Integration of response, tolerability and dropout in flexible-dose trials: a case study in depression

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Introduction

The difficulties arising when analyzing depression trials are manifold, as a comprehensive model, in addition to the efficacy endpoints, should account for: (i) flexible dosing schemes, (ii) dropout events, and (iii) drug-related adverse effects and their potential inter-relationships. Simplified modelling approaches that neglect some of the above aspects may yield biased results.

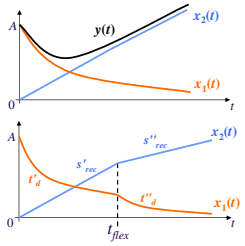
In this work we investigate an integrated approach based on the joint population modelling of response, tolerability and dropout. The proposed methodology is used to analyze data from a flexible-dose, placebo-controlled, Phase II depression trial. As an extension of previous work[1,2], in this study we account for flexible dosage regimen and adverse events as covariates in the dropout model.

Methods: HAMD model

The time course of the HAMD score was described as the sum of a Weibull and a linear function[3]. The dose escalation was included in the model as a covariate on two of the four structural parameters. The population model was implemented in WinBUGS 1.4.3[4].

$$\begin{cases} \dot{x}_1(t) = -\dfrac{b+1}{t_d^{b+1}} x_1(t) t^b & x_1(0) = A \\ \dot{x}_2(t) = s_{rec} & x_2(0) = 0 \\ y(t) = x_1(t) + x_2(t) = A e^{-(t/t_d)^{b+1}} + s_{rec} t \end{cases}$$

$$t_d = \begin{cases} t'_d & 0 \le t \le t_{flex} \\ t''_d & t > t_{flex} \end{cases} \qquad s_{rec} = \begin{cases} s'_{rec} & 0 \le t \le t_{flex} \\ s''_{rec} & t > t_{flex} \end{cases}$$



Methods: dropout model

We investigated three different dropout mechanisms: missing completely at random (MCAR), at random (MAR) and not at random (MNAR)[5]. The dropout probability was modulated using three covariates: time course of clinical outcome, dose escalation, and occurrence of clinically relevant adverse events. The quantity $\Delta_{HAMD}(t)$ is defined as the baseline score minus the HAMD at time t.

PLACEBO ARM

$$h(t) = (\alpha+1)\lambda(\lambda t)^{\alpha} exp(-\theta_1 \Delta_{HAMD}(t) - \theta_2 F)$$

DRUG ARM

$$h(t) = (\alpha+1)\lambda(\lambda t)^{\alpha} exp(-\theta_1 \Delta_{HAMD}(t) - \theta_2 F + \theta_3 H)$$

$$F = \begin{cases} 0 & \text{No escalation} \\ 1 & \text{Escalation} \end{cases} \qquad H = \begin{cases} 0 & \text{No headache events} \\ 1 & \text{At least one headache event} \end{cases}$$

Arm	Param.	2.5%	50%	97.5%	Hazard change
Placebo	θ_1	0.0476	0.0807	0.122	–80.4 %
	θ_2	0.0282	0.425	1.246	–37.8 %
Drug	θ_1	0.0436	0.0671	0.0960	–74.2 %
	θ_2	0.218	0.861	1.642	–58.7 %
	θ_3	0.0346	0.417	0.921	+53.9 %

Table 1: Posterior percentiles of covariate parameters in the hazard function, and percentage hazard change (for θ_1, Δ_{HAMD} = 20 is assumed)

Results: joint model

The proposed method performed well in terms of goodness-of-fit to HAMD data (Figure 1).

With respect to previous approaches[1,2], which used only the HAMD score as a covariate in the hazard model, the inclusion of dose escalation and drug-related adverse events yielded a comprehensive description of the dropout process, as witnessed by parameter estimates (Table 1), and modified Cox-Snell residuals[5] (Figure 2, top).

Comparison of the dropout mechanisms via the Deviance Information Criterion[6] suggested a MNAR dropout process in both treatment arms (Table 2). The ability of the proposed model to reproduce realistic dropout patterns was assessed through Kaplan-Meier visual predictive checks[7] (Figure 2, bottom).

Arm	Model	HAMD DIC	Dropout DIC	Total DIC
Placebo	MCAR	4856.200	262.975	5119.175
	MAR	4856.200	262.974	5119.174
	MNAR	4860.440	242.846	5103.286
Drug	MCAR	4587.440	341.293	4928.733
	MAR	4587.440	336.860	4924.300
	MNAR	4576.950	311.910	4888.860

Table 2: DIC scores of MCAR, MAR and MNAR dropout models

Results: HAMD data

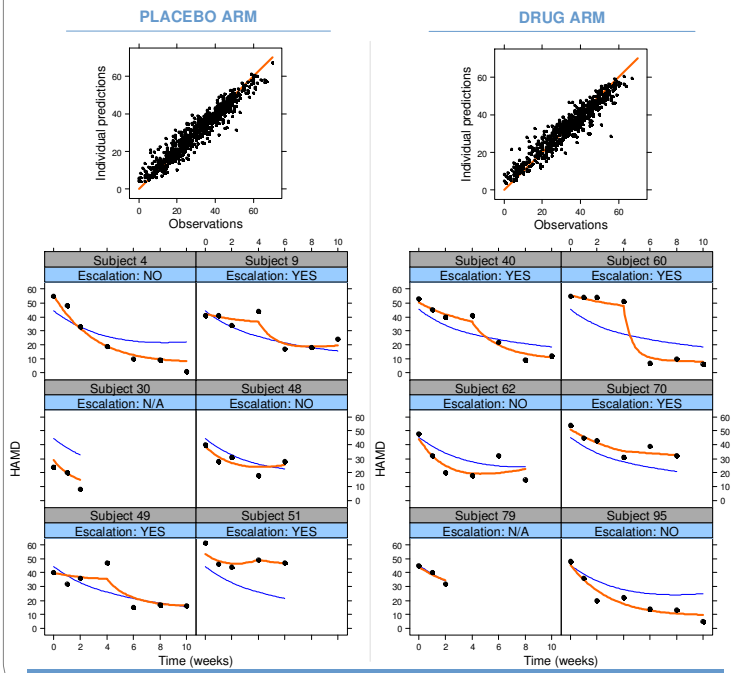


Figure 1: Individual predictions *vs* observations (top) and individual fittings (bottom)

Results: dropout data

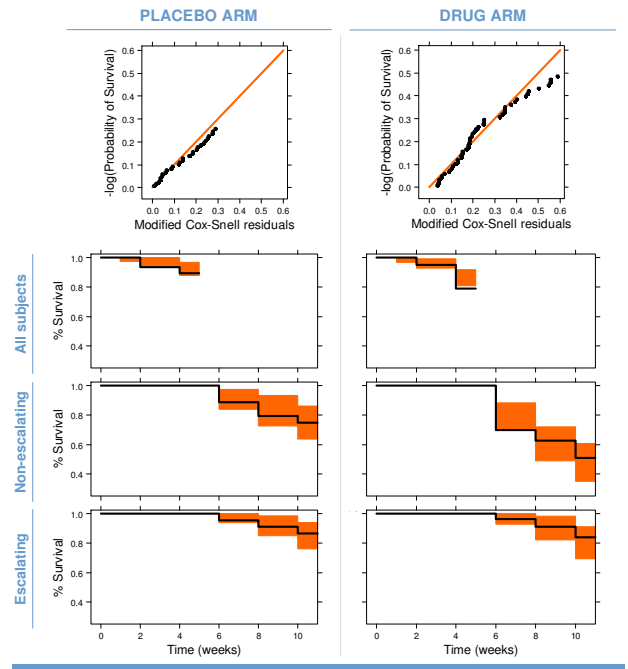


Figure 2: Diagnostic plot of modified Cox-Snell residuals (top) and dropout VPC (bottom)

Conclusions

- Our results show the feasibility of a joint model accounting for the HAMD time course, discontinuities in the dosing schedule, dropouts and adverse events.
- In the study here analyzed, the dropout process was influenced by all such aspects.
- Comprehensive modelling approaches that integrate all the relevant information are necessary to provide a thorough assessment of antidepressant drug response.

References

1. Russu A, Marostica E, De Nicolao G, Hooker AC, Poggesi I, Gomeni R, Zamuner S, Integrated model for clinical response and dropout in depression trials: a state-space approach, PAGE 19th Meeting, Abstract 1852, 2010
2. Hooker C, Gomeni R, Zamuner S, Time to event modeling of dropout events in clinical trials, PAGE 18th Meeting, Abstract 1656, 2009
3. Gomeni R, Lavergne A, Merlo-Pich E, Modelling placebo response in depression trials using a longitudinal model with informative dropout, *Eur. J. Pharm. Sci.* **36**, 4–10, 2009
4. Lunn DJ, Thomas A, Best N, Spiegelhalter D, WinBUGS – A Bayesian modelling framework: concepts, structure and extensibility. *Stat. Comput.* **10**, 325–337, 2000
5. Hu C, Sale ME, A joint model for longitudinal data with informative dropout, *J. Pharmacokinet. Pharmacodyn.* **30**, 83–103, 2003
6. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A, Bayesian measures of model complexity and fit, *J. R. Statist. Soc. B* **64**, pp. 583–639, 2002
7. Holford N, The visual predictive check: superiority to standard diagnostic (Rorschach) plots, PAGE 14th Meeting, Abstract 738, 2005

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