Supplementary Material

Modeling of Parkinson's Disease Progression and Implications for Detection of Disease Modification in Treatment Trials

Overview of the Data

Supplementary Table 1. Descriptive statistics of PPMI and PASADENA data used in the analysis

		PPMI Parkinson's disease cohort	PASADENA Placebo cohort
	Original number of participants included in the analysis	401	105
MDS-UPDRS part III (OFF)	Total number of longitudinal observations	3,347	819
	Mean duration of individual data longitudinal collection (sd)	6.5 years (3.0)	1 years (0.1)
	Mean frequency of data collection (sd)	9.9 months (11.3)	1.7 months (0.4)
MDS-UPDRS part II	Total number of observations	5,795	829
	Mean duration of individual data longitudinal collection (sd)	7.5 years (3.1)	1 (-)
	Mean frequency of data collection (sd)	6.7 months (5.0)	1.7 months (0.4)
MDS-UPDRS part I	Total number of observations	5,769	826
	Mean duration of individual data longitudinal collection (sd)	7.5 years (3.1)	1 (-)
	Mean frequency of data collection (sd)	6.7 months (5.0)	1.7 months (0.4)
Symptomatic treatment	Percentage of subjects with use of symptomatic treatments at any time of follow-up	> 90%	65%
	Mean of percentage of time under symptomatic treatment across subjects (sd)	82.4% (17.9)	79.4% (32.0)
	Mean of median levodopa-equivalent total daily dose across subjects (sd)	217 (197)	158 (106)
Exploratory statistics on covariates for PPMI PD cohort	Sex	F | M (33% | 67%)	
	Mean age at diagnosis (sd)	62.8 years (4.3)	
	Mean time from diagnosis (sd)	205 days (207)	
	Mean baseline part III (sd)	21.2 (8.8)	
	Mean baseline DaT-SPECT putamen SBR average	0.81 (0.3)	

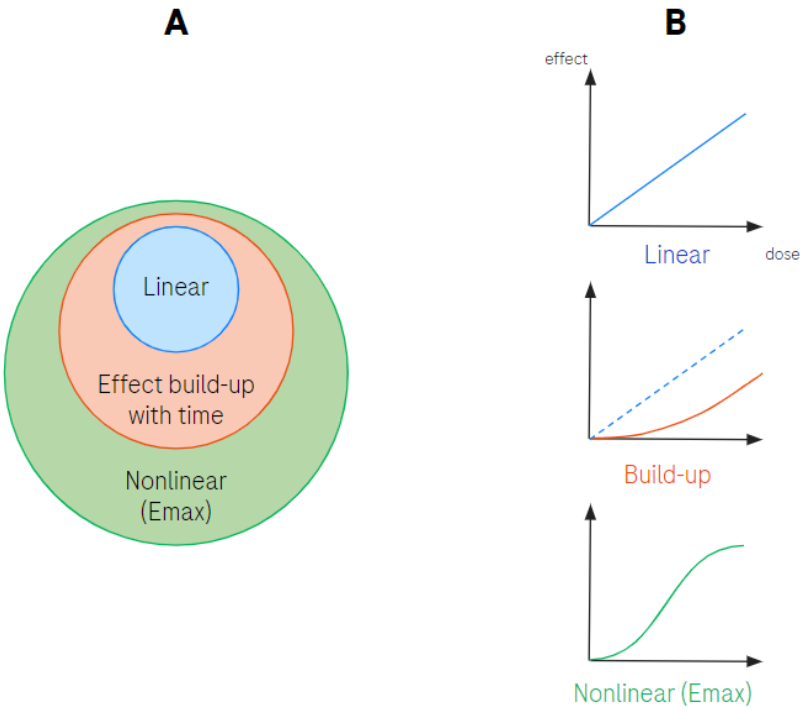
Pool of Models

There is a variety of possible ways to model progression and effect of symptomatic treatment thus proposing a unique mathematical framework for doing so is always, by definition, reductive. While still limited, creating a model ensemble (pool of models) covering a wider space of possible ways for modeling the disease progression and impact of treatment is a valid approach to reduce uncertainty in the prediction of these processes. Here, a total of 32 mathematical models were designed to characterize the PPMI MDS-UPDRS parts I, II, and III longitudinal data, to estimate the natural progression of the disease and the effect of symptomatic treatments. We built this pool of structural models by increasing step-by-step complexity in how to account for the natural progression of the disease and in how to account for the effect of symptomatic therapies.

For the models of natural disease progression, we tested linear, logistic or Gompertz growth models. The structure of linear models generally contains two parameters: the baseline and the growth rate. The logistic and Gompertz structural models contain one additional parameter: the saturation threshold which corresponds to an estimate of the maximal score of the scale as "seen" from the analyzed data.

For the models of the effect of symptomatic treatments, we tested 3 modeling modalities of increasing level of complexity as illustrated in Supplementary Figure 1:

- The effect is linearly proportional to the daily dose;
- The effect of a same amount of daily dose increases with time, i.e. effect builds up with time;
- Same as the previous point but includes a nonlinear relationship between the dose and the effect (sigmoid [Emax] model).



Supplementary Figure 1. Various model formulations for describing the effect of symptomatic treatments on disease progression (A) and visuals of the corresponding relationships (B).

On the 32 possible structural model equations, we tested 3 different residual error models to quantify the unexplained variability leading to a total of 96 models on which data fitting for MDS-UPDRS parts I, II and III was performed.

Model Averaging

To average the results of data fitting with the 96 models, we applied a filter following the fitting in order to not exclude the failed fits and/or fits resulting in unrealistic parameter estimates. The model was excluded from the model averaging evaluation if one of the following criteria was met:

- Relative standard error of any of the parameter > 50%
- Bayesian information criteria (BIC) higher than 20% more of the minimal BIC obtained throughout the 96 models
- Estimation progression > 20 points/year

We report below the main parameter estimates (baseline, progression, saturation, and symptomatic effect) in terms of mean value as well as standard deviation obtained throughout the selected models. These estimates are close to the ones reported within the core of the manuscript with the logistic growth model.

Supplementary Table 2. Summary of parameter estimates of models of the time course of MDS-UPDRS parts III (off), II, and I. The LEDD effect denotes the strength of the LEDD effect on the score. It corresponds to a negative or positive change of the score normalized by the median dose of LEDD used by subjects. Note that the progression is calculated by equation 3 in the text. The reported standard deviation is calculated as the standard deviation of population values estimated throughout all selected models from the 96 models.

	Baseline score (sd)	**Progression (sd)**	**Saturation threshold median (sd)**	**Symptomatic effect (sd)**
MDS-UPDRS part III (off)	20.7 pts (0.6)	3.0 pts/year (1.3)	55.7 pts (8.2)	- 0.7 (0.7)
MDS-UPDRS part II	5.1 pts (0.3)	1.2 pts/year (0.4)	26.8 pts (6.8)	- 0.6 (0.2)
MDS-UPDRS part I	4.7 pts (0.4)	0.8 pts/year (0.3)	15.5 pts (1.6)	+ 0.4 (0.2)

Mathematical Formulation of the Regression Problems

The 96 models were evaluated using population (nonlinear mixed-effect) approach. In this section, we develop the approach for the logistic growth model as described in the core of the manuscript.

MDS-UPDRS part I, II, and III scores were modeled independently. The regression problem was formulated using a population approach where the 4 (population) parameters (or fixed effects) were associated to random effects.

$$y_{ij} = f(t_{ij};\beta,\eta_i) + e_{ij}, 1 \le i \le N, 1 \le j \le n_i$$

Where N denotes the number of individuals and n_i the number of data points of individual i.

β and η_i are the 4x1 vectors of fixed and individual effects. ε_{ij} denotes the residual errors and are expressed as follows:

$$e_{ij} = g(t_{ij};\beta,\eta_i)\cdot\varepsilon_{ij}, 1 \le i \le N, 1 \le j \le n_i$$

where ε_{ij} is a random variable with mean 0 and variance taken equal to 1 for identifiability reason.

$$\varepsilon_{ij} \underset{i.i.d}{\sim} \mathcal{N}(0,1)\ \ 1 \le i \le N, 1 \le j \le n_i$$

g, the (residual) error model, can take many forms. In our analysis, we have used constant error model: $g(t_{ij};\beta,\eta_i) = a_i$; proportional error model: $g(t_{ij};\beta,\eta_i) = b_i \cdot f(t_{ij};\beta,\eta_i)$; and combined error model $g(t_{ij};\beta,\eta_i) = a_i + b_i \cdot f(t_{ij};\beta,\eta_i)$.

The vector of population parameters β is composed by four parameters: S_0, the score at baseline, θ, the saturation threshold of the logistic growth, T_{prog} the progression parameter and α the symptomatic treatment effect parameter.

Individual parameters, S_0, T_{prog} and θ were assumed to be log-normally distributed to prevent for negative values, e.g.,

$$\log(S_0) \sim \mathcal{N}\left(\log\left(S_{0_{\text{pop}}}\right), \omega_{S_0}^2\right)$$

However, parameter α was assumed to be normally distributed to allow for both positive (treatment increasing the score) or negative values (treatment decreasing the score).

$$\alpha \sim \mathcal{N}\left(\alpha_{pop}, \omega_{\alpha}^2\right)$$

We assumed no correlation between the random effects associated to the two parameters. We reported in Table 1 of the manuscript the population parameter estimates and their precision as 95% confidence interval as well as inter-individual variability (I.I.V) in terms of coefficient of variation (for log-normally distributed parameters) or standard deviation (for normally distributed parameters).

For MDS-UPDRS part I, the residual model leading to the best fit was a combined error model with $a_i = a = 1.8$ points and $b_i = b = 0.3$. For MDS-UPDRS parts II and III, the best residual error models were proportional error models with $b_i = b = 0.4$ for part II and $b_i = b = 0.2$ for part III.

Covariate Model Building

The logistic model was used to search for significant covariates predictive of the progression. Effect of age, time from diagnosis, baseline MDS-UPDRS part III, sex and Hoehn and Yahr stage were considered as potential covariates for the baseline, growth and symptomatic treatment effect parameters. A stepwise covariate model (SCM) was used with inclusion threshold at 1% (difference in -2 x Log-likelihood of 6.63 points) and exclusion threshold at 0.01% (difference in -2 x Log-likelihood of 15.13 points).[1]

Covariates age, time from diagnosis and MDS-UPDRS part III baseline were considered as continuous covariates while sex and Hoehn and Yahr stage were considered categorical.

For continuous covariates, the covariate model was formulated as follows (here for a parameter log-normally distributed):

$$\log(S_0) = \log\left(S_{0_{\text{pop}}}\right) + \beta \cdot age + \eta_i$$

while for categorical covariates (e.g. sex):

$$\log(S_0) = \log\left(S_{0_{\text{pop}}}\right) + \beta \cdot \mathbb{I}_{g_i=male} + \eta_i$$

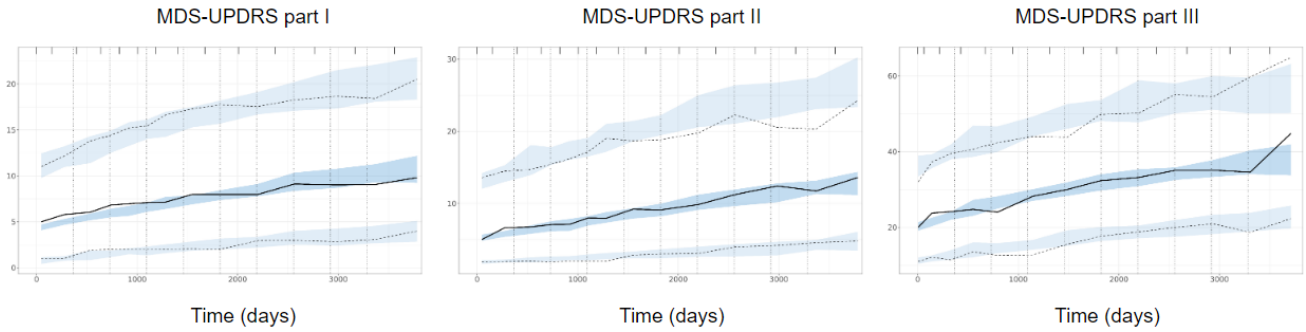
For MDS-UPDRS part I, no covariate was identified.

For MDS-UPDRS part II, the MDS-UPDRS part III at baseline (diagnosis) was identified as a significant covariate of MDS-UPDRS part II at baseline. The association was positive (beta = 0.2, 95% CI = [0.1 – 0.4]) meaning that the higher MDS-UPDRS part III the higher MDS-UPDRS part II at baseline. The reference objective function (-2 x Log-likelihood) without covariates was 23963 points. The model with covariate had an improvement of the objective function of 37 points.

For MDS-UPDRS part III, the Hoehn and Yahr stage was identified as a significant covariate of baseline parameter estimates (beta = 0.5, 95% CI = [0.4 - 0.6]): the positivity of the beta parameter indicates that the higher the stage, the higher the baseline. The reference objective function without covariates was 17733 points. The model with covariate led to a reduction of the objective function of 89 points.

Internal Evaluation

The prediction-corrected visual predictive check (pcVPC) for MDS-UPDRS part I, II, and III are presented in Supplementary Figure 2.



Supplementary Figure 2. Internal evaluation of PPMI model on PASADENA placebo data. Prediction-corrected visual predictive check (pcVPC) of PPMI model prediction (blue shaded areas, 90% confidence interval around the 5th, 50th, and 95th percentiles) with data from PPMI (black lines). Left panel: MDS-UPDRS part I; Middle panel: MDS-UPDRS part II; Right panel: MDS-UPDRS part III off. Time in days.

External Evaluation on PASADENA Year 1 Placebo Data

We report below the numerical predictive check for the external evaluation of the models (developed with PPMI data) on PASADENA year 1 placebo data.

Supplementary Table 3. Numerical predictive check for models built on PPMI and externally evaluated with PASADENA placebo data for 1 year.

	Below 10th percentile	**Below 50th percentile**	**Above 90th percentile**
MDS-UPDRS part III off	11%	46%	12%
MDS-UPDRS part II	17%	48%	9%
MDS-UPDRS part I	10%	59%	7%

Progression Models for PPMI Prodromal Cohort

MDS-UPDRS parts II and III from the prodromal cohort were analyzed by means of linear growth model to estimate the lag time between parts III and II onset. To avoid estimation problems due to the low volume of the dataset, the data after phenoconversion were still kept for the analysis. In the prodromal cohort the growth for part III was estimated at 3 points/year, similar to the growth of part II. However, for part II, the growth was estimated to less than 0.5 points/year, so significantly lower than after PD diagnosis. The growth parameters were estimated with relatively low uncertainty (residual standard error of 3% for both part III and part II).

Sensitivity Analysis with Respect to Genetic Screening

To check if the modeling still stands if genetic screening is not conducted, we performed a sensitivity analysis including also the genetic forms of PD and estimated the progression parameters. The result of the sensitivity analysis is presented in Table 1 below and shows that the inclusion of the data from patients with genetic forms of PD does not significantly modify the disease progression estimates:

Subscore	With or w/o genetic forms	Estimated progression	S0 (baseline)		θ (plateau)		α (symptomatic)		T_{prog}	
			Estimate	I.I.V (CV)	Estimate	I.I.V (CV)	Estimate	I.I.V (s.d)	Estimate	I.I.V (CV)
Part II	Without	1 point/year	5.5	69%	21.3	21%	-0.5	2.8	84	81%
	With	1 point/year	4.8	73%	19.4	27%	-0.3	2.8	75	80%
Part III	Without	3 points/year	20.5	41%	43.3	23%	-0.6	2.8	122	87%
	With	3 points/year	19.9	43%	45.4	18%	-1.1	2.8	137	111%

Summary of parameter estimates for MDS-UPDRS part II and part III comparing the situation where data from patients with genetic forms of PD were excluded (as reported in the core manuscript) or included.

Derivation of Half-Time and Progression from the Logistic Growth Model

In the logistic growth model (equation 1), the parameter T_{prog} is a progression parameter from which the half-time of progression can be calculated as follows.

$$halftime = \frac{T_{prog}}{S_0 + 0.5(\theta - S_0)}$$

The model parameters were used to estimate a linearized natural disease progression speed, considered as a valid approximation of growth for the first years of the disease:

$$progression = \frac{\theta - S_0}{2 \cdot halftime}$$

Clinical Trial Simulation

The equation (2) in the manuscript comes from the difference between the linearized progression without treatment ($progression_i \cdot time$) and with treatment ($progression_i \cdot (1 - potency) \cdot time$).

We assume the endpoint is continuous and that both virtual treated and control group have same size $\frac{n}{2}$. Then effect is estimated from sampling the following distribution:

$$\hat{E}_i(t) = \mathcal{N}(effect_i(t), \sigma_i \cdot \frac{2}{\sqrt{n}})$$

The term $effect_i(t)$ is calculated from equation (2) in the manuscript and σ_i denotes the standard deviation of the scores for endpoint i. To estimate the standard deviation, we simulated the MDS-UPDRS part II and III progression models and calculated, at different time points between year 1 and 5, the standard deviation of the simulated data. Simulations were replicated 100 times. We averaged the value over the number of replicates and over the first 5 years and use the resulting values as parameters σ_i in equation (5). Following this process, σ_i was 7.3 and 12.3 for MDS-UPDRS part II and III respectively.

REFERENCE

1. Jonsson EN and Karlsson MO. Automated covariate model building within NONMEM. *Pharm Res* 1998; 15: 1463-1468.