Placebo and drug response assessment on Unified Parkinson's Disease Rating Scale using longitudinal Item Response Modelling

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Introduction and Objective

An Item Response Model (IRM) with 3 latent variables [1] has been used to describe baseline 44-item Unified Parkinson's Disease Rating Scale (UPDRS) data from 2 clinical trials in early [2] and advanced [3] Parkinson's disease (PD). The objective of the current investigation was to employ the IRM in description of the time course and drug effect in advanced PD subjects based on longitudinal UPDRS data.

Methods

Data

- Baseline UPDRS from early [2] and advanced [3] Parkinson's disease
- Longitudinal (24 weeks) from advanced Parkinson's disease [3]
  - Ropinirole versus placebo, adjunct therapy to L-dopa
  - Individually titrated doses between 6 and 24 mg/day

Model

The response for each UPDRS item (*Yj*) is a function of a latent variable describing an unobservable *disability* for each subject (D_i), modelled as a random effect. The relationship between the UPDRS total score and D_i is characterized by the collection of item characteristic curves. The probability for a response (*0, 1, k, .. K*) for each item is described by Eqs. 1-2, where a_j (slope/discrimination) and b_j (difficulty/location) are item specific parameters [1], being fixed to previously estimated values during longitudinal model development.

$$P(Y_{ij} \geq k) = \frac{e^{a_j(D_i - b_{jk})}}{1 + e^{a_j(D_i - b_{jk})}} \quad \text{Eq. 1}$$

$$P(Y_{ij} = k) = P(Y_{ij} \geq k) - P(Y_{ij} \geq k+1) \quad \text{Eq. 2}$$

To assess change in symptoms over time (*t*) and treatment effect, linear ($Slope_j$) and exponential ($Extent_j$ and $Onset_j$, respectively, of symptom relief) models were explored in D_i. Given the individual titration, exposure independent drug effects (disease modifying [DM_j] on $Slope_j$ and symptomatic [SY_j] on $Extent_j$) were employed (Eqs. 3-4). $Advanced_j$ reflects a mean shift in D_i for advanced PD patients, compared to the disability level in patients with early stage PD.

$$D_i(t) = D_{i,0} + Advanced_j + (Slope_j + DM_j) \cdot t \quad \text{Eq. 3}$$

$$D_i(t) = D_{i,0} + Advanced_j + (Extent_j + SY_j) \cdot (1 - e^{-Onset_j \cdot t}) \quad \text{Eq. 4}$$

All modelling and simulations were performed using NONMEM version 7.3 [4].

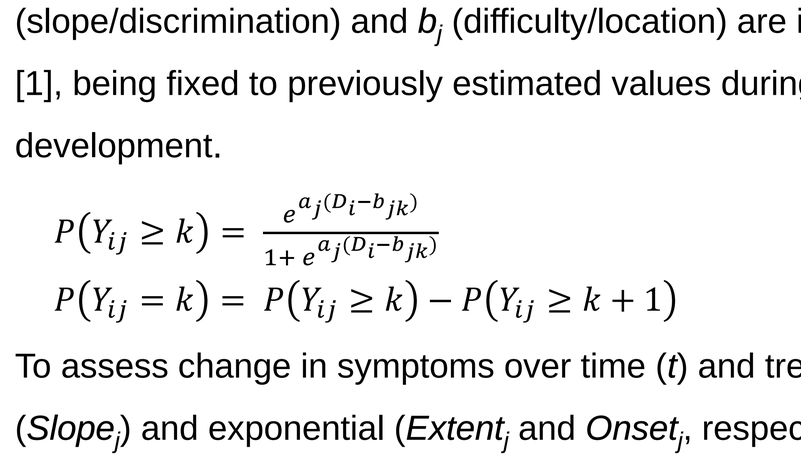

Figure 2. Graphical illustration of improvement in disability over time following placebo and ropinirole treatment, respectively.

Conclusions

- ✓ **Gradual onset of symptom relief by drug and placebo were adequately described by IRM.**
- ✓ **Short trial duration prevented characterisation of symptom progression and the effect of the drug on the progression.**
- ✓ **The use of multiple latent variables revealed differentiated symptom relief by placebo among various aspects of the clinical endpoint.**

Results

Data

Totally, 72,167 (552 patients) UPDRS recordings were used (Table 1 , Fig 1).

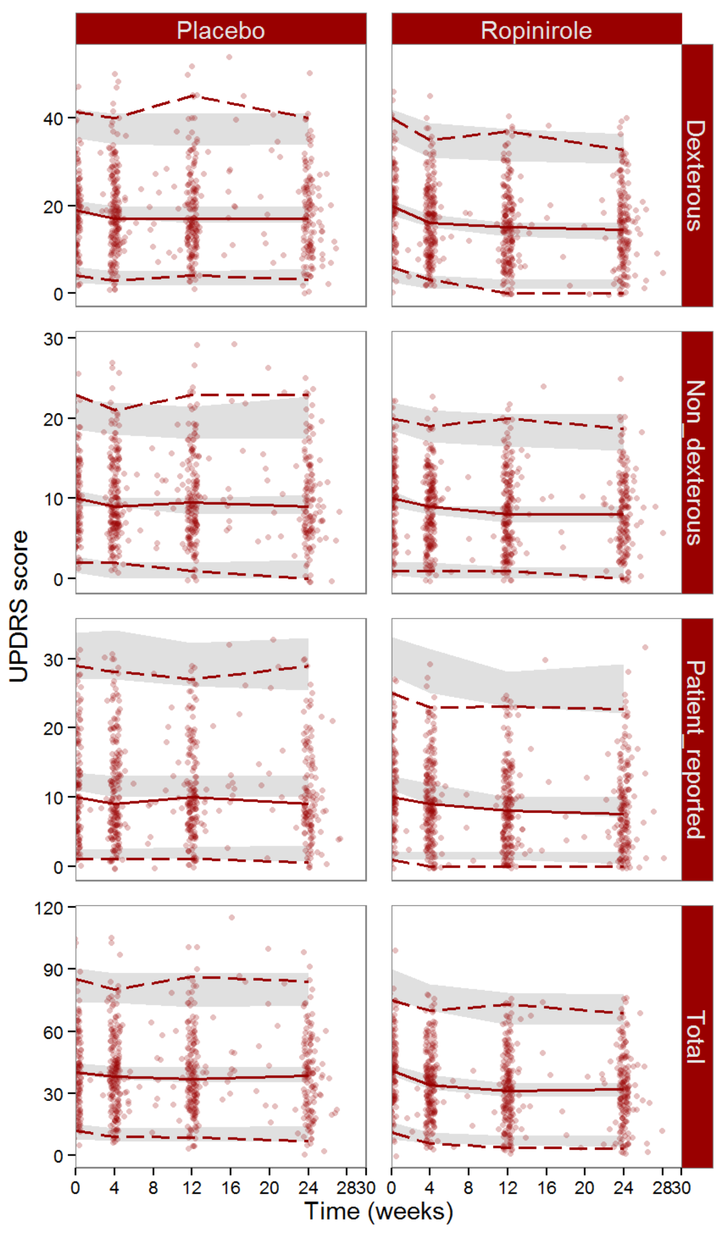

Figure 1. Visual predictive checks by treatment. The observed data (symbols) are shown as the total UPDRS score and as the sum of dexterous, non-dexterous or patient reported items. The solid and dashed lines represent the 2.5th, 50th and 97.5th percentiles of the observed data, respectively, and shaded areas the simulation-based 95% confidence interval for corresponding percentiles.

Table 1. Number of observations [number of patients].

Early PD		
Baseline		7,004 [161]
Advanced PD		
Baseline	Placebo	8,330 [190]
	Ropinirole	8,765 [201]
Longitudinal	Placebo	22,882 [189]
	Ropinirole	25,186 [200]

Model

The exponential model resulted in statistically significantly better description of the longitudinal data than the linear model. The placebo time course parameters were estimated for each latent variable ($Extent_j$ ranging from -0.30 to -0.058), and drug effects could not be differentiated statistically among latent variables but one common drug effect, *SY* -0.54 ([-0.61;-0.47] 95% CI), was estimated. The model described the observed data satisfactorily (Fig 1). An illustration of estimated models as change from mean *disability* is given in Fig 2. The improvement in symptoms over time corresponded to an approximate change in total UPDRS of -2 ([-4; -1] 95% CI) points in the placebo group and an additional improvement corresponding to an approximate change in total UPDRS of -10 ([-11; -8.5] 95% CI) points in the ropinirole group.

References

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Disclosure

S. Jönsson, G. Gottipati*, M.O. Karlsson, and E. L. Plan are (*was) employed at Uppsala University. S. Yang and C. Chen are employees of GlaxoSmithKline, London, UK. Uppsala University has received funding from GlaxoSmithKline, London, UK.

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