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 baseline model could predict the frequency distributions of all scores for all items of the PANSS scale.
- The probability of each score of each PANSS item was 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 disease states of patients at baseline.
- A baseline model was fitted to placebo data of all patients to estimate the placebo-related change in disease state over time (DS) in the longitudinal placebo data.
- Tested placebo models were: linear, power, asymptotic (equation 1) and Weibull.

\[
DS_{ij} = DS_{i,base} - P_{max} \times (1 - e^{-(x/\tau)^{a}}) \]

Equation 1.

Results

- An asymptotic model, with IV 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 \(P_{max}\), \(\tau\), and the correlation between \(P_{max}\) and \(DS_{base}\) were estimated.

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 (\(\tau\)) is rather similar for all three sub-scales.