rating questionnaire, with “yes” or “no” questions, with a maximum score of 13 points, covering the clinical features of RBD.²¹ A cut-off value ≥ 6 represents the best cut-off value for detecting RBD (sensitivity=0.84, specificity=0.96) in PD.²⁶

ICB symptoms were also evaluated at BL, 6 months, and annually starting at year 1, using the short version of the QUIP. This is a self-completed screening instrument specifically developed and validated to detect the presence of current ICB symptoms in PD. In this study, the presence of ICB symptoms was defined by a score ≥ 1 on any of the four items related to ICDs (gambling, hypersexuality, compulsive buying and compulsive eating) or related behaviors (hobbyism, punting and walkabout).²² We did not include the item related to dopaminergic dysregulation syndrome since this disorder is uncommon in early PD, as patients are rarely on high-dose levodopa early in the disease.

As depression may be a risk factor for ICBs,²⁷ we included the 15-item Geriatric Depression Scale (GDS-15), which has 15 dichotomous (yes/no) questions generating a score that

ranges from 0 to 15. It has been studied and validated in young and old PD patients.²⁸ GDS-15 was treated as a continuous covariate for analysis.

Total LEDD was calculated for every participant, as well as the percentage of participants taking a DA and the DA LEDD specifically.²⁹ As antidepressants are a risk factor for RBD,³⁰ antidepressant use was also determined, as well as use of RBD medications (e.g., clonazepam and melatonin).

Statistical analysis

Probable RBD status (RBD+ or RBD-) was measured at BL, month 6, and months 12, 24, 36, 48, and 60. The pRBD status can change at each of these time points, thus pRBD is time-varying or time-dependent (TD). Along with baseline pRBD, we examined a TD and a modified time-dependent (mTD) pRBD in our analysis. RBD status assessed by questionnaire can fluctuate during the evolution of PD,^{7,31,32} while vPSG-assessed RBD tends to persist over time.⁶⁻⁸ This can be due to the lower accuracy of questionnaires compared to PSG, but also to spontaneous changes in clinical, but not polysomnographic, manifestations of the parasomnia. Based on these assumptions, in the mTD pRBD, we treated subjects as pRBD+ from the first month onward from the time the patient first had a RBDSQ score ≥ 6 .

Differences in baseline demographic and clinical characteristics between baseline pRBD+ and pRBD- were analyzed with the use of Student's t-test or Wilcoxon rank-sum test for continuous variables, and chi-square test or Fisher's Exact test for nominal variables. Time to first development of ICB symptoms was evaluated using Cox proportional-hazards (PH) and generalized estimating equations (GEE) logistic regression models. Probable RBD status was examined in three different ways: baseline pRBD, TD pRBD and mTD pRBD.

We first considered a Cox PH model with baseline pRBD and potential other baseline covariates (age, sex, MDS-UPDRS part III (continuous), GDS-15 (continuous), RBD medication use (yes/no), and antidepressant use (yes/no)). The model including baseline covariates only examined covariates' long-term effects on ICB symptom development over the 5-year period. Subjects with symptoms of ICB at BL were excluded (n=83), and we assumed all other subjects were symptom free prior to participating in the study. To limit the number of predictors in the final multivariate model we implemented a screening procedure. PH for a covariate was examined by including the interaction of time and the covariate (a TD coefficient) in a model with only pRBD and the covariate. If the p-value of the interaction was <0.10 , PH was considered to not be satisfied and the interaction along with the covariate main effect was retained in the multivariate model.³³ If PH did not appear to be violated, we proceeded to fit a Cox regression model with only the candidate covariate and pRBD status. If the p-value of the covariate was less than 0.10, the predictor was included in the multivariate model. Baseline age and antidepressant use were forced in to the final model based on clinical relevance. Hazard ratios (HR) along with 95% confidence intervals were estimated using Cox regression. The final cox regression model adjusted for age, baseline antidepressant use, sex and the interaction of months and sex (PH was not satisfied for sex). Schoenfeld's test did not indicate a violation of PH in the final model.³⁴ We present these results for completeness acknowledging that relating the risk for ICB symptom development considering pRBD status at baseline only is not optimal since pRBD status changes over time.

Next, Cox PH models including TD covariates were fit. Including a TD covariate in a survival model examines the short-term effect of a covariate on the development of the event.³⁴⁻³⁶

Specifically, we related the pRBD status from the last visit with hazard of developing ICB symptoms at the current visit (i.e., a one-visit lag time relationship between covariate and event). The models examining the TD and mTD pRBD considered the following covariates for adjustment: baseline age, sex, baseline MDS-UPDRS III (continuous), TD GDS-15 (continuous), TD RBD medication use (yes/no), TD LEDD (continuous), TD DA use (yes/no),

and TD antidepressant use (yes/no). The final multivariate model was selected using the same screening procedure as for the baseline covariates model. Age, TD antidepressant use and TD DA use were forced in to the final models regardless of statistical significance. The mTD and TD pRBD final Cox regression models adjusted for age, TD antidepressant use, TD DA use, TD GDS-15, sex and the interaction of months and sex (PH was not satisfied for sex). Schoenfeld's test did not indicate a violation of PH in the final model. HRs and 95% confidence intervals are reported. Survival probabilities are estimated from the final models and used to illustrate effects of the covariates.³⁷ In relating the serial measurements to ICB symptoms, missing data for covariates resulted in a reduced number of events in the models. As a sensitivity analysis, we used last observation carried forward (LOCF) to impute missing values for the TD covariates.

Evaluating pRBD in a TD manner is limited by the frequency of study visits (i.e., how often pRBD status is updated). In this study, we were limited by visits every 6 months and then annually. While the biological effect of relating pRBD to ICB symptom development is not certain, it is plausible that a shorter evaluation relating pRBD to the possible risk of ICB symptoms would be reasonable. In fact, as soon as one has RBD, susceptibility to develop ICB could be increased, especially in the face of DA exposure. In order to evaluate the instantaneous association of pRBD with ICB symptom development, we fit a GEE logistic regression model. The GEE model allows us to associate the pRBD status and ICB symptoms development captured at the same visit, which cannot be evaluated using a Cox regression model. All other TD covariates were treated instantaneously (no lag effect) as well. All patients (n = 401) were included in this analysis. Similar to the Cox regression models, data after a subject has developed ICB symptoms or was censored, whichever occurred first, was not used in the model. We considered both TD and mTD pRBD. To fit the GEE model, we first determined the optimal time trend (linear, quadratic, or non-linear) for a model with (TD and mTD) pRBD alone using quasilikelihood information criterion (QICu).³⁸ An unstructured covariance structure was used. The non-linear (categorical time) model was optimal using the model selection criteria. Due to model fit issues, a model with all candidate

predictors could not be fit. Therefore, we implemented a variable screening procedure in order to limit the number of predictors in the final models. To screen the predictors, a GEE model with the candidate covariate and the interaction of pRBD and time was fit. If the p-value of the covariate was <0.10 the covariate was retained in the multivariate model. QIC was used to determine whether the interaction of the covariate and time were included. Age, TD antidepressant use and TD DA use were forced in to the final models based on clinical relevance. The final multivariate models for TD and mTD pRBD adjusted for age, TD antidepressant use, TD DA use, and TD GDS-15. Data were analyzed using SAS 9.4 Software (SAS Institute, Cary, NC) and R.³⁹

Results

Descriptive statistics

The BL clinical characteristics of PD patients are shown in Table 1. Out of the 401 subjects, 89 (22%) patients did not have data available at the 5-year follow up. 24.9% of PD patients were pRBD+ at BL. Prevalence of pRBD increased to 36.9% at year 5. Out of the 401 subjects, 213 (53.12%) did not change RBD status over the five years; of them, 43 (20.2%) subjects had pRBD at all their visits, and 170 (79.8%) never had pRBD. In 188 participants (46.9%) RBD status changed over the 5-year period.

The cumulative prevalence of patients who had pRBD at some point increased from 24.9% at BL to 58.0% over the follow-up. Forty-three patients were treated for their RBD at some point during the observation period. At BL, RBD+ patients had higher MDS-UPDRS part III and GDS-15 scores, and were more likely to take antidepressant and RBD medications (Table 1).

The overall prevalence of patients screening positive for ICB symptoms increased from 20.7% at BL to 26.3% at year 5. The prevalence of each ICB symptom over time is illustrated in Figure 1.

At BL, patients screening positive for ICB symptoms were more frequent in pRBD+ group compared to pRBD- (28.0% vs. 18.3%, $p=0.04$). Prevalence of ICB symptoms slightly increased from baseline to year 5 only in pRBD+, and the between-group difference remained significant at year 5 (pRBD+ = 32.0%; pRBD- = 18.3%, $p=0.007$).

Mean GDS-15 score in the whole sample was 2.32 ± 2.47 , median 2.0 (range 0, 14) at BL. At follow-up, mean GDS-15 score was 2.79 ± 2.81 , median 2.0, (range 0, 15), $n=313$.

Impact of pRBD on incident ICBs

Excluding participants with baseline ICB symptoms ($n=83$), 124/318 (39%) patients developed ICB symptoms over the 5-year period. The percentage of participants with incident ICB symptoms was not statistically different based on BL RBD status (pRBD+ = 47%, pRBD- = 37%). Results of univariate and multivariate HR estimates for BL Cox model and TD pRBD are illustrated in Table 2. Baseline pRBD was not associated with an increased risk for development of ICB symptoms (unadjusted HR=1.36, 95% CI (0.92, 2.02), $p=0.125$; adjusted HR=1.17, 95% CI (0.77, 1.77), $p=0.458$).

In the TD pRBD model, an increased risk for incident ICBs was not observed in pRBD patients (unadjusted HR=1.43, 95% CI (0.97, 2.10), $p=0.069$; adjusted HR=1.27, 95% CI (0.84, 1.90), $p=0.257$). In the mTD pRBD model, the risk for ICB symptoms was higher in pRBD patients in unadjusted (HR=1.48, 95% CI (1.02, 2.14), $p=0.038$) but not adjusted (HR=1.29, 95% CI (0.88, 1.90), $p=0.202$) models (see Table 3a).

In the TD pRBD model, variables associated with an increased risk for incident ICB symptoms were TD DA use (HR=1.64, 95% CI (1.03, 2.64), $p=0.039$), TD GDS-15 (HR=1.12, 95% CI (1.06, 1.19), $p<0.0001$), and male sex. The effect of sex varied over time; as time progressed, ICBs symptoms became increasingly more common in males (year 3: HR=2.10, 95% CI (1.20, 3.67), $p=0.009$; year 4: HR=3.04, 95% CI (1.37, 6.73), $p=0.006$, year 5:

HR=4.40 95% CI (1.5-12.8) $p=0.007$). Similar analyses in the mTD pRBD model led to identical results (see Table 3a).

As showed in Table 3b, according to HR estimates for LOCF (allowing to impute missing values for the TD covariates), in mTD RBD Cox model the risk for ICB symptoms was higher in pRBD patients in unadjusted (HR=1.52, 95% CI (1.06, 2.18), $p=0.023$) but not adjusted (HR=1.33, 95% CI (0.91, 1.94), $p=0.134$) models.

Instantaneous association of pRBD with ICB symptom development

GEE logistic regression model, allowing to assess the pRBD status and ICB symptoms development captured at the same visit, showed that pRBD+ had an increased risk for ICBs symptoms at BL (HR: 1.75, 95% CI (1.04-2.97) $p=0.035$) and at year 4 (HR: 3.23, 95% CI (1.21-8.63); $p=0.020$). However, results were not significant after adjusting for covariates related to ICBs development (see Tables 4-5).

Discussion

This study found that depression, DA use and male sex are strong predictors of the development of ICB symptoms, while RBD is not robustly associated with incident ICBs.

Younger age or younger age at disease onset, male sex, DA use, and depression are known risk factors or correlates for ICBs in PD.^{20,40,41} In this study, incident ICBs through the 5-year follow-up period were correlated with DA use and depression, but not with age. While most previous cross-sectional studies found an association between ICBs and younger age, the few longitudinal studies conducted have reported conflicting results.^{3,42,43} The current study, performed on a large, de novo PD cohort with a long follow-up period, suggests that younger age is not a risk factor when controlling for confounding factors.

Male sex has been shown to be associated with ICBs in PD, in both cross-sectional and longitudinal studies.^{3,41,44} Interestingly in our study, the effect of sex varied over time; male

sex was not associated with an increased risk to develop ICBs over the first two years of follow-up, but as time progressed ICBs became increasingly more common in males. Sex differences in the prevalence of ICBs have been reported for some type of ICBs in PD (e.g. hypersexuality being more prevalent in men, buying and eating in women).^{44,45} Future studies should investigate the relationship between sex and timing in the development of each ICD/ICB, in order to better study the trajectories of the evolution of each ICBs under DA treatment.

Depression has been shown to be associated with ICBs in PD patients as well as in general population, mainly in cross-sectional studies.⁴⁶⁻⁴⁸ Recently, a longitudinal study performed on the same cohort as the present study showed that depression predisposes to development of ICDs in PD.²⁰ In that study, patients were considered depressed if they had a GDS-15 score ≥ 7 or if they were taking antidepressants indicated for depression. In the present study, we decided to look at the impact of TD depression, based on GDS-15 score as continuous measure, on the development of ICBs. Results of this longitudinal analysis support the role of depressive symptoms as a risk factor for developing ICBs.

The present study found a significant association between pRBD and ICBs in cross-sectional analyses, as well as an increased risk for ICB symptoms in pRBD patients in longitudinal univariate analysis, while only a trend towards an increase risk was observed after adjustment for covariates. Similar results were obtained when imputing missing values for the TD covariates by means of LOCF.

The relationship between RBD and ICBs is controversial; an association has been observed in several cross-sectional studies,¹²⁻¹⁴ but others studies failed to find such a correlation.¹⁵⁻¹⁷ Conflicting results may be ascribed to methodological differences in assessing RBD and ICBs, or to insufficient power due to low number of patients with ICBs. In a recent study on early PD patients followed for 3 years, the prevalence of ICBs was not associated to RBD, but only with DA use, apathy and severity of motor fluctuations, according to a multiple

imputation analysis.¹⁷ Recently, a meta-analysis including 10 observational cross-sectional studies and involving data from 2781 PD patients found that RBD was associated with a more than twofold increased risk of developing ICBs, even after stratifying subgroups based on methods for diagnosing RBD and ICBs.¹⁸ Finally, another longitudinal analysis was recently performed using the PPMI cohort data, finding that pRBD at baseline was an independent predictor of ICD development over time.¹⁹ However, a cut-off of ≥ 5 on the RBDSQ was used to define pRBD, as in general population, while a cut-off ≥ 6 has been shown to be the best value for detecting RBD in PD.²⁸ Furthermore, the study only looked at the long-term effect of baseline pRBD, and did not look at the time-dependent effect of pRBD and other time-varying covariates in predicting ICBs with a specific time lag. Finally, results were not adjusted for LEDD, and only DA use was considered, but this covariate was not included in the Cox PH model but was rather taken into account by stratifying the sample in DA users and non-users.

Our study failed to demonstrate a clear association between RBD and the development of ICBs. A possible explanation can be that ICB rates didn't increase much over the 5 years, rising just from 20.7% at BL to 26.3% at year 5. Actually, in a longitudinal prospective study from a French PD cohort including 411 PD patients with duration of disease at baseline of 2.6 y, the prevalence of ICBs was found to increase from 19.7% at baseline to 32.8% at 5 years.³ Therefore, one may think that the impact of BL or TD pRBD may only manifest itself once disease manifests for longer and ICB rates increase more significantly, either due to disease impact or to longer or greater exposure to dopaminergic treatments.

A main limitation of the present study is the fact that ascertainment of RBD was questionnaire-assessed and not confirmed by video polysomnography at baseline and during follow-up. However, the RBDSQ in PD has been found to show a moderate to high sensitivity and specificity (0.842 and 0.962 respectively) using a cut-off ≥ 6 .²⁶ Moreover, no information from bedpartner or caretaker was available, potentially leading to an underestimate of the prevalence of both RBD and ICBs. Furthermore, RBD status, especially assessed by

questionnaire, can fluctuate during the evolution of PD,^{4,30,31} while PSG-assessed RBD has been found to persist over time.³⁻⁵ This can be due to the lower accuracy of the questionnaire compared to PSG, but also to spontaneous changes in the clinical, but not polysomnographic, manifestations of the parasomnia.⁶⁻⁸ In order to take into account this phenomenon, a set of analyses was performed in PD patients according to the “modified time-dependent” RBD model (i.e., considering subjects as pRBD+ from the first month onward that the patient had an RBDSQ score ≥ 6).

This study investigated the relationship between RBD and ICBs in PD in a longitudinal approach. Strengths of this study are the use of a large *de novo* PD cohort with a long follow up, the use of validated tools to assess RBD, ICBs and depression, and a sound, comprehensive statistical plan.

In this analysis, we examined several time-relationships between pRBD and ICB symptom development: the long-term effect of baseline pRBD, the one visit-lag, and the instantaneous association. These analysis methods are limited in that they only utilize one pRBD status at a time in the model estimation. Further studies could include analyses that incorporate more complex models utilizing the entire covariate history of pRBD, such as a joint model.

In conclusion, DA use, depression, and male sex, but not clearly pRBD, are strongly associated with ICB symptom development in early PD. Further longitudinal studies are needed to further elucidate the association between RBD and ICBs in this population.

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AUTHOR CONTRIBUTIONS

MLF, JF, BP, DW, AM and FD contributed to the conception and design of the study; JF and BP contributed to the acquisition and analysis of data; MLF, JF, BP and FD contributed to the drafting the text and preparing the figures.

POTENTIAL CONFLICTS OF INTEREST

Nothing to report

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FIGURE TITLES

Figure 1: Frequency of Impulsive-Compulsive Behaviors at baseline and during the 5-years follow-up.

Figure 2: Survival Probability Estimates for pRBD+ vs pRBD-

Figure 3: Survival Probability Estimates for Male vs Female

FIGURE LEGENDS

Figure 1: no legend

Figure 2: Estimates generated from the mTD pRBD Cox model for a patient pRBD+ at baseline (and all subsequent visits) versus pRBD- at all visits leaving all other factors equal (male subject age 61 years with no DA or antidepressant use at any visit and GDS-15 of 2 at all visits).

Figure 3: Estimates generated from the mTD pRBD Cox model for a male versus female patient leaving all other factors equal (pRBD+ at all visits, age 61 years with no DA or antidepressant use at any visit and GDS-15 of 2 at all visits).

Table 1: Baseline (BL) clinical and demographic characteristics of PD patients

	Total sample n=401	BL RBD+ n=100	BL RBD- n=301	p-value
Age (yrs., mean \pm SD)	61.5 \pm 9.8	61.3 \pm 9.9	61.6 \pm 9.7	0.82 [§]
Gender Male [nb (%)]	263 (65.6)	73 (73.0)	190 (63.1)	0.07 [†]
PD duration [yrs.(med; range)]	4.3 (0.4; 35.8)	3.5 (0.4; 26.1)	4.4 (0.7; 35.8)	0.09 [¶]
H&Y				0.67 [£]
Stage 0 [nb (%)]	0 (0)	0 (0)	0 (0)	
Stage 1 [nb (%)]	178 (44.4)	41 (41)	137 (45.5)	
Stage 2 [nb (%)]	221 (55.1)	59 (59)	162 (53.8)	
Stage 3-5 [nb (%)]	2 (0.5)	0 (0)	2 (0.7)	
MDS-UPDRS III (mean \pm SD)	20.8 \pm 8.81	22.3 \pm 8.8	20.3 \pm 8.8	0.047 [§]
LEDD (mg)	0 (0)	0 (0)	0 (0)	NA
LEDD DA (mg)	0 (0)	0 (0)	0 (0)	NA
DA user nb (%)	0 (0)	0 (0)	0 (0)	NA
GDS-15 score (med; range)	2 (0; 14)	2 (0; 12)	2 (0; 14)	0.001 [¶]
GDS-15 depressed* [nb (%)]	57 (14)	25 (25)	32 (11)	0.0004 [¶]
ICBs [nb (%)]	83 (20.7)	28 (28)	55 (18.3)	0.04 [†]
ICD4 [nb (%)]	48 (12.0)	21 (21.0)	27 (9.0)	0.001 [†]
ICD-RB [nb (%)]	46 (11.5)	13 (13.0)	33 (11.0)	0.58 [†]
Antidepressant use [nb (%)]	75 (18.7)	28 (28.0)	47 (15.6)	0.006 [†]
RBD medication use [nb (%)]	19 (4.7)	10 (10.0)	9 (3.0)	0.004 [†]

PD = Parkinson's disease; RBD: REM sleep behavior disorder; yrs.= years; med= median; SD: standard deviation; nb: number; H&Y: Hoehn and Yahr Stage; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease rating Scale; LEDD: Levodopa Equivalent Daily Dose, DA: dopaminergic agonist, GDS-15: Geriatric Depression Scale; *according to GDS-15 score ≥ 5 ; ICB: Impulse Control disorder Behaviors; ICD4: according to the Questionnaire for Impulse Compulsive disorder in Parkinson's Disease (QUIP, impulse control disorders including pathological gambling, compulsive eating, compulsive sexual behavior and compulsive shopping; ICD-RB: ICD-related behaviors including punding, hobbyism and walkabout.

[§] Student's t-test

[¶] Wilcoxon Rank Sum test

[†] Chi-square test

[£] Fisher's Exact test

Table 2**2a: Hazard Ratio (HR) Estimates for Baseline pRBD**

Model	Parameter	HR	HR 95% CL	p-value	# of ICB Events
Unadjusted	Baseline pRBD	1.363	(0.918, 2.023)	0.1245	124
Univariate adjustment:					
Age	Baseline pRBD	1.349	(0.908, 2.003)	0.1378	124
Antidepressant use	Baseline pRBD	1.296	(0.863, 1.946)	0.2118	124
GDS-15	Baseline pRBD	1.283	(0.860, 1.915)	0.2217	124
MDS-UPDRS III	Baseline pRBD	1.349	(0.907, 2.005)	0.1394	124
RBD Medication Use	Baseline pRBD	1.357	(0.910, 2.022)	0.1341	124
Sex and Sex*months	Baseline pRBD	1.325	(0.891, 1.969)	0.1642	124
Multivariate Model	Baseline pRBD	1.170	(0.773, 1.770)	0.4579	124
Multivariate Model	Age	0.982	(0.964, 1.001)	0.0656	124
Multivariate Model	Antidepressant use	1.274	(0.804, 2.020)	0.3027	124
Multivariate Model	GDS-15	1.059	(0.989, 1.134)	0.1026	124
	Sex* (male vs female)				124
	6 months:	0.905	(0.502, 1.630)	0.7391	
Multivariate Model	12 months:	1.045	(0.638, 1.712)	0.8618	
	24 months:	1.393	(0.928, 2.092)	0.1100	
	36 months:	1.858	(1.120, 3.080)	0.0164	
	48 months:	2.477	(1.208, 5.077)	0.0133	
	60 months:	3.302	(1.250, 8.724)	0.0159	

2b: HR Estimates for Time-Dependent RBD Cox Models

Model	Parameter	HR	HR 95% CL	p-value	# of ICB Events
Unadjusted	TD pRBD	1.428	(1.022, 2.138)	0.0380	118
Age	TD pRBD	1.434	(1.024, 2.141)	0.0370	118
Antidepressant use	TD pRBD	1.384	(0.986, 2.106)	0.0592	118
LEDD	TD pRBD	1.271	(1.051, 2.202)	0.0260	118
DA Use	TD pRBD	1.465	(0.889, 1.882)	0.1789	117
GDS-15	TD pRBD	1.287	(0.869, 2.030)	0.1895	91
MDS-UPDRS III	TD pRBD	1.408	(1.007, 2.119)	0.0461	118
RBD Medication Use	TD pRBD	1.386	(0.988, 2.097)	0.0576	118
Sex and Sex*months	TD pRBD	1.373	(0.983, 2.069)	0.0617	118
Multivariate Model	TD pRBD	1.266	(0.842, 1.902)	0.2569	117
Multivariate Model	Age	0.985	(0.966, 1.005)	0.1416	117
Multivariate Model	TD Antidepressant use	0.989	(0.627, 1.562)	0.9634	117
Multivariate Model	TD DA use	1.644	(1.025, 2.635)	0.0390	117
Multivariate Model	TD GDS-15	1.122	(1.061, 1.186)	<0.0001	117
	Sex* (male vs female)				117
	6 months:	0.835	0.459, 1.519)	0.5544	
Multivariate Model	12 months:	1.004	(0.608, 1.658)	0.9875	
	24 months:	1.452	(0.947, 2.230)	0.0880	
	36 months:	2.101	(1.205, 3.670)	0.0091	
	48 months:	3.039	(1.374, 6.738)	0.0062	
	60 months:	4.397	(1.508, 12.859)	0.0068	

pRBD: probable REM behavior disorder; CI: confidence interval; ICB: Impulse Control disorder Behaviors; MDS-UPDRS III: Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III; GDS-15: Geriatric Depression Scale-15 Items; TD: Time Dependent; LEDD: Levodopa Equivalent Daily Dose, DA: dopaminergic agonist;

Table 3**3a. Hazard Ratio (HR) Estimates for modified Time-Dependent pRBD Cox Models**

Model	Parameter	HR	HR 95% CL	p-value	ICBs (n)
Unadjusted	mTD pRBD	1.478	(1.022, 2.138)	0.0380	118
Univariate adjustment:		1.481	(1.024, 2.141)	0.0370	
Age	mTD pRBD	1.441	(0.986, 2.106)	0.0592	118
Antidepressant use	mTD pRBD	1.328	(0.869, 2.030)	0.1895	118
LEDD	mTD pRBD	1.521	(1.051, 2.202)	0.0260	118
DA Use	mTD pRBD	1.293	(0.889, 1.882)	0.1789	117
GDS-15	mTD pRBD	1.461	(1.007, 2.119)	0.0461	91
MDS-UPDRS III	mTD pRBD	1.440	(0.988, 2.097)	0.0576	118
RBD Medication Use	mTD pRBD	1.426	(0.983, 2.069)	0.0617	118
Sex and Sex*months	mTD pRBD	1.478	(1.022, 2.138)	0.0380	118
Multivariate analysis	mTD pRBD	1.288	(0.873, 1.901)	0.2025	117
	Age	0.985	(0.966, 1.005)	0.1417	117
	TD Antidepressant use	0.986	(0.626, 1.553)	0.9517	117
	TD DA use	1.652	(1.031, 2.646)	0.0368	117
	TD GDS-15	1.122	(1.060, 1.186)	<0.0001	117
	Sex* (male vs female)				117
	6 months:	0.835	(0.459, 1.519)	0.5542	
	12 months:	1.004	(0.608, 1.658)	0.9869	
	24 months:	1.453	(0.947, 2.230)	0.0871	
	36 months:	2.103	(1.205, 3.670)	0.0089	
	48 months:	3.043	(1.374, 6.738)	0.0061	
	60 months:	4.403	(1.508, 12.859)	0.0067	

3b. Hazard Ratio (HR) estimates for LOCF modified Time-Dependent pRBD Cox Models

Model	Parameter	HR	HR 95% CL	p-value	ICBs (n)
Unadjusted	mTD pRBD	1.519	(1.022, 2.138)	0.0380	124
Univariate adjustment:					124
Age	mTD pRBD	1.523	(1.024, 2.141)	0.0370	124
Antidepressant use	mTD pRBD	1.465	(0.986, 2.106)	0.0592	124
LEDD	mTD pRBD	1.557	(1.051, 2.202)	0.0260	124
DA Use	mTD pRBD	1.351	(0.889, 1.882)	0.1789	124
GDS-15	mTD pRBD	1.518	(0.869, 2.030)	0.1895	124
MDS-UPDRS III	mTD pRBD	1.504	(1.007, 2.119)	0.0461	124
RBD Medication Use	mTD pRBD	1.491	(0.988, 2.097)	0.0576	124
Sex and Sex*months	mTD pRBD	1.475	(0.983, 2.069)	0.0617	124
Multivariate analysis	mTD pRBD	1.334	(0.915, 1.944)	0.1342	124
	Age	0.983	(0.964, 1.002)	0.0822	124
	TD Antidepressant use	1.028	(0.665, 1.588)	0.9022	124
	TD DA use	1.590	(1.007, 2.510)	0.0467	124
	TD GDS-15	1.123	(1.063, 1.186)	<0.0001	124
	Sex* (male vs female)				124
	6 months:	0.888	(0.493, 1.599)	0.6923	
	12 months:	1.024	(0.625, 1.678)	0.9250	
	24 months:	1.362	(0.908, 2.043)	0.1356	
	36 months:	1.811	(1.095, 2.997)	0.0208	
	48 months:	2.409	(1.179, 4.922)	0.0159	
	60 months:	3.204	(1.218, 8.428)	0.0183	

pRBD: probable REM Sleep Behavior Disorder; ICB: Impulse Control disorder Behaviors; mTD pRBD: modified Time-Dependent probable REM Sleep Behavior Disorder; LEDD: Levodopa Equivalent Daily Dose, DA: dopaminergic agonist; GDS-15: Geriatric Depression Scale 15 items; MDS-UPDRS III: Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III; TD: Time Dependent.

Table 4: Odd Ratio (OR) Estimates for Time-Dependent RBD GEE Models – Univariate Adjustment Analysis

Adjustment Analysis					
Model	Parameter		OR	OR 95% CL	p-value
Unadjusted	TD pRBD	Baseline:	1.758	(1.041, 2.968)	0.0348
		6 months:	0.621	(0.228, 1.688)	0.3499
		12 months:	1.840	(0.88, 4.925)	0.2246
		24 months:	1.543	(0.694, 3.433)	0.2875
		36 months:	1.751	(0.693, 4.429)	0.2365
		48 months:	3.229	(1.208, 8.634)	0.0195
		60 months:	1.655	(0.466, 5.877)	0.4357
Univariate adjustment: Age	TD pRBD	Baseline:	1.756	(1.038, 2.971)	0.0358
		6 months:	0.621	(0.228, 1.692)	0.3518
		12 months:	1.821	(0.682, 4.860)	0.2315
		24 months:	1.569	(0.704, 3.496)	0.2702
		36 months:	1.771	(0.700, 4.476)	0.2273
		48 months:	3.286	(1.234, 8.756)	0.0173
		60 months:	1.620	(0.457, 5.748)	0.4551
Univariate adjustment: Antidepressant use	TD pRBD	Baseline:	1.712	(1.011, 2.900)	0.0454
		6 months:	0.606	(0.222, 1.654)	0.3282
		12 months:	1.763	(0.650, 4.778)	0.2653
		24 months:	1.454	(0.654, 3.233)	0.3587
		36 months:	1.636	(0.643, 4.165)	0.3018
		48 months:	3.088	(1.149, 8.304)	0.0255
		60 months:	1.610	(0.455, 5.697)	0.4598
Univariate adjustment: LEDD	TD pRBD	Baseline:	1.757	(1.041, 2.966)	0.0348
		6 months:	0.580	(0.108, 3.120)	0.5253
		12 months:	1.313	(0.421, 4.099)	0.6391
		24 months:	1.378	(0.566, 3.351)	0.4798
		36 months:	1.519	(0.565, 4.083)	0.4073
		48 months:	4.417	(1.276, 15.290)	0.0190
		60 months:	1.419	(0.311, 6.482)	0.6515
Univariate adjustment: DA Use	TD pRBD	Baseline:	1.757	(1.040, 2.966)	0.0350
		6 months:	0.692	(0.252, 1.900)	0.4752
		12 months:	1.914	(0.713, 5.139)	0.1978
		24 months:	1.581	(0.704, 3.549)	0.2673
		36 months:	1.784	(0.711, 4.475)	0.2175
		48 months:	3.316	(1.272, 8.645)	0.0142
		60 months:	1.736	(0.402, 7.501)	0.4603
Univariate adjustment: GDS-15	TD pRBD	Baseline:	1.513	(0.877, 2.609)	0.1365
		6 months:	0.529	(0.198, 1.414)	0.2040
		12 months:	1.720	(0.623, 4.751)	0.2957
		24 months:	1.304	(0.575, 2.958)	0.5249
		36 months:	1.558	(0.657, 3.694)	0.3140
		48 months:	2.686	(0.971, 7.436)	0.0571
		60 months:	1.506	(0.508, 4.471)	0.4604
Univariate adjustment: MDS-UPDRS III	TD pRBD	Baseline:	1.776	(1.050, 3.004)	0.0323
		6 months:	0.630	(0.231, 1.720)	0.3675
		12 months:	1.879	(0.701, 5.038)	0.2103
		24 months:	1.552	(0.697, 3.454)	0.2821
		36 months:	1.778	(0.700, 4.513)	0.2262
		48 months:	3.276	(1.225, 8.757)	0.0180
		60 months:	1.666	(0.470, 5.909)	0.4297
Univariate adjustment: RBD Medication Use	TD pRBD	Baseline:	1.770	(1.049, 2.987)	0.0326
		6 months:	0.623	(0.229, 1.696)	0.3541
		12 months:	1.859	(0.693, 4.991)	0.2182
		24 months:	1.565	(0.701, 3.490)	0.2743
		36 months:	1.781	(0.703, 4.513)	0.2234
		48 months:	3.271	(1.225, 8.731)	0.0180
		60 months:	1.668	(0.475, 5.860)	0.4250
Univariate adjustment: Sex	TD pRBD	Baseline:	1.737	(1.028, 2.936)	0.0392
		6 months:	0.607	(0.223, 1.650)	0.3276
		12 months:	1.825	(0.680, 4.897)	0.2321
		24 months:	1.539	(0.692, 3.423)	0.2904
		36 months:	1.716	(0.678, 4.345)	0.2544
		48 months:	3.179	(1.185, 8.532)	0.0217
		60 months:	1.633	(0.458, 5.820)	0.4493

RBD: REM behavior disorder; GEE: Generalized Estimating Equation; TD: Time Dependent; pRBD: probable RBD; LEDD: Levodopa Equivalent Daily Dose, DA: dopaminergic agonist; GDS-15: Geriatric Depression Scale 15 Items; MDS-UPDRS III: Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III.

Table 5: OR Estimates for Time-Dependent RBD GEE Models – Multivariate Adjustment Analysis

Model	Parameter	OR	OR 95% CL	p-value
	TD pRBD			
	Baseline:	1.519	(0.875, 2.638)	0.1372
	6 months:	0.587	(0.216, 1.593)	0.2952
	12 months:	1.767	(0.627, 4.979)	0.2813
Multivariate Model	24 months:	1.366	(0.592, 3.150)	0.4643
	36 months:	1.616	(0.691, 3.780)	0.2683
	48 months:	2.813	(1.057, 7.488)	0.0384
	60 months:	1.536	(0.474, 4.974)	0.4740
Multivariate Model	Age	0.985	(0.969, 1.002)	0.0763
Multivariate Model	TD Antidepressant use	0.939	(0.647, 1.362)	0.7383
Multivariate Model	TD DA use	1.436	(0.925, 2.230)	0.1067
Multivariate Model	TD GDS-15	1.166	(1.111, 1.224)	<0.0001

GEE: Generalized Estimating Equation; CI: confidence interval; TD: Time Dependent; pRBD: probable REM behavior disorder; DA: dopaminergic agonist; GDS-15: Geriatric Depression Scale 15 Items.