Multinomial logistic functions in Markov-chain models for modeling sleep architecture: external validation and covariate analysis

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Introduction

The evaluation of the dynamics of sleep stage distribution through the night is considered a key feature in clinical studies investigating the treatment effects of new molecules for primary insomnia [1].

A mixed-effect Markov-chain model based on piecewise linear multinomial logistic functions has been recently proposed [2, 3] to characterize the time course of transition probabilities between sleep stages in insomniac patients treated with placebo.

Objectives

The aims of this work were to:

A. further develop the model proposed in [2, 3],
B. perform the external validation of model structure and parameters estimates,
C. explore the covariate effects.

Methods

Data

- Two clinical studies were considered, A and B, with N_A = 116 and N_B = 81 insomniac patients, and similar protocols.
- B was used for external validation only.
- In each study, sequences of sleep stages at each 30-second nighttime interval were obtained from the first night of placebo administration.
- Recorded sleep stages were awake (AW), stage 1 (ST1), stage 2 (ST2), slow-wave sleep (SWS) and REM sleep (REM).

Multinomial logistic functions in a Markov-chain model

The time course of sleep stages was assumed to obey to a Markov-chain model, and a population approach was implemented with NONMEM VI. In particular, the relationship between times and individual transition probabilities between sleep stages was modeled through piecewise linear multinomial logistic functions [3]:

\[ \log\frac{p_{ij}(t)}{1-p_{ij}(t)} = \sum_{k=1}^{K} \alpha_k f_k(t) \]  

where \( p_{ij}(t) \) is the probability of moving from sleep stage \( i \) at time \( t \) to sleep stage \( j \) at time \( t \) for subject \( i \), and similarly for \( p_{ij}(t) \).

Five sub-models were built, each one modeling the transitions from a specific sleep stage.

Development of the model, validation and covariates analysis

Model building was based on dataset A and guided by model adequacy criteria (log likelihood ratio test and Akaike information criteria) and internal validation based on simulation (and re-estimation); posterior predictive checks (PPCs) as suggested by Gelman et al. [5], and visual predictive checks and visual estimation checks as presented in [4].

External validation of the final model was based on dataset B and related to the evaluation of objective function values (OFVs), distributions of empirical Bayes estimates (EBEs), parameter values and posterior predictive checks (PPCs) as suggested by Gelman et al. [5].

Age, gender and BMI were explored within NONMEM through stepwise covariate modeling [6] on dataset A. Linear and piecewise linear additive effects were tested on each logit at each different nighttime break-point.

Results

- The final model presented the following specifications with respect to [3]: \( r \) equal to \( k \) in Eq. 1; significant correlations in sub-models AW, ST1 and ST2; time elapsed since the last change in sleep stage as a further predictor of the logits, through piecewise linear additive functions; parameters in sub-model AW estimated as different values between initial sleeplessness and rest of the night; reduced number of model parameters (four transition probabilities were fixed to zero and knots number in piecewise-linear functions was reduced to one).
- OFV reduction is shown in Table 1 (column 3). PPC on study A (Fig. 2) indicated a good agreement between simulated and observed efficacy endpoints in most cases.

Conclusions

- Previously proposed mixed-effect Markov-chain models for describing sleep architecture of insomniac patients treated with placebo [2, 3] were improved in terms of predictive performance and model parsimony.
- The final model was successfully validated with data from a new study.
- Age, gender and BMI were detected as influential covariates: their clinical relevance deserves further exploration in a wider population of insomniac subjects.

References


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