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, 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. 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.

\[
\begin{align*}
    x_i(t) &= \frac{a_i}{a_{i0}}(1-e^{-t/t_{i0}}) + x_{i0} \\
    k_i(t) &= k_{i0} \\
    y_i(t) &= x_i(t) + x_{i0} = A e^{(t-t_{i0})/\alpha_i} + x_{i0}
\end{align*}
\]

Results: joint model

The proposed method performed well in terms of goodness-of-fit to HAMD data (Figure 1). With respect to previous approaches, 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 (Figure 2, top).

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

Results: dropout data

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