Table S1. Impact of PD Medications on Progression of NMS from Year 1 to Year 2 in Treated PD Subjects

Variable	PD Subjects Treated at Year 1		Univariate Analysis	
	Year 1 (N = 227)	Year 2 (N = 218)	Parameter Estimate (95% CI)	p-value
Total LED			0.001 (-0.001, 0.002)	0.4902
Mean (SD)	291.91 (221.75)	419.84 (294.67)		
(Min, Max)	(30.30, 1575.00)	(100.00, 2000.00)		
Missing	56	50		
LED Subtotal - Levodopa +/- Entacopone			0.001 (-0.001, 0.002)	0.3310
Mean (SD)	410.53 (250.84)	503.95 (317.92)		
(Min, Max)	(50.00, 1500.00)	(50.00, 2000.00)		
Missing	161	137		
LED Subtotal - Dopamine Agonists			-0.001 (-0.005, 0.003)	0.6274
Mean (SD)	153.87 (79.94)	192.93 (135.08)		
(Min, Max)	(30.30, 375.00)	(7.50, 825.00)		
Missing	157	135		
LED Subtotal - other PD meds			-0.001 (-0.006, 0.004)	0.6144
Mean (SD)	70.47 (77.97)	81.55 (88.32)		
(Min, Max)	(0.00, 400.00)	(-0.00, 300.00)		
Missing	56	50		
Classes of PD Medications*				
Levodopa +/- Entacopone	82 (36.12%)	107 (49.08%)	0.323 (-0.448, 1.094)	0.4020
MAO-B Inhibitors	97 (42.73%)	104 (47.71%)	-0.149 (-1.007, 0.709)	0.7170
Dopamine Agonists	80 (35.24%)	99 (45.41%)	0.014 (-0.771, 0.799)	0.9704
Amantadine	23 (10.13%)	30 (13.76%)	-0.236 (-1.481, 1.009)	0.6908
Anticholinergics	6 (2.64%)	7 (3.21%)	-1.233 (-4.260, 1.794)	0.3213
Levodopa + DA	7 (3.08%)	17 (7.80%)	-1.161 (-2.843, 0.521)	0.1585
Any 2 classes besides Levodopa + DA	62 (27.31%)	84 (38.53%)	0.321 (-0.434, 1.076)	0.3983
Any 3 classes	6 (2.64%)	20 (9.17%)	-0.206 (-1.784, 1.372)	0.7844

Note: All univariate analyses control for Baseline MDS-UPDRS Part I.
*Subjects may be taking more than one class of PD medication.

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Table S2. Baseline NMS Total and Subdomains as Predictors of 2 Year Change in Motor Disability Scores in PD Subjects

Variable	Change from BL to Year 2 (N = 280)	Total NMS		Cognitive/Psychiatric		Sleep		Autonomic	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
MDS-UPDRS Part III Score		0.036	0.7945	-0.154	0.6448	0.043	0.9085	0.252	0.5446
Mean (SD)	6.29 (9.25)	(-0.233, 0.305)		(-0.809, 0.502)		(-0.696, 0.782)		(-0.565, 1.069)	
(Min, Max)	(-28.00, 45.00)								
Missing	0								
Tremor Score		-0.005	0.3291	-0.009	0.4594	-0.018	0.2012	-0.001	0.9712
Mean (SD)	0.09 (0.34)	(-0.015, 0.005)		(-0.033, 0.015)		(-0.045, 0.010)		(-0.031, 0.030)	
(Min, Max)	(-0.91, 1.18)								
Missing	1								
PIGD Score		0.005	0.2798	0.004	0.7338	0.009	0.4924	0.011	0.4664
Mean (SD)	0.13 (0.34)	(-0.004, 0.015)		(-0.020, 0.028)		(-0.017, 0.036)		(-0.019, 0.040)	
(Min, Max)	(-0.80, 1.80)								
Missing	1								

Note: All analyses control for age, gender, disease duration, and side most affected.

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Statistical Methods (supplemental material)

T-tests or Chi-square were used to compare baseline demographics and PD characteristics between groups and compare the 2-year change in NMS scores between treated versus untreated PD subjects.

Linear mixed models were used to test for changes in NMS over time separately in each group and for differences between groups over time. In the latter models, an interaction for visit and group was tested before testing for between-group differences over time. A significant test of interaction indicates a difference in rates of change over time between groups. If the test of interaction was not significant at the 0.1 level, the interaction term was removed from the model and a test for group difference over time was reported. Models without the interaction term assume similar rates of change in the two groups; therefore, a test for group difference over time was only reported in cases where the interaction was not significant.

Linear models were used to examine the univariate relationship between demographic and clinical predictors and either baseline or 2-year change in MDS-UPSRS Part I score (NMS) or the 2 year change in NMS. Any variables with univariate associations with p-values <0.20 were included in a multivariable model. Then, a backwards selection process was used to remove variables individually, until all remaining variables were significant at the 0.10 level.

To avoid collinearity with some of the variables, the following rules were followed when fitting the multivariable models: For the CSF biomarkers, if the individual markers were significant in a univariate manner, they were considered in the multivariable model. CSF ratios were only considered in the multivariable model if both of the individual markers were non-significant. Similarly, for the DatScan® variables, if the contralateral putamen or caudate measures were significant in a univariate manner, they were considered in the multivariable model. If not, but ipsilateral putamen or caudate measures were significant in a univariate manner, they were considered in the multivariable model.

Linear mixed models were also used to examine the impact of PD medications on NMS total and subdomain scores over time, in the subset of PD subjects who started treatment by year 1. Since no PD subjects were treated at baseline, only year 1 and year 2 time points were included in these

models, while adjusting for baseline NMS score.

Finally, linear models were used to examine whether baseline NMS total or subdomain scores were predictive of 2-year changes in the following motor disability scores: MDS-UPDRS motor score, tremor and PIGD scores. These models adjusted for age, sex, disease duration, and side most affected.