Modeling and Simulation of Placebo Response and Dropout Patterns in Treatment of Schizophrenia

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Background

Variable and higher placebo response within and among clinical trials can substantially affect conclusions about the efficacy of new antipsychotic drugs. Developing a robust placebo model accounting for the factors like dropouts, patient characteristics, and trial design is crucial in order to facilitate better recognition of drug effect.

Objectives:

i) to develop a model for placebo response in schizophrenia as measured with the Positive and Negative Syndrome Scale (PANSS) under varying clinical trial conditions, accounting for dropout and relevant predictors of the placebo response

ii) to compare different Time to Event (TTE) modeling approaches used to describe the dropout patterns following placebo treatment in schizophrenia

Modeling Approaches

Pooled placebo PANSS total data (n=1338), 3 phase II &12 phase III trials, which included acute and chronic, long-and short-term studies

Placebo Response Modeling:

Structural Base Model Building

Placebo-associated change in PANSS score was well described by the Weibull placebo model and the Indirect Response Model (IRM)[1]

$$PANSS = BASL * \left(1 - PMAX\left[1 - EXP^{-\left[\frac{TIME}{TD}\right]}\right]^{POW}\right)$$

Weibull Placebo Model

$$\frac{dPANSS}{dt} = Kin - Kout(1 + SLOP * CEON) * PANSS$$

Indirect Response Model

Covariate Modeling

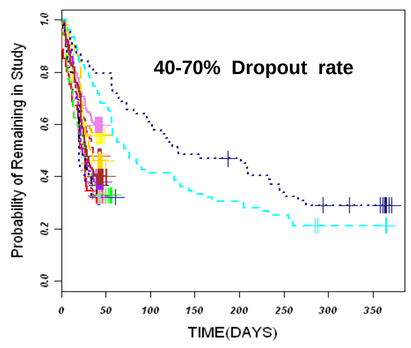
Systematic identification of covariates that contribute to high placebo response and dropouts were investigated. Final Weibull and IRM placebo base model using stepwise covariate model building approach, within PsN was used. Strict forward inclusion and backward exclusion criteria was set to identify clinically relevant covariates (ΔOFV of 10.83, P< 0.001). Both linear and non-linear covariate relationship were explored.

Placebo Response and high dropout rate: Potential covariates

Patient factors	Trial design factors

• Disease condition,
• Gender, weight, age, race
• Disease duration,
• PANSS baseline score
• Change in PANSS
  • From baseline
  • Between two last visits
	• Duration of trial
	• PANSS measurement frequency
	• Study site
	• Administration route
	• Dosage regimen
	• Clinical trial phase

Fig 1: Kaplan-Meier plot of observed dropouts across the studies



Dropout Modeling: Previously, the exponential hazard model to predict the risk of dropout was attempted[1]. In addition, predictors of dropout, and alternative TTE models like the Weibull and the Gompertz hazard models were examined together with different dropout patterns

- Missing Completely At Random (MCAR): independent of PANSS
- Missing At Random (MAR): depends on last observed PANSS
- Missing Not At Random (MNAR): dropout depends on predicted PANSS

Overview of model structure of different dropout models

Dropout Pattern	Exponential Hazard Model	Weibull Hazard Model	Gompertz Hazard Model
MCAR	$h(t) = \gamma$	$h(t) = \gamma\lambda(t)^{(\lambda-1)}$	$h(t)= \gamma\varphi^{(t)}$
MAR	$h(t) = \gamma * exp(-PANSS_{Last} * \beta 1)$	$h(t)=\gamma\lambda(t)^{(\lambda-1)} * exp(-PANSS_{Last} * \beta 1)$	$h(t)= \gamma\varphi^{(t)} * exp(-PANSS_{Last} * \beta 1)$
MNAR	$h(t) = \gamma * exp(-PANSS_{Pred} * \beta 2)$	$h(t)=\gamma\lambda(t)^{(\lambda-1)} * exp(-PANSS_{Pred} * \beta 2)$	$h(t)= \gamma\varphi^{(t)} * exp(-PANSS_{Pred} * \beta 2)$

γ: baseline hazard; β1, β2: parameters relating hazard to PANSS; λ & φ :shape parameter in Weibull and Gompertz hazard models respectively

Results

Covariate Model:

Weibull Placebo Model	POP (95% CI*)	Remarks
BASL (baseline PANSS score)	91.1 (90.1- 91.8)	-
TD (days) (time course of placebo effect)	12.7 (11.2 - 14.6)	-
PMAX (maximum placebo effect)	0.087 (0.072 - 0.102)	-
POW (shape Parameter)	1.24 (1.15 - 1.35)	-
σ (residual variability)	7.29 (6.7 - 7.9)	-
BASL-DIS (acute vs. chronic)	-0.038 (-0.06 - -0.014)	chronic patients had 3.8% lower PANSS BASL
PMAX-DUR (short vs. long-term)	-1.4 (-1.7 - -1.1)	long-term studies shown 140% lower placebo effect (worsening)
TD-US (USA vs. Non-USA)	0.36 (0.08-0.57)	time course of placebo effect lasted for longer duration (36%) for studies in Non-USA
σ -ADM (oral vs. IM,SL)	-0.274 (-0.33 - -0.19)	SL & IM had 27% lower residual error compare to oral route
σ -DIS (acute vs. chronic)	0.50 (0.31-0.74)	50% higher residual error for chronic patients
σ -US (USA vs. Non-USA)	-0.28 (-0.34- -0.25)	Non-USA studies shown 28% lower residual error
IIV BASL (exponential) (CV%)	16 (14-16)	-
IIV PMAX (additive)	19 (17-20)	-
IIV σ (exponential) (CV%)	40 (34-44)	-

* 95% CI from 2,000 bootstrap samples; IRM-covariate model also resulted in similar covariate-relationship (data not shown)

Dropout Modeling:

Fig 2: Objective function value (OFV) for different base dropout models

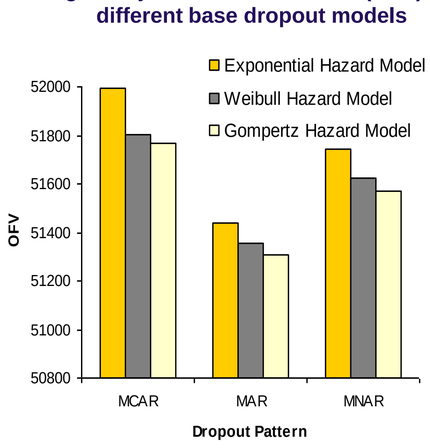


Fig 3: Visual predictive checks (VPC)- Kaplan-Meier plot of observed dropout (blue) with 5th and 95th percentiles of simulated dropout (green shaded) using different TTE base dropout models (MNAR) for all the placebo data

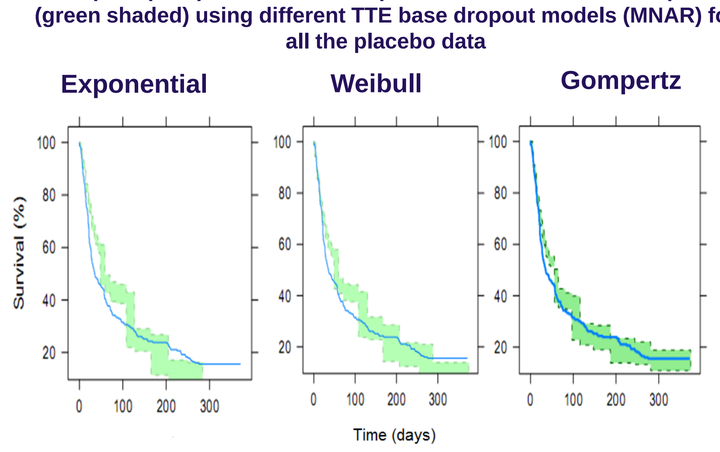
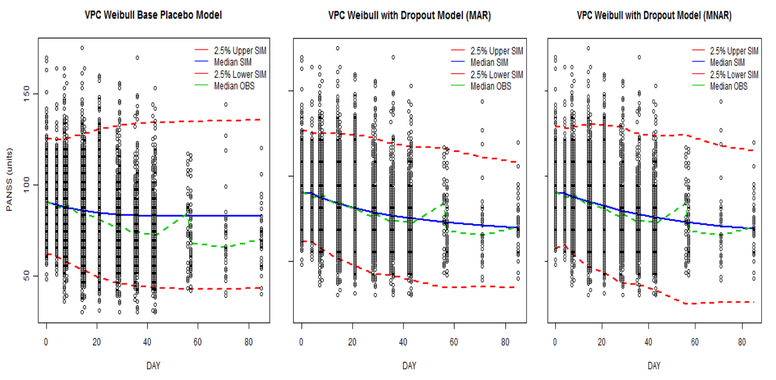


Fig 4: 1000 simulations VPC for Weibull placebo model
Left: without covariate & dropout model, Middle & Right: with covariate & dropout model



- Incorporation of the exponential dropout model improved the VPC of the PANSS score (Fig 4)
- Based on OFV, the Gompertz dropout model with MAR dropout pattern seems to describe the observed data best
- Further, simulations using predictors of dropout for all the TTE models are in progress

Predictors of dropout: Females, subjects in long-term studies and chronic patients had lower probability of dropping out from trials compared to males, subjects of short-term trials and acute schizophrenic patients

Summary

- Covariate analysis with the Weibull placebo model identified disease condition, study site, administration route and trial duration as contributing factors for the variable placebo response
- The exponential, Weibull and Gompertz hazard models performed equally well for short-term trials, while for long-term trials and for the entire pooled dataset, the Gompertz model was shown to be superior
- The probability of dropout from a trial depends on the change in PANSS score from baseline, PANSS last score and the predicted PANSS score

1) Pilla Reddy V. et al., Placebo Response Modeling in Schizophrenia using Positive and Negative Syndrome Scale. 6th International Symposium (2010) on Advances in Simulatenous Pharmacokientic/Pharmacidynamic Modelling, Noordwijkerhout, The Netherlands,
2) Hu C, Sale M. A joint model for nonlinear longitudinal data with informative dropout. J. Pharmacokinet. Pharmacodyn. 2003;30:82-103

Full project title: Mechanism-based PK-PD modeling platform

This study/ work was performed within the framework of the Dutch Top Institute Pharma project D2-104. Partners in this project include:

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