Item Response Theory for the Analysis of the Placebo Effect in Phase 3 Studies of Schizophrenia

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Background

- In clinical trials for schizophrenia, disease severity and changes in this parameter are commonly quantified using the positive and negative syndrome scale (PANSS).
- PANSS is generally analyzed as a continuous scale, however it is a composite psychological and functional scale divided into 3 sub-scales of 7 positive, 7 negative, and 16 general items.

Objectives

- Investigate a new approach based on item response theory (IRT [1]) to simultaneously analyze the individual scores of all 30 PANSS items.

Methods

Patients and Data

- 1650 schizophrenia patients from 3 Phase 3 studies; 344 placebo, 948 paliperidone (3, 6, 9, 12, or 15 mg), 358 olanzapine (10 mg).
- Duration of treatment 42 days, scheduled visits on day 0, 4, 8, 15, 22, 29, 36 & 42.
- 102,481 records of PANSS item-level data.

Model building

- The probability of each score of each PANSS item was modeled as ordered categorical data.
- Parameters describing the probability curves for each score were modeled as fixed effects.
- The underlying disease state (*DS*) of each individual was modeled as random effect with a mean of 0 and fixed variance of 1. One disease state variable was derived for the positive, negative and general scale, with an estimated correlation.
- Baseline data of all patients were used to set the reference distribution of the probability curves, which were subsequently fixed when modeling the placebo-related change in *disease state* over time (DS_{ij}) in the longitudinal placebo data.
- Tested placebo models were: linear, power, asymptotic (equation 1) and Weibull.

$$DS_{ij} = DS_{i,base} - P_{max} \cdot (1 - e^{-\ln(2)/t_{1/2} \cdot t_j}) \qquad \textbf{Equation 1.}$$

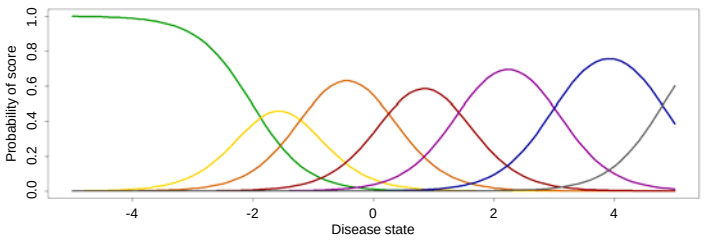

Figure 1. *Example of probability distributions for each score in one item (score 1 = green, 2 = yellow, 3 = orange, 4 = red, 5 = purple, 6 = blue, 7 = grey) versus disease state. The location and the shape of each curve for each item is determined relative to distribution of disease states of patients at baseline.*

Reference

[1] PAGE 21 (2012) Abstr 2318 [www.page-meeting.org/?abstract=2318]

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Results

- The baseline model could predict the frequency distributions of all scores for all items of the PANSS scale.

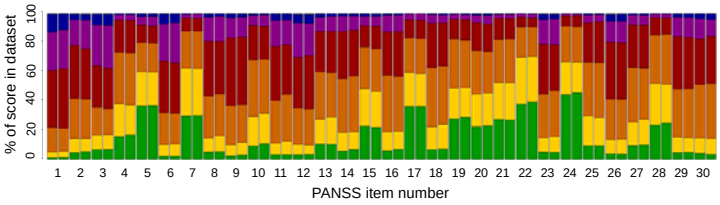

Figure 2. *Frequency distribution at baseline of each score (see color code figure 1) as observed for each item in the dataset (left bar of each item) and as simulated for each item by the model (right bar of each item).*

- At baseline, the correlations between disease states on the positive, negative, and general sub-scales within individuals were relatively low.

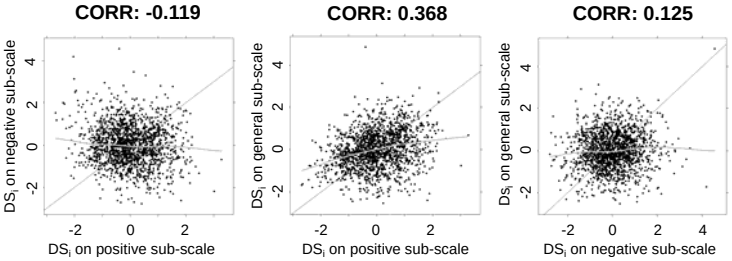

Figure 3. *Correlations between individual disease states (DS_i) on positive, negative and general sub-scales, including loess smoother.*

- An asymptotic model, with IIV on P_{max} (equation 1), was found to be most appropriate to describe the placebo response in all 3 sub-scales.
- For each sub-scale different values for P_{max}, $t_{1/2}$, and the correlation between P_{max} and $DS_{i,base}$ were estimated.

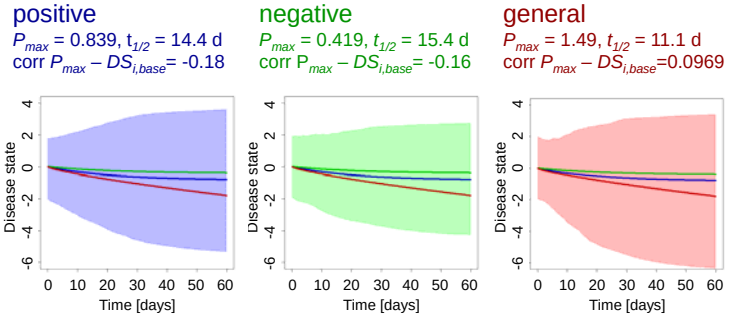

Figure 4. *Change of disease state over time in the placebo model of a typical individual (lines (same in all 3 for reference), blue = positive scale, green = negative scale, red = general scale). Shaded areas indicate the 95% prediction interval for each sub-scale based on 1000 simulations.*

Conclusions

- IRT modeling allows for the description of PANSS data on the individual item level.
- Within individuals, the influence of schizophrenia on the different subscales is different in magnitude (both for baseline and for placebo response (P_{max}))
- The time-course of the placebo response ($t_{1/2}$) is rather similar for all three sub-scales.