Modeling of the Placebo Response in Parkinson's Disease

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Introduction and Motivation

The objective of this study was to investigate the predictability of the placebo response in Parkinson's disease (PD) subjects participating in a randomized clinical trial (RCT).

The magnitude and the variability of the placebo response confound the efficacy evaluation of experimental therapies.

Identifying covariates associated with this PD placebo response may help mitigate its effect, increase the study power, and result in a better RCT design in future studies.

Study Designs and Patients

Mild to moderate PD subjects were enrolled and received placebo (oral, TID) treatment for three months in a blinded administration. Ninety-four patients completed the study.

The placebo response was measured with:

- MDS-UPDRS part III (Primary endpoint)
- MDS-UPDRS part I, II, and IV
- IGAC, PGAC
- PDQ-39 (Parkinson's Disease Questionnaire)
- ESS (Epworth Sleep Scale)
- FSS (Fatigue Severity Scale)

In addition, the Multidimensional Psychological Questionnaire (MPsQ), a questionnaire designed to assess various psychological traits was administered at baseline

Table 1: Patient baseline characteristics

Parameters		
Age [years]	Mean	64
	SD	9
Gender	Female	38 (36.2%)
	Male	67 (63.8%)
MDS-UPDRS-III	Mean	28.31
	SD	11.96
Hoehn & Yahr	Mean	1.82
	SD	0.53

Study Results

The average placebo response defined as change in MDS-UPDRS part III was small with an average decrease of:

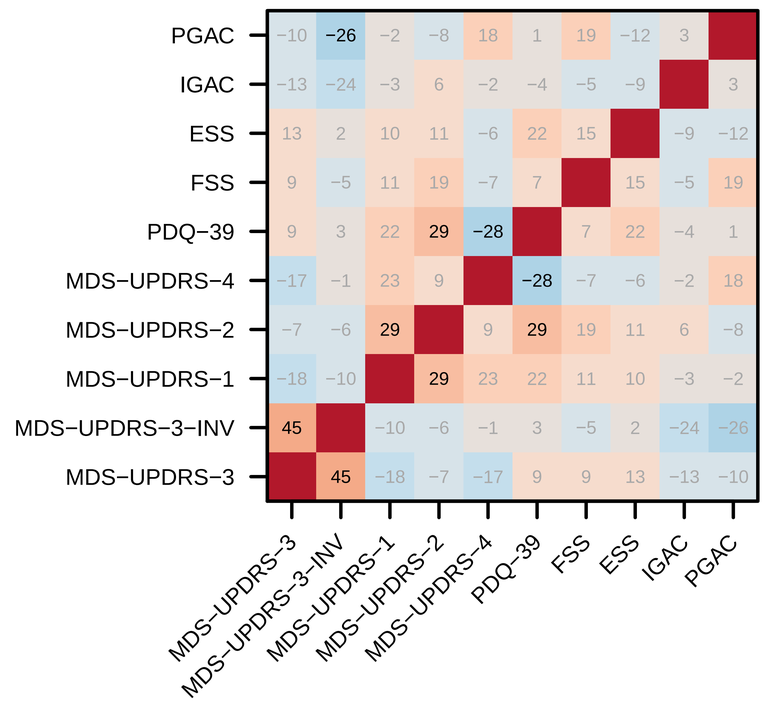
- 1.61 (p=0.001) after 30 min (acute)
- 1.76 (p=0.008) after 1 month
- 1.12 (p=0.112) after 3 months

A significant placebo response was also observed for the PDQ-39, FSS, and ESS after one month of placebo administration.

Consistency of the placebo response

After three months, the placebo reponse was not consistent across endpoints with very few significant correlations.

Figure 1 Correlation between the endpoints after three months of placebo administration.



Prediction of placebo response

Linear regressions were fitted to model the placebo response as measured by each endpoint. These models used as covariates:

- Baseline values of the endpoints,
- Demographics,
- MPsQ facets.

Table 2 Multivariate descriptive analysis to estimate the predictivity of the placebo response.

	N	Pop. R^2	p-value
MDS-UPDRS-3	94	33.2%	<0.001
MDS-UPDRS-1	93	11.0%	0.084
MDS-UPDRS-2	94	14.5%	0.037
MDS-UPDRS-4	88	22.4%	0.007
PDQ-39	94	23.2%	0.003
FSS	92	11.4%	0.078
ESS	93	15.7%	0.029
IGAC	84	43.1%	<0.001
PGAC	94	43.4%	<0.001

The population R-squared (Pop. R^2) represents the performance of the models: by how much could the models reduce the variability of the patients' response.

An important part of the models' predictions was linked to the regression to the mean effect.

Conclusions

With this study, we identify covariates associated with the placebo response in Parkinson's disease RCTs.

These covariates are related to the baseline intensity of PD, the patient's psychological traits and other factors.

This study is a significant step towards the prediction of the placebo response in Parkinson's disease RCTs.

The prediction of the placebo response can be used as a covariate in the statistical analyses to mitigate the variability of placebo response and improve study power.