Modeling of Parkinson’s disease progression and impact of endpoint selection on probability of study success

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What does this mean for the PD community?
- While the voice of the patient is and should remain of highest importance when it comes to evaluating drug effect, MDS-UPDRS part III as an endpoint might require trials in early PD of at least 3 to 5 years duration. However, meaningful change can be detected in Part III and could predict change in Part II.

Conclusions
- We present a comprehensive mathematical modeling of progression of MDS-UPDRS parts I, II and III in early PD. Aligned with what already published, we found that progression of MDS-UPDRS part III is significantly faster than part II. Part III progression in patients with late-onset disease was significantly faster than in those with early onset.
- Disease modifying trials with the typical 2-year duration will have a challenge to demonstrate meaningful impact on MDS-UPDRS part II even with a large sample size.
- MDS-UPDRS part II may be a valuable alternative because effect could be detected earlier and translate into effect on part III at a later time point.

Background
- Quantitative approaches such as disease progression models constitute relevant tools to elucidate the quantitative relationship between the patient population and the progression of an endpoint or measure of efficacy1,2.
- MDS-UPDRS part II measures motor signs as assessed by clinicians, while MDS-UPDRS part III measures the motor aspect of daily living and is a patient self-reported assessment of motor symptoms and their impact on daily functions.
- It is critical to predict:
  - The observed change in the MDS-UPDRS parts when a treatment is slowing down the disease and if the parts are expected to change simultaneously or if one will precede the other.
  - The probability to detect disease modification in treatment trials using either one part or the other.

Methodology

Data from PPMI-2 and PASSADENA
- Data from PPMI-2, both PD and prodromal cohorts - was used for the model development. After excluding for genetic forms of PD, we used data from 401 and 65 subjects in the PD and prodromal cohorts respectively.
- Data from PASSADENA was used for model’s evaluation.

MDS-UPDRS is defined as an input of the mathematical model of disease progression3.

Disease progression modeling
- Nonlinear mixed-effect modeling was used to describe the MDS-UPDRS part III longitudinal data assuming a logistic growth and direct effect of symptomatic treatment (LEDD) on the clinical score1.

\[ y(t) = \frac{\theta_2}{1 + e^{-(t-\theta_1)/\theta_3}} + \theta_4, \]

where \( y(t) \) is the clinical score at time \( t \), and \( \theta_1, \theta_2, \theta_3, \theta_4 \) are parameters to be estimated.

The natural disease progression in early PD was significantly faster for MDS-UPDRS part III with approximately 3 points/year versus part II which progressed by approximately 1 point/year.

Clinical trial simulations
- The magnitude of effect of treatments expected to change disease progression trajectory can be modeled as a linear function of time:

\[ \text{effect}(t) = \text{progression} \times \text{treatment} \times t \]

where the subscript denotes the endpoint (e.g. MDS-UPDRS part II or part III). The term progression is a number between 0 and 1, where 0 indicates no effect and 1 indicates a total inhibition (stopping) of the progression. The term \( t \) denotes the duration of the trial.

- To quantify the probability of success of trials using either MDS-UPDRS part II or part III, we simulated 10'000 clinical trials with a sample size of 500 or 1'000 estimated effect by sampling a normal distribution4.

\[ \text{effect}(t) = \text{normal}(0, \text{effect}_{\text{mean}}, \text{effect}_{\text{SD}}) \]

where \( \text{effect}_{\text{mean}} \) denotes the standard deviation of the scores for endpoint I calculated through simulations of the MDS-UPDRS part II and part III disease progression models. A statistical test can then further be calculated with the signal-to-noise ratio and treatment success declared if the p-value is lower than 5%.

Results
- The moderate level of correlation between inter-individual variations of MDS-UPDRS part II and III progression supports the hypothesis of a link between the dynamics of the two parts (Figure 1).
- Using the prodromal cohort data, the estimated difference between part III and part II onsets is 5 years (Figure 2).
- Under the assumption that a disease modifying factor is the same for both MDS-UPDRS parts III and II, we illustrate why the effect could be different given the difference in the natural progression (Figure 3).
- Applying the clinical trial simulations, we found that the probability of success is consistently higher when using MDS-UPDRS part III than with part II (Figure 4).
- With a potency of 35% slowing down the disease progression, and a trial of 1’000 subjects, we estimated that effect on part II could be detectable 2 years after effect on part III (4.5 versus 2.5 years).

Discussion
- With faster progression, earlier onset and link to part III, MDS-UPDRS part III may offer an advantage for identifying quicker and with smaller trials compounds effectively slowing down the disease.
- The model also provides important novel observations for the prodromal population. We estimated, through modeling MDS-UPDRS part III before PD (prodromal cohort) that part III was at the level of part III baseline (i.e. 5 points) approximately 5 years before diagnosis.
- To our knowledge, this is the first time that a link in terms of time delay is established between MDS-UPDRS part III and II based on a data-driven approach combining both prodromal and PD cohorts of PPMI.
- Our work provides a novel approach to model-based analysis of MDS-UPDRS progression for trials detecting voice of the patient in early disease but provides options to utilize the scale.
- There should be concerted efforts to develop novel patient-centric measures sensitive to change in early PD. Such efforts should happen together with the extension of disease modeling approaches for clinical measures of how a patient feel, function and survives5.

Further information
- The framework used for clinical trial simulations is simplistic and based on strong assumptions (e.g. same potency on both parts) and thus theoretical. Highlighting the need to analyze real trial data to check the predictions obtained regarding MDS-UPDRS part II and part III crosstalk.
- We have used LEDD as the driver of pharmacodynamics effect on disease progression. A more refined analysis considering not only the dose but also the class of molecules is an important next step as it can have important implications for clinical trial design.
- We identified a moderate correlation between the estimated natural disease progression of MDS-UPDRS part II and part III, between part I and II, but not between part II and I. This is consistent with the fact that both part II and part III are about the motor domain and that both parts II and I are self-reported questionnaires. It would be interesting to study if a model integrating the two dependent variables and relying on the assumption of a “mechanistic link” between the two can successfully fit the data.
- MDS-UPDRS part II and III could be modeled with two compartments and the progression of part II would be proportional to the part III progression. In such a model MDS-UPDRS part II would lag behind part III due to its lower score at baseline and it slower effect.
- We didn’t add a placebo effect in the models while evaluating predictions with PASSADENA data. Further evaluation is required given recent findings in literature on transient placebo effect6.

References

Disclosures
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