Confirmation of symptomatic and disease modifying effects of levodopa using the ELLDOPA study

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Introduction

The symptomatic relief of levodopa in Parkinson's disease has been well established, but controversy exists about possible disease modifying effects.

Objectives

- Analyze the ELLDOPA study using a disease progress model that describes the time course of the disease, placebo and drug effects.
- Quantify symptomatic and disease modifying effects of levodopa

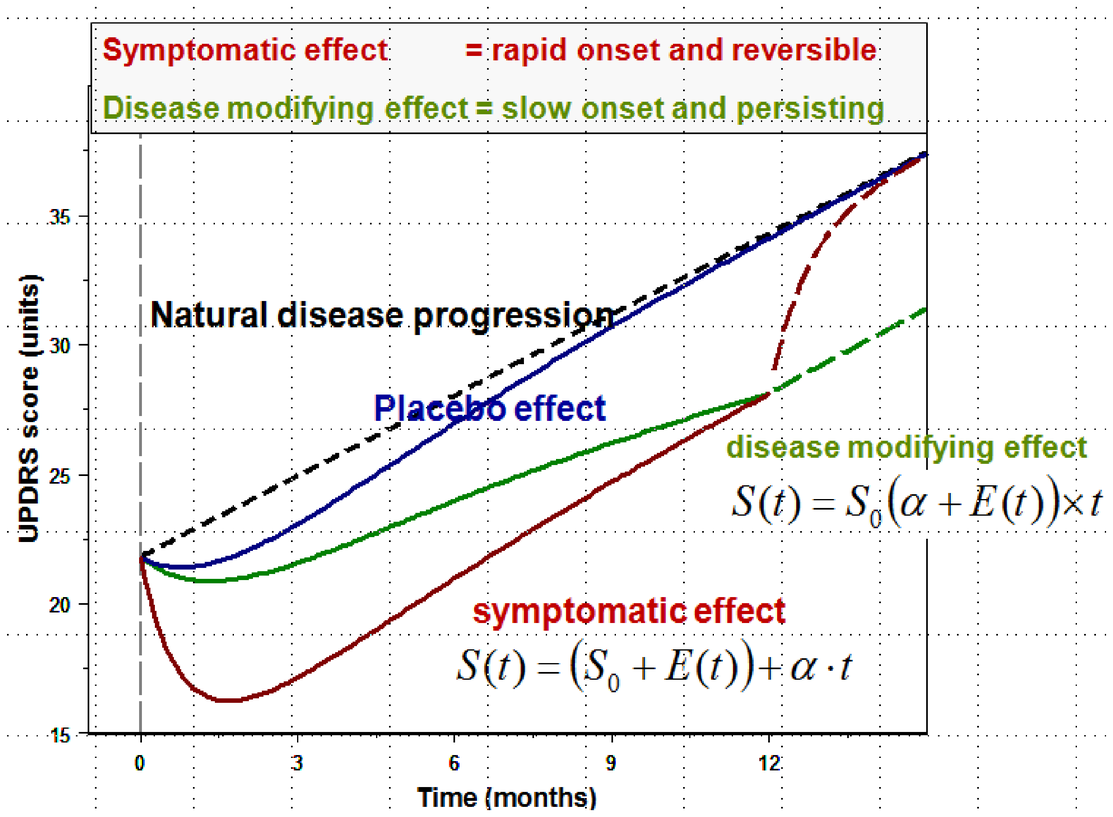

Figure 1 Treatment effects in Parkinson's disease for 12 months treatment followed by withdrawal

Methods

Data

In the ELLDOPA trial [1] 361 patients with early PD received a carbidopa-levodopa combination 3 times daily of
150 mg (n=92), 300 mg (n=88), 600 mg (n=91) or a matching placebo (n=90) for a period of 40 weeks followed by withdrawal period of 2 or 4 weeks.

Model

- Mixed effects disease progression model [2].
- Subjects with fast or slow onset of placebo effect were identified using a mixture model
- The onset and offset of the placebo were described using a Bateman function with similar onset and offset half-lives. A proportional random effect for the between subject variability in the maximum placebo effect was assumed, allowing for both positive (nocecbo) and negative (placebo) changes relative to the UPDRS baseline
- Delayed symptomatic effect (transient change in the offset of the disease progression curve)
- Immediate disease modifying effect (persistent change in the slope of the disease progression curve)
- Drug effects were investigated using linear, E_{max} or dose-insensitive effects

Results

Parameter estimates for the disease progression model

Description	Value	Units	RSE	BSV
Baseline UPDRS (S0), pop 1	22	UPDRS units	-4.2%	
Baseline UPDRS (S0), pop 2	29.3	UPDRS units	-6.4%	0.145 (10.6%)
Disease progress rate (α)	12.2	units/year	-9.0%	0.476 (17.1%)
Placebo maximum, pop 1 & 2	-5.88	% of S0	-40.8%	8.9 (85.5%)
Fraction placebo max, pop 1	0.705		-9.2%	
T½ Placebo effect, pop 1	79.4	days	-7.5%	
T½ Placebo effect, pop 2	19.2	days	-9.5%	
E_{max} symptomatic effect	-65.1	% of S0	-23.5%	0.277 (40.1%)
ED_{50} symptomatic effect[1]	1.56	mg/L	-48.3%	
T½ sympt. Effect (washout)	27.7	days	-30.4%	4.65 (25.8%)
T½ sympt. Effect (onset)	-7.49	% of T½ washout	> 50%	
E_{max} disease mod. Effect	-39.8	% of α	-22.8%	0.517 (62.7%)

[1] The steady state concentration of levodopa was based on the allometrically scaled nominal clearance of 1 L/hr and dose normalized to a daily dose of 300 mg

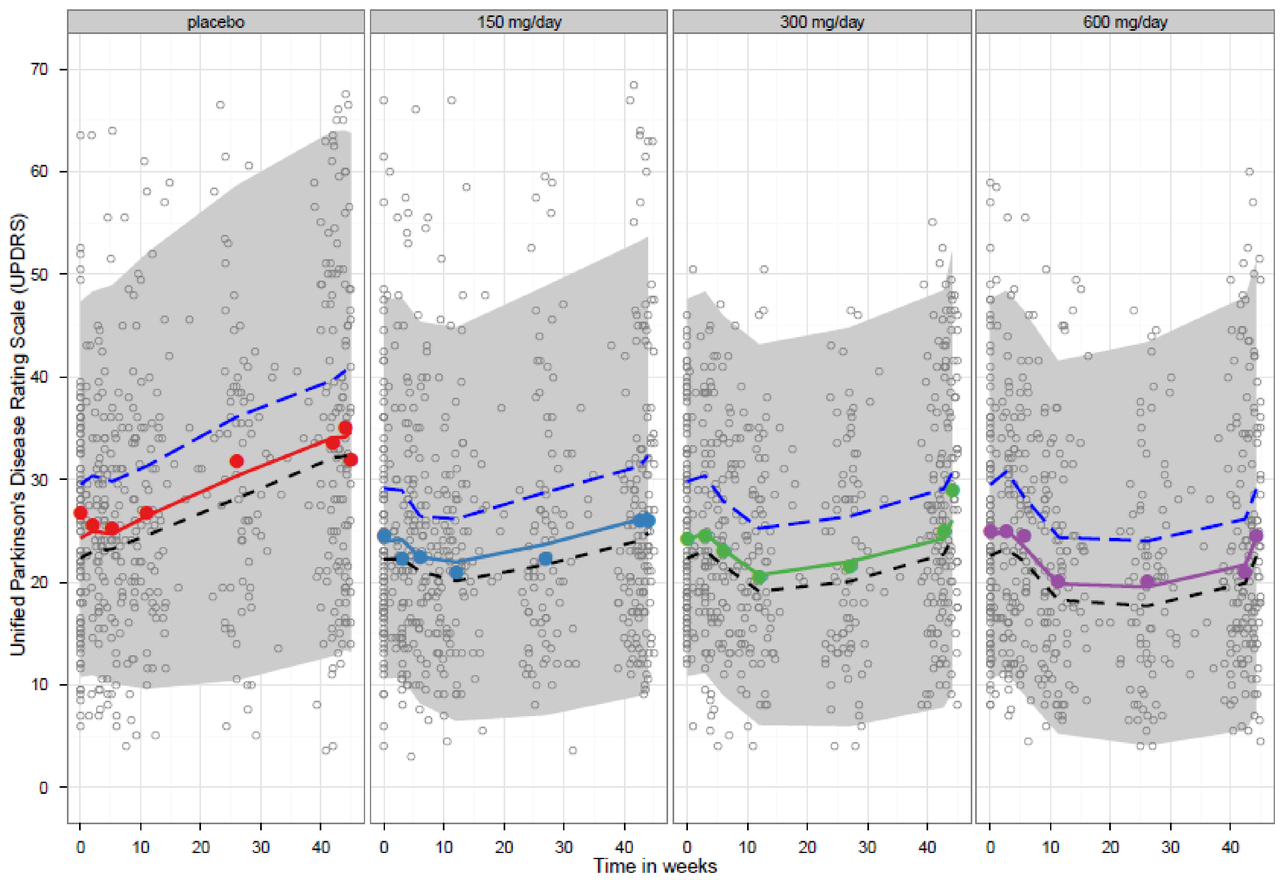

Figure 2 Visual predictive check of the disease progression model with a combined symptomatic and disease modifying effect
The individual observations are shown as open symbols. The closed symbols reflect the median of the observations per visit. The solid line shows the prediction for the median total UPDRS score The gray area shows the predicted variability for 90% of the population.
The black dashed line shows the predicted median for the population with a slow onset and washout of the placebo effect (population 1) and the blue dashed line the predicted median for the population with a fast onset and washout of the placebo effect (population 2)

Conclusions

- A model based analysis, in which assumptions are made explicit and tested when possible, allows more powerful inferences about the type of treatment effect compared to change from baseline methods.
- Approximately 30% of the patients showed a fast onset and washout of the placebo effect while 30% had a much slower placebo effect. Both nocebo and placebo responses were predicted which is consistent with the results of Ma et al. [3] after analyzing inactive treatment effects in 3 clinical studies (DATATOP, ELLDOPA and TEMPO)
- This analysis confirms that levodopa has disease modifying effects [2]

Literature

[1] Fahn, S., D. Oakes, et al. (2004). "Levodopa and the progression of Parkinson's disease." N Engl J Med. 351(24): 2498-2508.
[2] Holford, N. H., P. L. Chan, et al. (2006). "Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments." J Pharmacokinet Pharmacodyn 33(3): 281-311.
[3] Ma, S.C. and Holford N. H. (2011). "Quantifying Disease Progress with Inactive Treatments in Multiple Parkinson's Disease Trials." PAGE PAGANZ 11 (2011)

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