A Mixed-Effects Model with a Markov Property Characterizing the Time-Course & Severity Levels of Extrapyramidal Side Effects

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Background & Objectives

- Extrapyramidal side effects (EPS) associated with antipsychotics are often assigned different severity levels giving rise to data consisting of repeated events of ordered categories. This type of data can be modeled using a proportional odds model; however this model assumes independency between the different observations.
- Markov models assume that future events are dependent on present events. Our aim was to build a Markov model using a compartmental structure [1,2] which can characterize the probabilities of the transitions of the patients between different EPS severities over a continuous time scale.

Methods and Materials

- **Data:** Three phase-III, placebo controlled studies testing paliperidone taken at daily doses of 3-15 mg p.o. in patients with schizophrenia (placebo: n=320; paliperidone: n=867). Patients spontaneously recorded the incidence of EPS, the severity of which was graded by clinicians.
- **Approach & implementation of the Markov property in NONMEM:** A 3-compartment model was used (fig.1). All compartments were reset after an observation and the compartment corresponding to the observed EPS state of the patient was initialized with (AMT=1) indicating a 100% probability at each time point (table.1). The probabilities were left to flow between the compartments and the rate constants which correspond to the transition probability constants were estimated. The analysis was performed by estimating the likelihood of the data using the Laplacian estimation method in NONMEM 7.

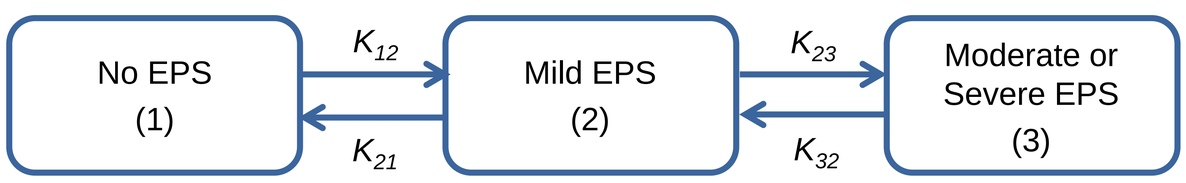

Fig.1. Compartmental model structure

Table.1. Data set structure (EPS: 1= No EPS, 2=Mild EPS, 3=Moderate or severe EPS). The red bordered cells indicate how the Markov property is introduced.

ID	TIME	TRT	EPS	DV	EVID	CMT	AMT
1	0	1	1	0	1	1	1
1	5	1	1	1	0	1	0
1	5	1	1	0	4	1	1
1	9	1	2	1	0	2	0
1	9	1	2	0	4	2	1

Results

An exponential decrease with respect to time in the rate of transitioning between different EPS states best described the placebo effect ($EPS_{Placebo}$). The effect of administration of paliperidone was added proportionally on top of the placebo effect. It was found that the rate of worsening of an EPS manifestation while taking paliperidone ($EPS_{Paliperidone}$) increased linearly with the model predicted area under the concentration-time curve (*AUC*).

$$K_{xy} = EPS_{Placebo} * (1 + EPS_{Paliperidone})$$

$$EPS_{Placebo} = Base_{xy} * e^{\left(-\frac{ln2}{t_{1/2\ xy}} * Time\right)}$$

$$EPS_{Paliperidone} = EFF * AUC$$

x: initial EPS state, *y*: future EPS state, K_{xy}: transition probability constant, $Base_{xy}$: transition probability constant baseline, $t_{1/2\ xy}$: half-life required for K_{xy} to diminish, *EFF*: slope for the effect of paliperidone administration on $EPS_{Paliperidone}$.

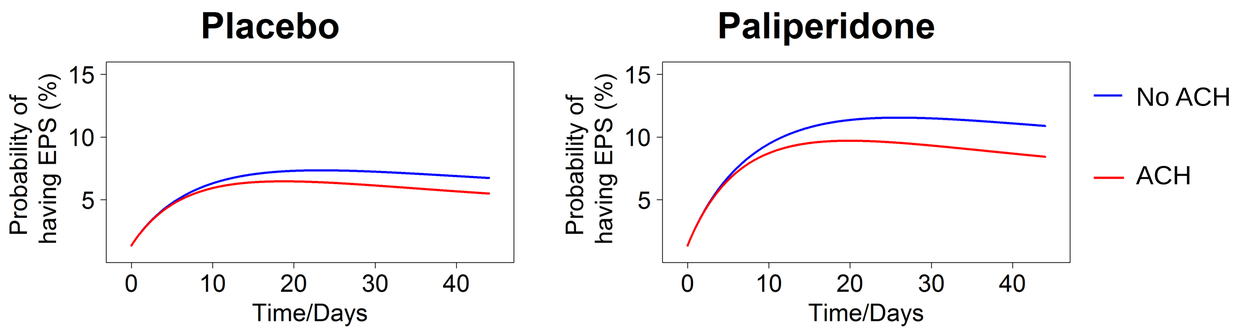

Figure.2.The probabilities of experiencing EPS of any severity after placebo and paliperidone administration. (ACH=anticholinergic co-administration)

To explain the shift in the observed proportions of patients experiencing different EPS grades before and after discharge from the hospital, it was significant to allow some parameters to differ before and after day 16.

Table.2. Parameter estimates and their associated 95% confidence intervals (CI) from 1000 bootstrap samples (ACH=anticholinergics, E.E.=Eastern Europe)

Parameter	Bootstrap Estimate (95% CI)	
	<= Day 16	> Day 16
$Base_{12}$ (day^{-1})	0.00945 (0.00601-0.0141)	
$Base_{21}$ (day^{-1})	0.0954 (0.0587-0.141)	0.0529 (0.0336-0.0824)
$Base_{23}$ (day^{-1})	0.217 (0.108-0.458)	0.0529 (0.0336-0.0824)
$Base_{32}$ (day^{-1})	0.0954 (0.0587-0.141)	
$t_{½}$ for K_{12}(days)	11.3 (7.83-17.5)	
$t_{½}$ for K_{23}(days)	4.31 (2.74-8.02)	11.3 (7.83-17.5)
$t_{½}$ for K_{21} & K_{32}(days)	24.3 (14.9-66.8)	
EFF ($L.mg^{-1}.day^{-1}$)	34.2 (14.3-66.1)	46.9 (17.3-102)
Effect of ACH on K_{23}	70.4 (41.7-87.3) % decrease	
Effect of Residence in E.E. on K_{21} & K_{32}	138 (43.6-318) % increase	
IIV-on $Base_{32}$, % coefficient of variation	142 (102-197)	

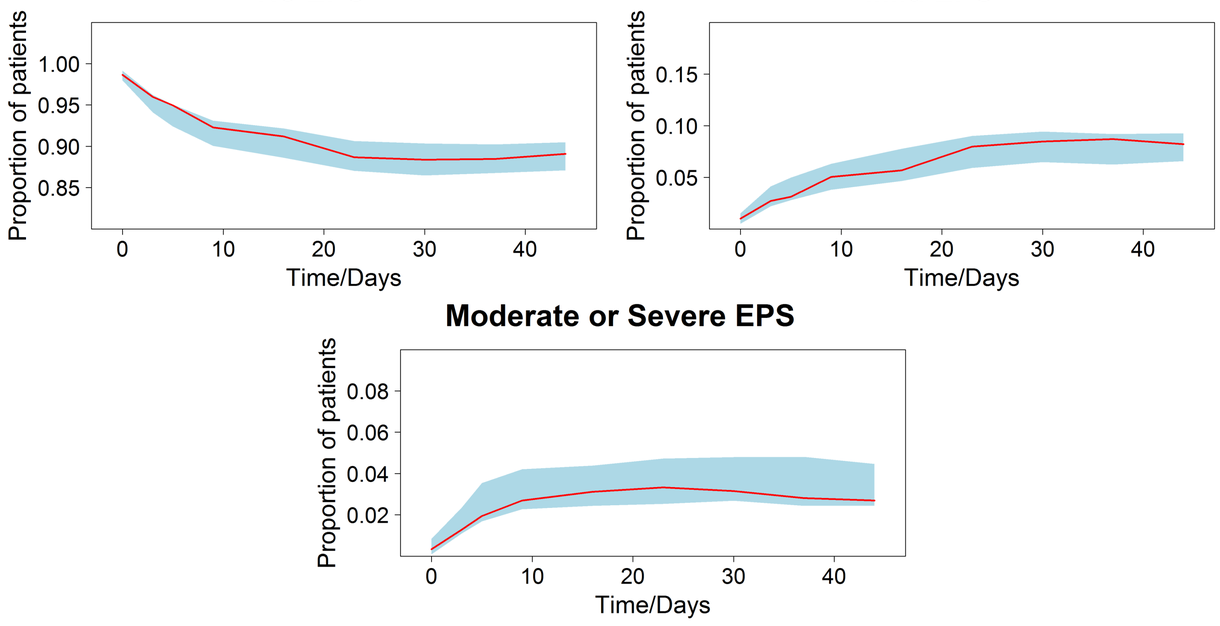

Figure.3. Visual predictive checks showing the proportions of the patients at each EPS state on planned visits in the observed data (red lines) with the corresponding 95% prediction intervals as constructed from 200 simulations (light blue region).

Conclusions

- The Markov property was successfully implemented in a mixed-effects compartmental model in NONMEM which was capable of characterizing the proportions of the patients with different severity levels of EPS over time. It was found that the transition probability constants of exhibiting EPS are proportional to the exposure to paliperidone.
- This approach was shown to adequately simulate longitudinal EPS data and may be useful for analyzing other categorical drug effect/side effect data.

References

1. Lacroix, B.D.,et al., Simultaneous modeling of the three ACR improvement thresholds – 20, 50 and 70% - in rheumatoid arthritis patients treated with certolizumab pegol. PAGE 19 (2010) Abstr 1811 [www.page-meeting.org/?abstract=1811]
2. Bergstrand, M., et al., Mechanistic modeling of a magnetic marker monitoring study linking gastrointestinal tablet transit, in vivo drug release, and pharmacokinetics. Clinical pharmacology and therapeutics, 2009. 86(1): p. 77-83