

HAM-D score analysis of patients under placebo with major depressive disorder using item response theory

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Introduction

- Specificity of the clinical trials evaluating antidepressant agents:
 - clinical endpoint: Hamilton depression rating score (HAM-D 17 items)
 - high placebo response
 - high rate of dropout
- Assumption: some items could be more predictive of the depressive severity
- Item Response Theory (IRT) is increasingly used in Pharmacometrics to model the disease progression using the whole available item-level information [1]

Objectives:

- To use IRT and pharmacometrics methodology to model the time course of response to placebo for patients suffering from a major depressive disorder
- To investigate which items are the most informative to characterize the severity of depression

Material and Methods

Data:

- 7 studies from the Servier clinical database on Agomelatine: 1 phase II and 6 phase III
- 2274 patients with HAMD ≥ 22 at inclusion
 - 932 patients in the placebo group
 - 1342 patients in treatment group but only data at baseline
- 2 study periods
 - evaluation of efficacy (obligatory period)
 - evaluation of safety (optional period)

- For each of the 17 items, score k from 0 to 4 or from 0 to 2 are recorded

Statistical models

- Let Y_{ijs} be the score for the subject i , the item s , and the j^{th} measurement
- Let T_i denotes the time to dropout for patient i
- Let D_{ij} refers to the unobserved (hidden) depressive disorder of subject i at time t_{ij}
- The statistical model for an observation (logistic model):

$$P(Y_{ijs} \geq k) = \frac{1}{1 + \exp(-a_s(D_{ij} - b_{s,k}))}$$

where a_s and $b_{s,k}$ denote the item specific parameters (slope or discrimination parameter and item location or difficulty parameter)

- The model for the latent variable D :

$$D_{ij} = f(t_{ij}, \theta_i)$$

where the function f is a structural model and θ_i the vector of individual parameter

- The dropout is modeled as an informative dropout [2] with the hazard function:

$$h(t, \theta_i) = h_0(t) \times \exp(\beta \times g(f(t, \theta_i)))$$

where h_0 is the baseline hazard, and β corresponds to the strength of the link between a function g of the depressive disorder D_{ij} and the hazard

- Tested model for f : Linear, Bateman, modified Bateman
- Tested model for g : no link, current value of f , difference from baseline, expit transformation of f , weighted difference from baseline
- Tested model for h_0 : Exponential, Weibull, Lognormal, Generalised gamma

Model selection

- Model discrimination was based on AIC and parameter precision (RSE < 50%)
- Model evaluation was done based on visual predictive check (VPC) with K=100 replicates of the HAM-D score, the item score and the Kaplan-Meier (dropout)

Software: Nonmem (7.3.0) and R (3.4.3)

Results (1: Evolution of depression)

Selected model

- Modified Bateman (Weibull + Exponential):

$$f(t, \theta_i) = D_{0,i} - D_{rem,i} \left(e^{-K_{rel,i}(t-Tlag)} - e^{-K_{rem,i}(t-Tlag)^{p_i}} \right)$$

with $T_{rel,i} = \log(2)/K_{rel,i}$, $T_{rem,i} = \log(2)^{\frac{1}{p_i}}/K_{rel,i}$

- Weibull + weighted difference from baseline for the link term:

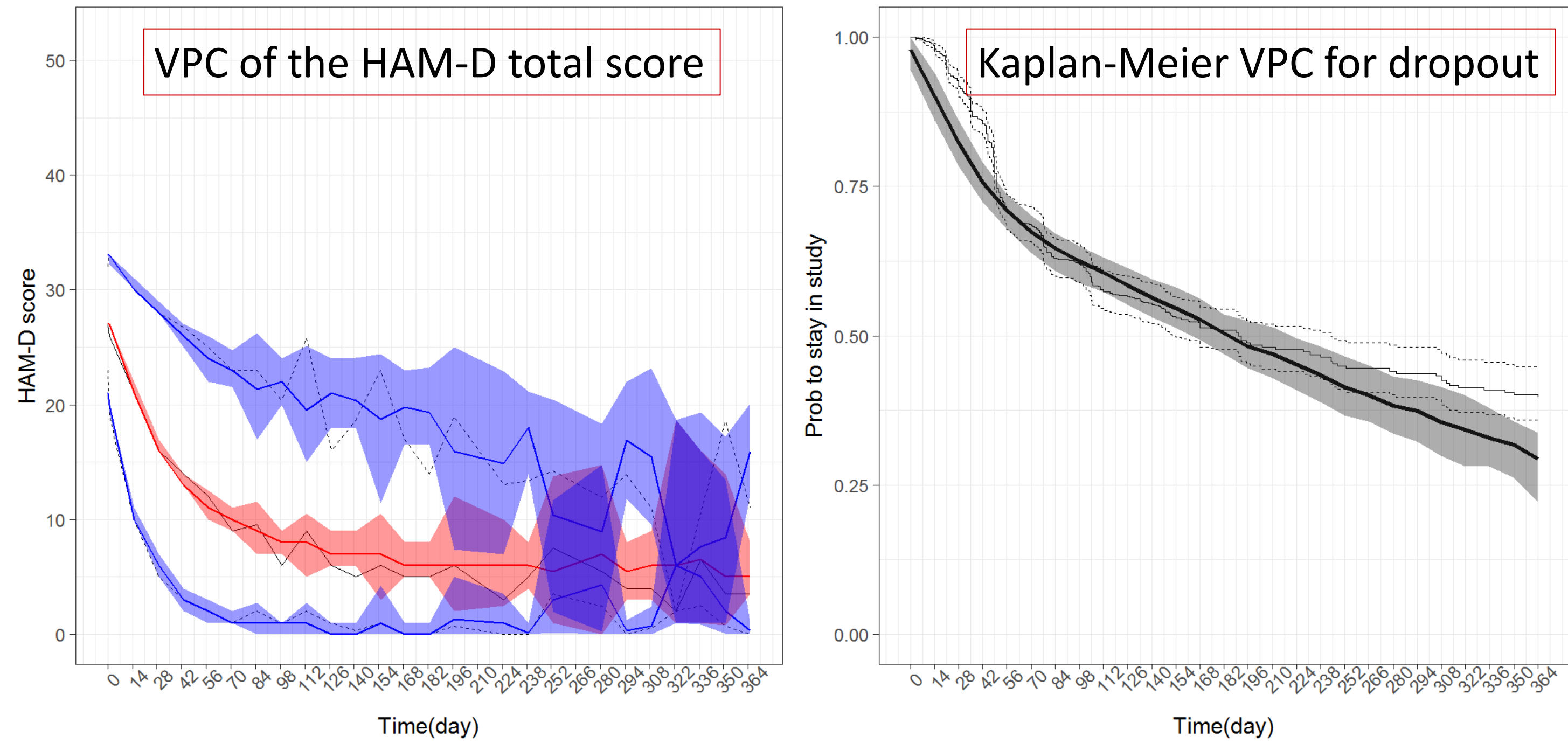
$$h(t, \theta_i) = \frac{k}{\lambda} \left(\frac{t}{\lambda} \right)^{k-1} e^{\beta \left(1 - \frac{D_{0,i} - f(t, \theta_i)}{\mu_{Drem}} \right)}$$

D_0 : value at baseline
 D_{rem} : magnitude of the placebo effect
 T_{rem} : half-life of remission
 T_{rel} : half-life of relapse
 T_{lag} : lag-time
 p : shape (depression)
 k : shape (dropout)
 λ : scale
 μ_{Drem} : fixed effect of D_{rem}

Parameter estimates for the model of the hidden variable and dropout

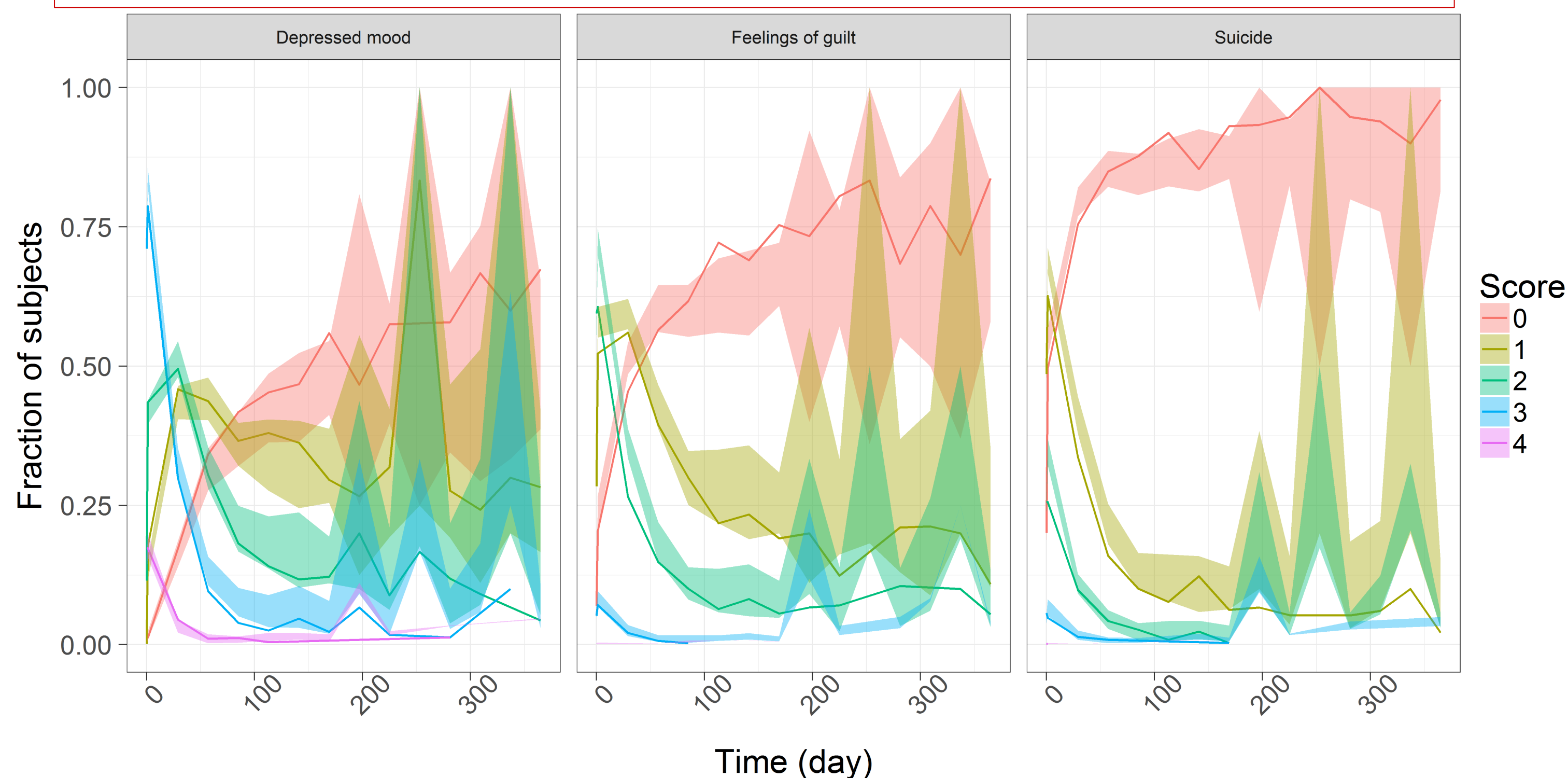
Parameters	Distribution	Fixed effects (rse%)	sd of random effects (rse%)
D_0	Normal	0 (FIX)	0.44 (4.49)
D_{rem}	Lognormal	7.15 (1.32)	0.12 (22.40)
T_{rem} (year)	Lognormal	0.16 (2.97)	0.62 (7.67)
T_{rel} (year)	Lognormal	0.93 (3.56)	0.88 (5.68)
p	Lognormal	0.77 (1.88)	0.52 (6.49)
T_{lag} (year)	-	0.03 (0.36)	-
k	-	1.97 (2.07)	-
λ	-	9.55 (4.50)	-
β	-	8.27 (2.07)	-

Visual Predictive Check (VPC) (K=100)



Left: Black lines corresponds to the median (solid line) and 5th and 95th percentiles (dashed line) of the observations. The blue lines represents the 90% prediction interval (PI) and red line the median of the simulations (with respectively their 90% confidence interval (CI) as the colored area). **Right:** Kaplan-Meier curve is showed as the solid black line with its 90% CI, and the median of the simulation is represented as the large solid black line with its 90% PI.

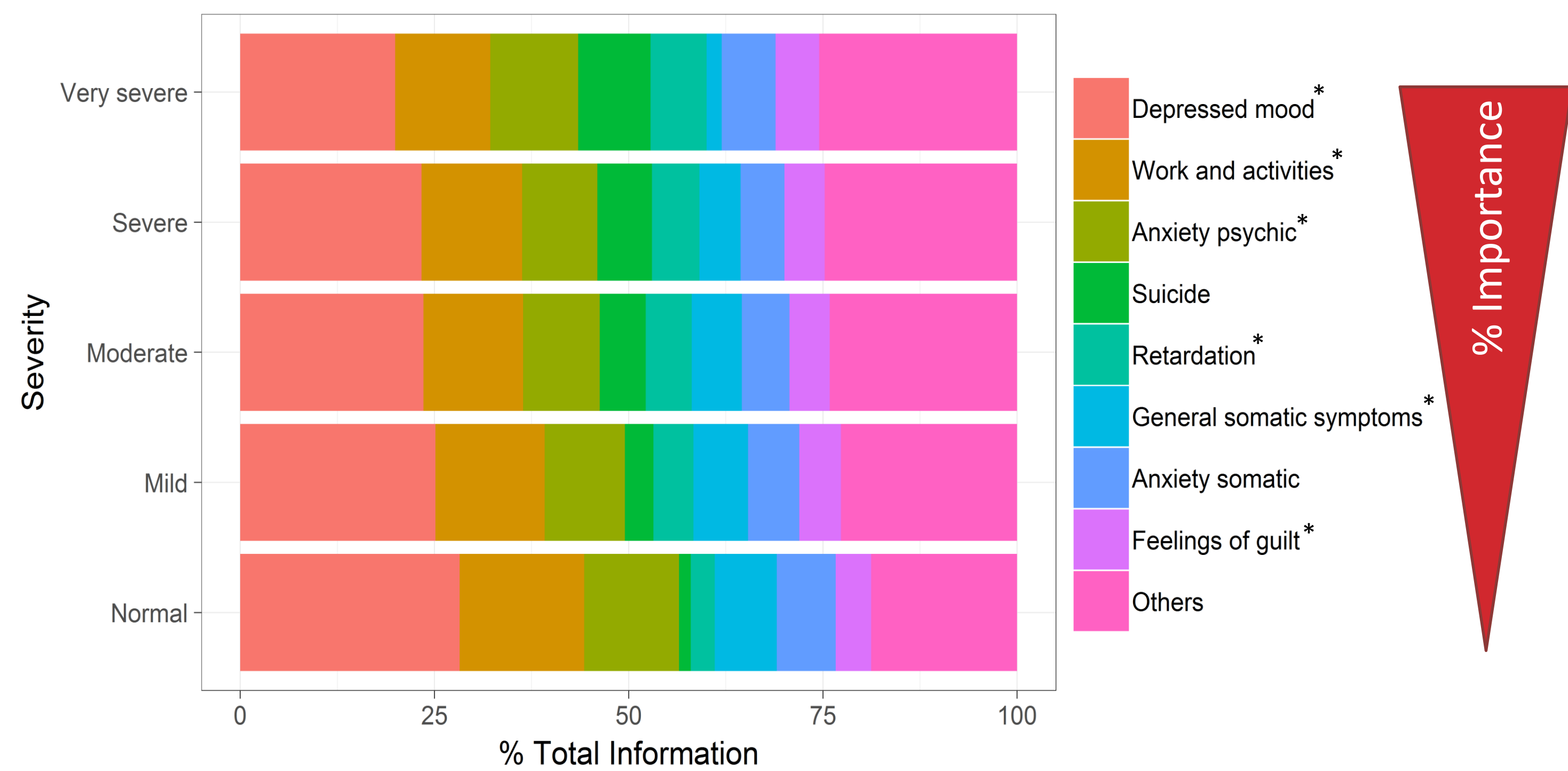
Subset of item level VPC of the probability for each score depending on time



Observed fraction of subjects is represented for each score as solid line and the 90% PI of the simulation as the colored area.

Results (2: Informative items)

Quantitative evaluation of the information content



Ranking of item by information content in five degrees of severity of the disease. Only items where the information represents over 5% of the total information at least for one degree of severity were shown.

*items used to diagnose depression [3].

Based on the optimal design theory and the work of [1,4], the fisher information of each item was computed depending on the depressive disorder. Then, the percentage of informativeness for each items was derived for several degree of severity. 8 items represent around 75% of the total information.

Conclusion

- A longitudinal IRT model has been developed and is a suitable method to describe the disease progression of depressed patients
- However, the dropout model can still be improved, by integrating the different study designs
- The use of the IRT made it possible to determine the most predictive items of the depressive state for a population under placebo (depressed mood, work and activities, anxiety psychic for the main ones). It would be interesting to compare it with treatment group

References

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- [4] S Buatois et. Al. (2017), Item Response Theory as an Efficient Tool to Describe a Heterogeneous Clinical Rating Scale in De Novo Idiopathic Parkinson's Disease Patients. *Pharm Res*, 34(10):2109-218