Multinomial Markov-chain model of sleep architecture in phase-advanced subjects

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Introduction

The phase-advanced sleep model, where subjects are asked to begin trying to sleep several hours before their usual bedtime, emulates transient insomnia and produces predictable sleep disruption qualitatively similar to insomnia. Recently, a mixed-effect Markov-chain (MEMC) model based on transition probabilities as multinomial logistic functions was developed using polysomnography (PSG) data after placebo dosing in insomniac patients [1,2]. The use of this MEMC model to describe PSG data in phase-advanced subjects could provide valuable insight into the sleep architecture and efficacy of sleep promoting drugs in patients with transient insomnia and insomnia.

Objectives

• Examine the sleep architecture in phase-advanced subjects compared to insomniac patients over the first 8 hours after sleep initiation.

• Incorporate enhancements to the MEMC model to describe current phase-advanced subject data.

Methods

Data

• PSG data were collected for 13 hours after placebo administration to phase-advanced subjects from two placebo-controlled, parallel studies [study 1 (N=11) and study 2 (N=16)] at two different sites (France and Japan).

• Subjects went to bed at 1800 (5 hours earlier than their typical bedtime) and remained in bed whether asleep or not until 0700 the following morning.

• Each PSG recording was divided into a sequence of 30-sec intervals, and each interval was assigned a sleep stage by an expert human scorer: awake (AW), stage 1 (ST1), stage 2 (ST2), slow-wave sleep (SWS), or REM.

Multinomial logistic functions in the Markov-chain model

• The relationship between time and individual transition probabilities between sleep stages was modeled through piecewise linear multinomial logit functions assuming a first-order Markov-chain model:

$$g_{ikm}(t) = log\frac{p_{ikm}(t)}{p_{ikk}(t)}$$

where $p_{ikm}(t)$ is the individual probability of moving from sleep stage k at time t-1 to sleep stage m at time t and similarly for $p_{ikk}(t)$.

• The transition probabilities were derived from the logits as

$$p_{ikm}(\mathrm{t}) = \frac{\exp\left(g_{ikm}(t)\right)}{\sum_{m\epsilon s}\exp\left(g_{ikk}(t)\right)}$$

where S is the sleep stages.

• Five sub-models were developed using NONMEM, each one for all transitions from sleep stage k.

Model development, validation and covariate analysis

• Transition probabilities depended on nighttime and time elapsed since last change in sleep stage.

• Modification to the MEMC model structure and predictors was performed for current data: 1) number of break points in the piecewise linear logit functions, 2) different likelihood of probability for each study based on relatively infrequent transitions and 3) study effect on individual transition probabilities.

• Model building was guided by log likelihood ratio test, AIC, posterior and visual predictive checks (VPCs and PPCs).

Results

Comparison of observed data and clinical endpoints

• Phase-advanced subjects generally displayed lower transition frequency from one sleep stage to another, shorter latency to sleep onset (LSO), different total time spent in sleep stages and displayed a higher propensity to stay in the existing sleep stage compared to insomniac patients (Figs. 1 and 2).

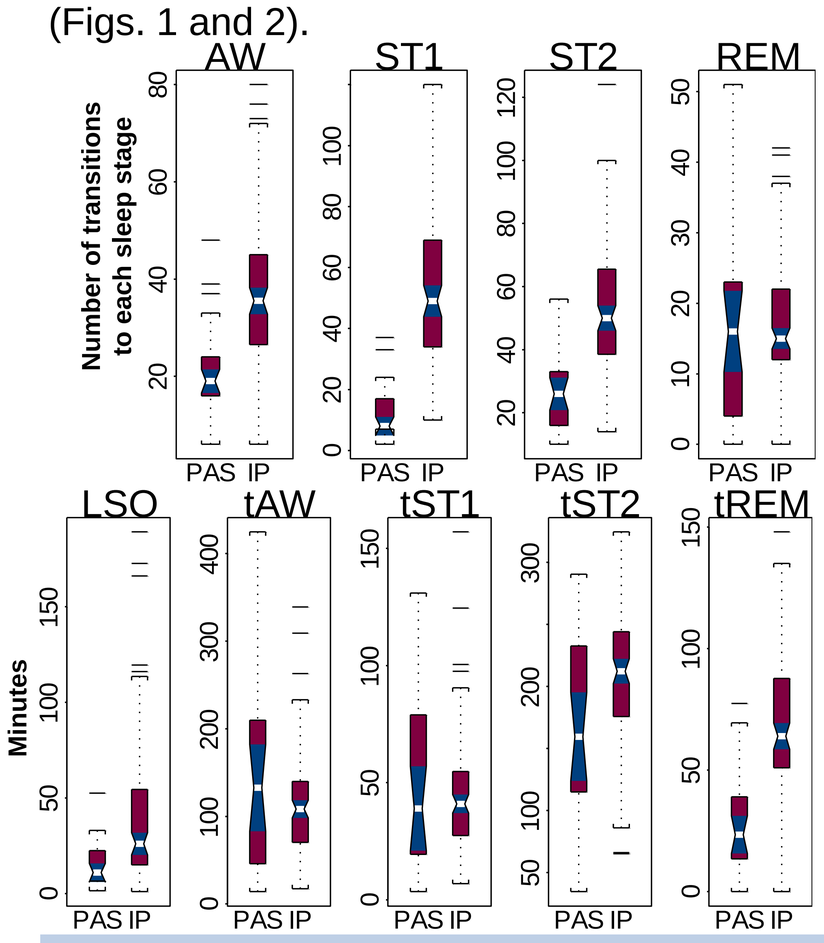

***Figure 1.** Observed clinical endpoint surrogates for phase-advanced subjects(PAS) and insomnia patients (IP).*

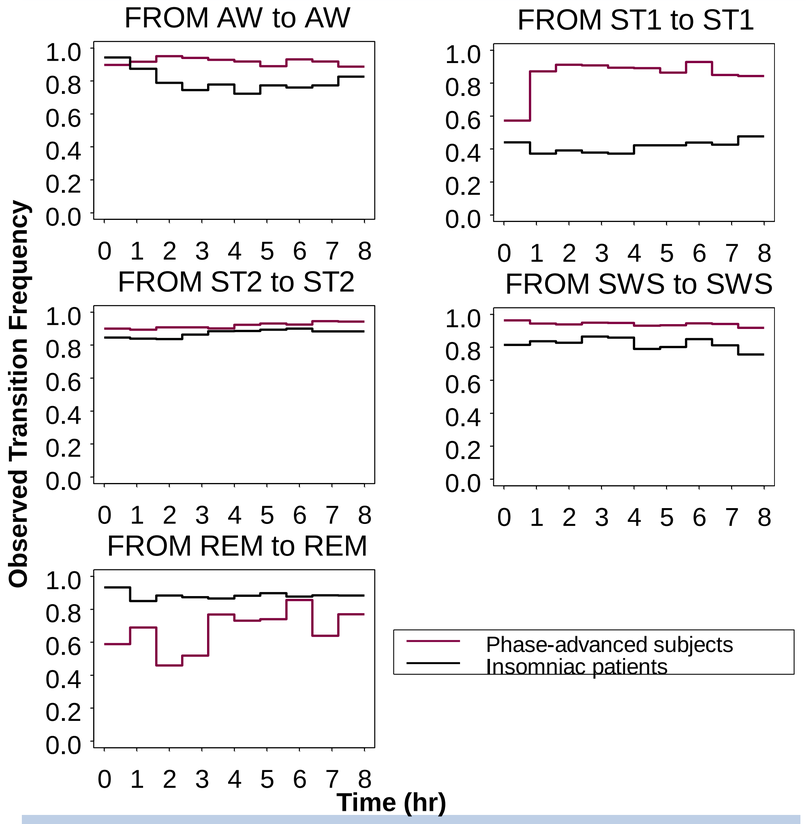

***Figure 2.** Observed transition frequencies from existing sleep stage over the first 8 hours.*

Multinomial mixed-effect Markov-chain model

• The MEMC model was fit to study data, including enhancements, to describe the sleep architecture in phase-advanced subjects. There were significant differences between studies 1 and 2 for most transitions, excluding “From_SWS”, during both night time (Fig. 3) and time elapsed since last change in sleep stage.

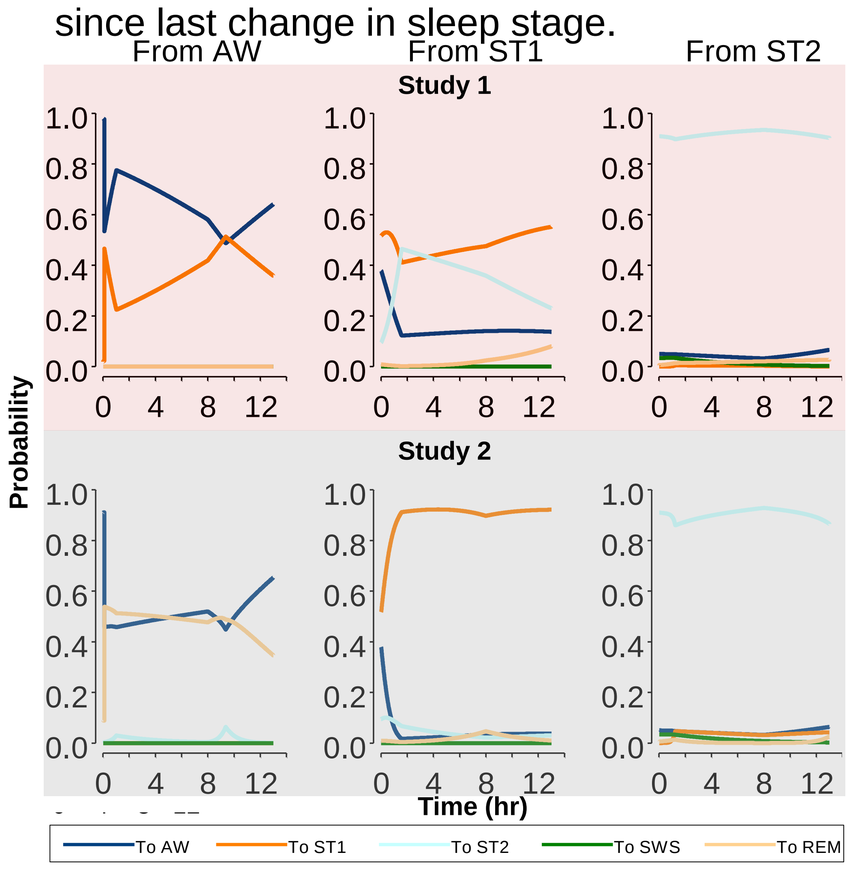

***Figure 3.** Typical individual profiles of transition probabilities for Study 1 and 2.*

•VPCs (Fig 4) and PPCs for the final model demonstrated general agreement between the statistics derived from raw and simulated data.

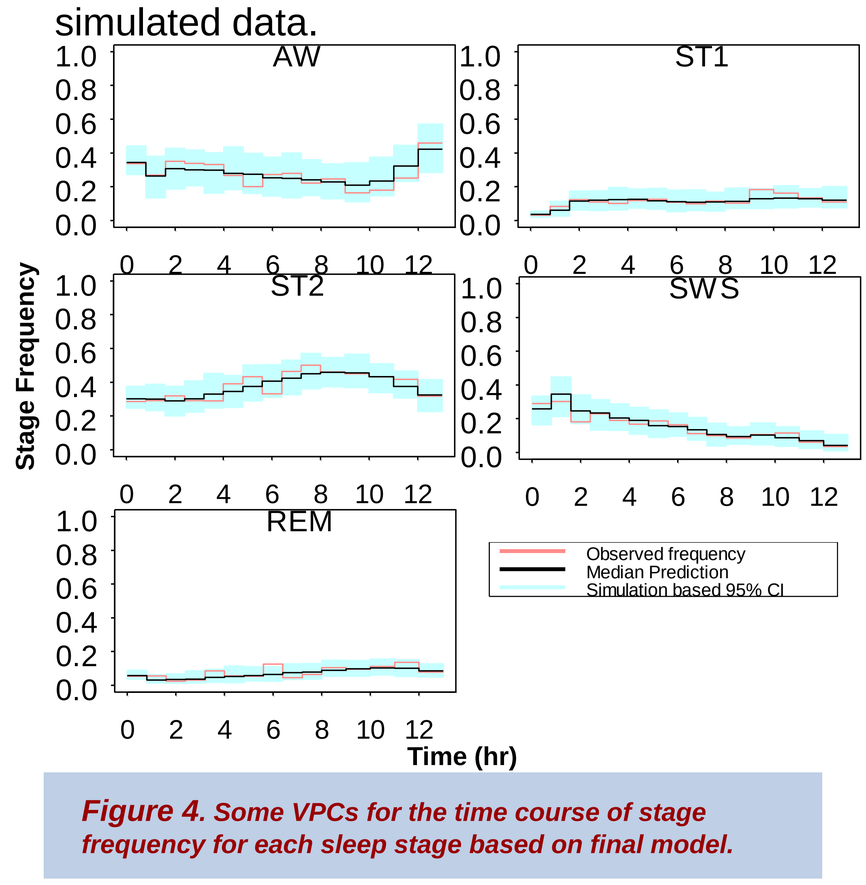

***Figure 4.** Some VPCs for the time course of stage frequency for each sleep stage based on final model.*

Conclusions

• Phase-advanced subjects and insomnia patients displayed different sleep architecture over the first 8 hours.

•The final MEMC model identified and described sleep stage transition probabilities differences between studies performed at different sites.

• The VPCs and PPCs demonstrated that the final MEMC model is robust for describing data characteristics and dynamic behavior of the sleep process in phase-advanced subjects .

References

[1] Bizzotto R, Zamuner S, De Nicolao G, Karlsson MO, Gomeni R. Multinomial logistic estimation of Markov-chain models for modeling sleep architecture in primary insomnia patients. J Pharmacokinet Pharmacodyn, 2010(online) DOI 10.1007/s10928-009-9148-2

[2] Mezzalana E, Bizzotto R, Sparacino G, Zamuner S. Multinomial logistic functions in Markov-chain models for modeling sleep architecture: internal validation based on VPCs. PAGE 2010;19