Dose-Response-Dropout Analysis for Somnolence in Pregabalin-treated Patients with Generalized Anxiety Disorder

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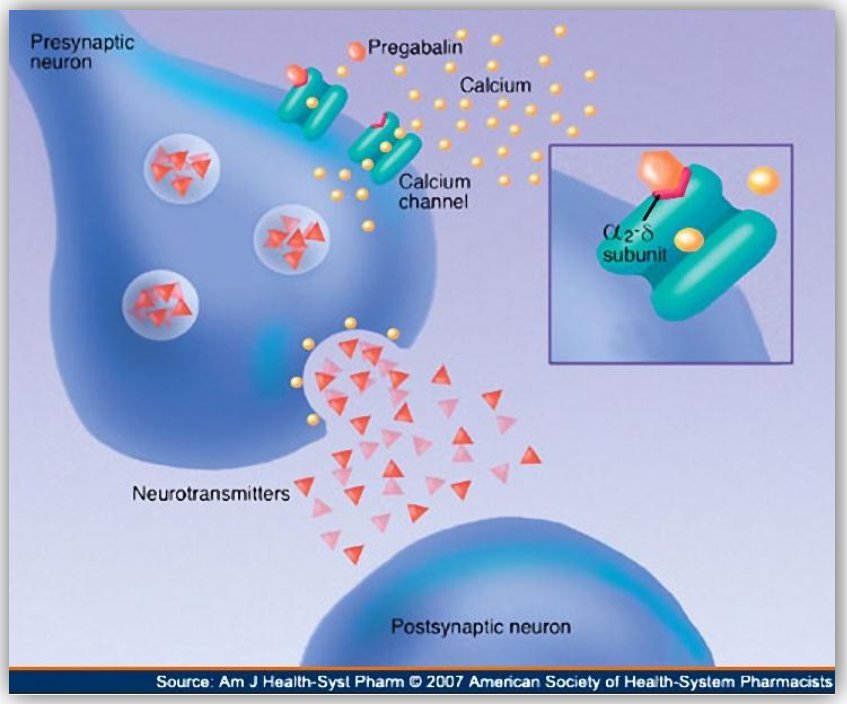
Outline

- Introduction
- Objective
- Methods
  - Incidence Model
  - Conditional Severity Model
  - Dropout Model
- Results
- Conclusions

Introduction

- Pregabalin (LYRICA®)
  - α_2-δ VGCC ligands
  - Inactive at GABA receptors
  - Linear PK characteristics
  - Indications
    - Neuropathic pains
    - Partial seizures
    - Generalized anxiety disorders
    - …
  - Common unwanted effects
    - Dizziness
    - **Somnolence**



Introduction

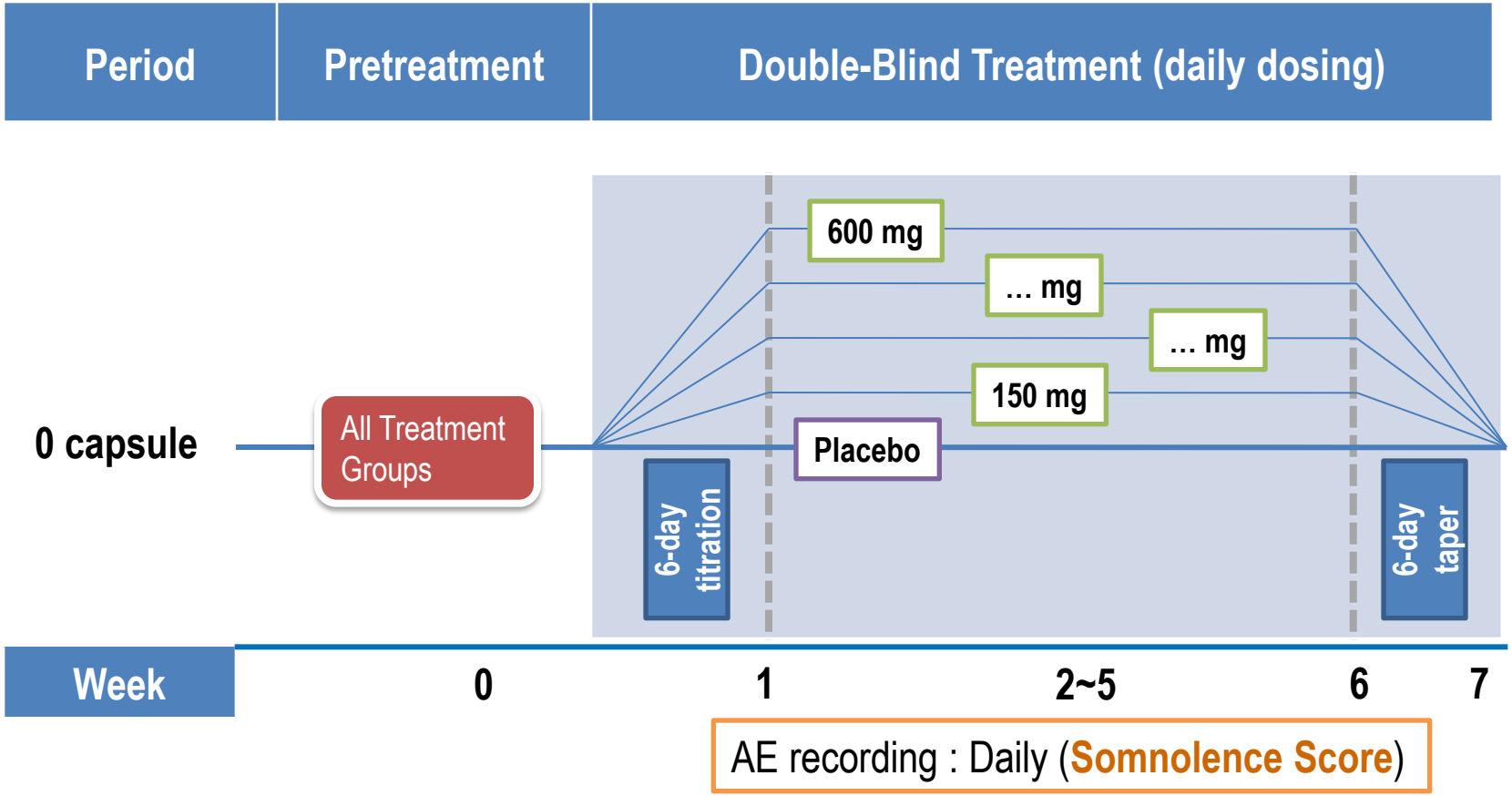
- 6 Double-blind, parallel, placebo-controlled, randomized studies
- Patients with Generalized Anxiety Disorder

Protocol	Duration	Dose
1008-021	5 weeks	Pregabalin 0, 150, 600 mg/day t.i.d. Lorazepam 6 mg/day t.i.d.
1008-025	5 weeks	Pregabalin 0, 150, 600 mg/day t.i.d. Lorazepam 6 mg/day t.i.d.
1008-026	5 weeks	Pregabalin 0, 150, 600 mg/day t.i.d. Lorazepam 6 mg/day t.i.d.
1008-083	5 weeks	Pregabalin 0, 300, 450, 600 mg/day t.i.d. Alprazolam 1.5 mg/day
1008-085	7 weeks	Pregabalin 200, 400 mg/day b.i.d. Pregabalin 0, 450 mg/day t.i.d.
1008-087	7 weeks	Pregabalin 0, 400, 600 mg/day b.i.d. Venafaxine 75 mg/day

b.i.d., twice daily; t.i.d., three times a day

Introduction

Study Scheme



Introduction

Study Data

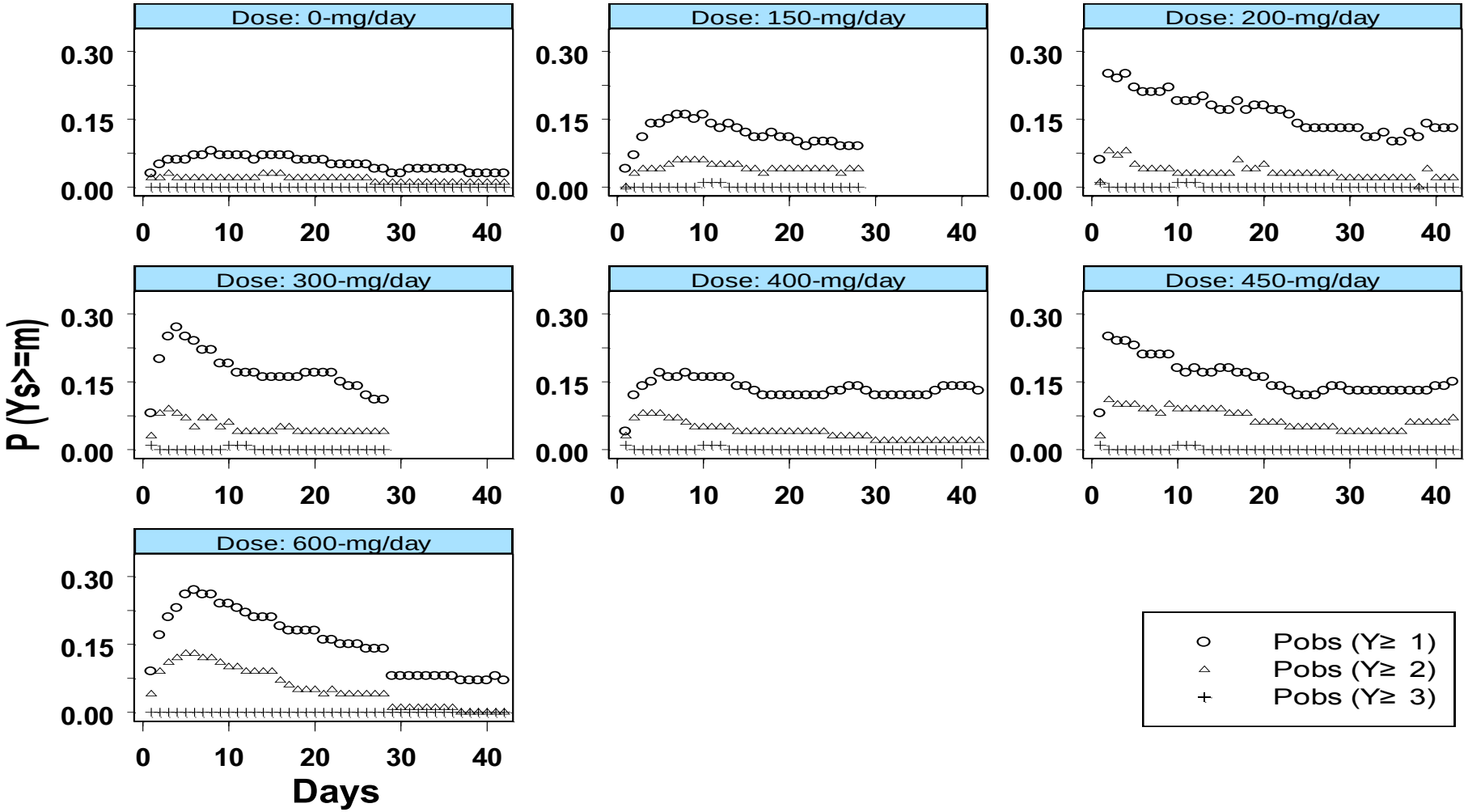
Dose (mg)	Number of Subjects					Number of Observations
	Total	AE=0	AE=1	Dropout=0	Dropout=1†	
0	484	427	57	358	126(45)	13918
150	210	161	49	171	39(13)	5247
200	77	53	24	55	22(7)	2773
300	91	59	32	81	10(3)	2438
400	185	139	46	145	40(16)	6829
450	178	125	53	138	40(18)	5386
600	405	269	136	290	115(73)	10627
total	1630	1233	397	1238	392(175)	47218

† Numbers in parenthesis indicate dropout by adverse events

Objective

- To describe pregabalin **exposure-response-dropout** relationship through dose-somnolence (AE) response modeling

Observed Somnolence



Methods – *Model building*

- Two stage method
  - *Incidence model*
  - *Conditional severity model*

Methods – *Incidence model*

- Logistic Regression

$$g\left[P\left(AE_i = 1\right)\right] = \log\left(\frac{p_i}{1-p_i}\right) = \beta + f_d$$

  - AE_i : AE response for subject i
    - ► $AE_i = 1 \rightarrow$ an AE at any time during the treatment
    - ► AE recorded only once for each subject (0 or 1)

      → No inter-individual random effect
  - β : Placebo effect
  - f_d : Treatment effect

Methods – *Incidence model*

- Treatment Effect (f_d)
  - Linear Dose-Response model

$$f_d(D_i) = \theta_{drg} \cdot D_i$$

  - Simple E_{max} model

$$f_d(D_i) = \frac{E_{\max} \cdot D_i}{ED_{50} + D_i}$$

  - Sigmoid E_{max} model

$$f_d(D_i) = \frac{E_{\max} \cdot D_i^{\gamma}}{ED_{50}^{\gamma} + D_i^{\gamma}}$$

  - D_i : Dose for subject i

Methods - *Conditional severity model*

- Proportional Odds Model

$$g[P(Y_{ij} \geq k \mid AE_i = 1, \eta_i)] = \beta_k + f_p + f_d + \eta_i$$

  - k : AE severity scores = 1,2,3 (mild, moderate, severe)
  - β_k : Baseline set of logit probabilities

$$\begin{aligned} \beta_1 &= \theta_1 && : Y \geq 1 \\ \beta_2 &= \beta_1 + \theta_2 && : Y \geq 2 \\ \beta_3 &= \beta_2 + \theta_3 && : Y \geq 3 \end{aligned}$$

  - f_p : Placebo effect
  - f_d : Treatment effect
  - η : Inter-individual random effect

Methods - *Conditional severity model*

- $f_p = PL \cdot (1 - e^{-k_{pbo} \cdot t})$
- $f_d = \frac{E_{\max} \cdot TDE}{ED_{50} + TDE} \cdot TOL$
- TDE = Time-dependent exposure effect

  $= D_{ij} \cdot (1 - e^{-k_{e0} \cdot t_j})$
- TOL = Tolerance effect with plateau

  $= e^{-K_{tol} \cdot t_j} + T_p$
- D_{ij} : Dose at t_j for subject i

Methods- *Conditional severity model with a Markov Element*

- To account for the **correlation between neighboring observations** within a subject

$$g[P(Y_{ij} \geq k \mid AE_i = 1, Y_{i,j-1} = h, \eta_i)] = \beta_{k,h} + f_p + f_{d,h} + \eta_i$$

$\beta_{k,h}$ represents β_k given $Y_{i,j-1} = h$ ($h = 0, 1, 2, 3$) such that

$$\beta_{1,h} = \theta_{1,h}$$
$$\beta_{2,h} = \beta_{1,h} + \theta_{2,h}$$
$$\beta_{3,h} = \beta_{2,h} + \theta_{3,h}$$
$$E_{\max,h} = \theta_{4,h}$$

Method - *Unconditional severity probability*

- Joint probability for incidence and severity

$$P(Y_j = m,\ AE = l) = P(Y_j = m \mid AE_i = l) \cdot P(AE = l), \quad m \in \{0,1,2,3\} \text{ and } l \in \{0,1\}$$

- Unconditional severity probability

$$P(Y_j = m) = P(Y_j = m,\ AE = 0) + P(Y_j = m,\ AE = 1), \quad m \in \{0,1,2,3\}$$

- Unconditional cumulative probability

$$P(Y_j \geq m) = \sum_{h=m}^{3} P(Y_j = h), \quad m \in \{0,1,2,3\}$$

Methods - *Incidence-dropout model*

$$Y = Y_{INC} \cdot Y_{DRP}$$

$$Y_{DRP} = P_{DRP} \cdot QUIT + (1 - P_{DRP}) \cdot (1 - QUIT)$$

- Y : Likelihood of observation
- Y_{INC} : Likelihood of observation for not modeling the dropout event
- Y_{DRP} : Likelihood of dropout/no-dropout
- P_{DRP} : Probability of dropout, $P_{DRP} = \theta_i$ (i = 0, 150,…, 600mg)
- $QUIT$: 1 for dropout, 0 for no-dropout

Methods - *Conditional severity-dropout model*

$$Y = Y_{SEV} \cdot Y_{DRP}$$

$$Y_{DRP} = P_{DRP1} \cdot QUIT + P_{DRP0} \cdot (1 - QUIT)$$

- Y : Likelihood of observation
- Y_{SEV} : Likelihood of observation for not modeling the dropout event
- Y_{DRP} : Likelihood of dropout/no-dropout
- P_{DRP1} : Probability of dropout (*QUIT* =1) at time *t* (days)
- P_{DRP0} : Probability of no-dropout (*QUIT* =0) up to time *t* (days)

Methods - *Conditional Severity-Dropout Model*

$$Y_{DRP} = P_{DRP1} \cdot QUIT + P_{DRP0} \cdot (1 - QUIT)$$

$$P_{DRP1} = P_{DRP10} \cdot P_{DRP11}$$

- $P_{DRP10} = \exp(-\lambda_m \cdot t_p), \qquad t_p = t - t_e$
- $P_{DRP11} = 1 - \exp(-\lambda_m \cdot t_e), \qquad t_e = 1\,\text{day}$

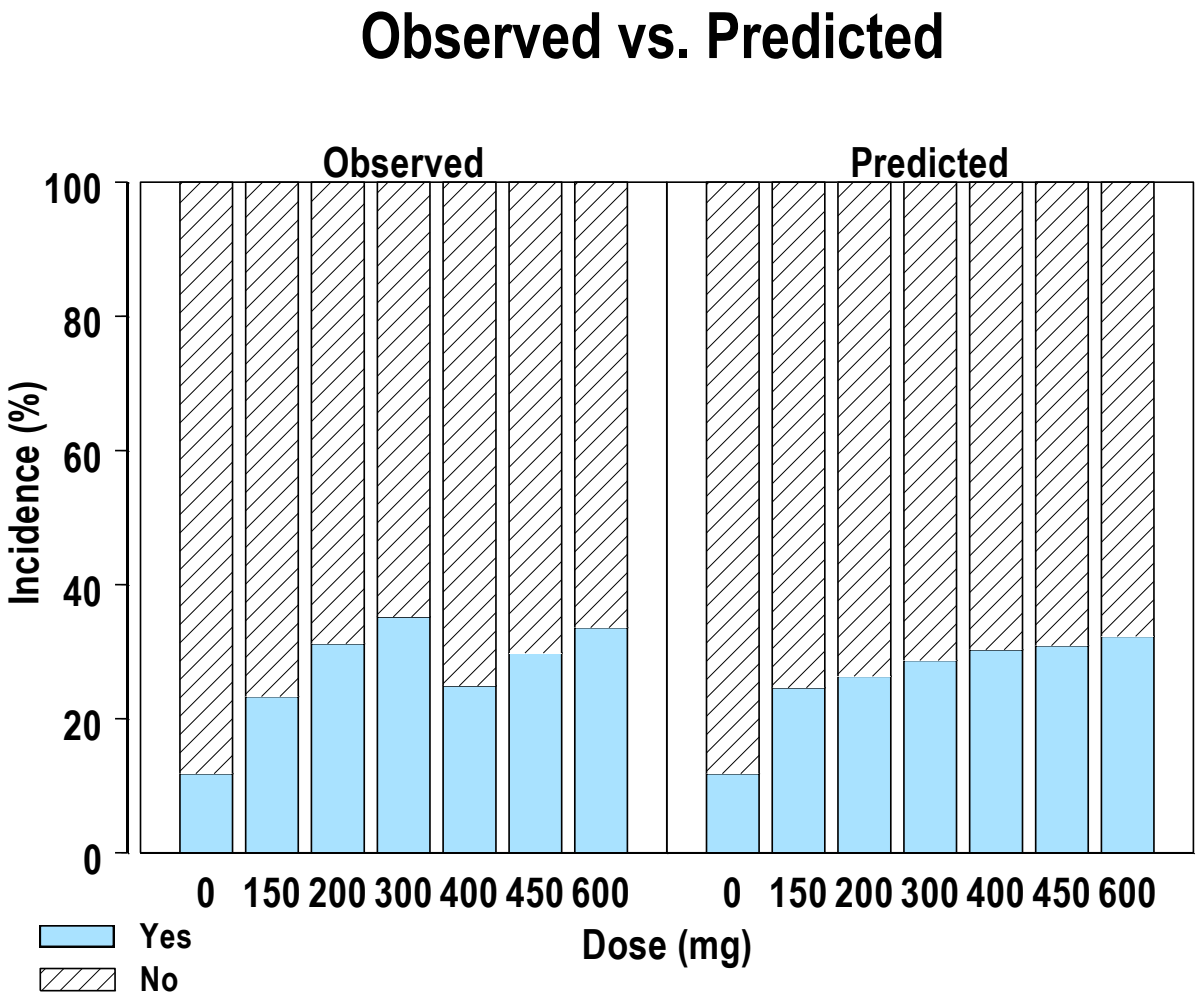
$$P_{DRP0} = \exp(-\lambda_m \cdot t)$$

- P_{DRP_1} : Probability of dropout (*QUIT* =1) at *t* (days)
- $P_{DRP_{10}}$: Probability of no-dropout up to t_p *(days)* (= previous observation time)
- $P_{DRP_{11}}$: Probability of dropout at t_e *(days)* (= elapsed time since t_p)
- P_{DRP_0} : Probability of no-dropout (*QUIT* =0) up to *t* (days)
- λ_m : Baseline hazard rates (m = 0,1,2,3)

Methods – *Model evaluation*

- **Incidence model**
  - ► *Nonparametric bootstrap* for 1000 simulated datasets
- **Severity model**
  - ► *Visual predictive check (VPC)*
    - Population-averaged IPRED of $P(Y_j \geq 1)$ for 100 datasets, simulated from $(\hat{\theta}, \hat{\omega}^2)$
  - ► *Posterior predictive check (PPC) (Yano et al., JPP, 2001)*
    - Population-averaged IPRED of $P(Y_j \geq 1)$ for 100 datasets, simulated from $(\hat{\theta}_n, \hat{\omega}^2)$ with $\hat{\theta}_n \sim N(\hat{\theta}, COV(\hat{\theta}))$, $n = 1,..,100$
    - $COV(\hat{\theta})$ obtained by $COVARIANCE in NONMEM

Results - *Incidence model*



Results - *Incidence model*

Observed vs. Predicted

Daily dose (mg/day)	Somnolence incidence (%)	
	Observed	Predicted* Mean **(95% CI)**
Placebo	11.8	11.79 (9.01~14.92)
150	23.3	24.62 (19.81~29.33)
200	31.2	26.34 (21.96~30.05)
300	35.2	28.70 (25.47~31.39)
400	24.9	30.28 (27.47~32.84)
450	29.8	30.90 (28.06~33.76)
600	33.6	32.29 (28.73~36.58)

* Obtained from non-parametric bootstrap (n=1000)

Final model parameters

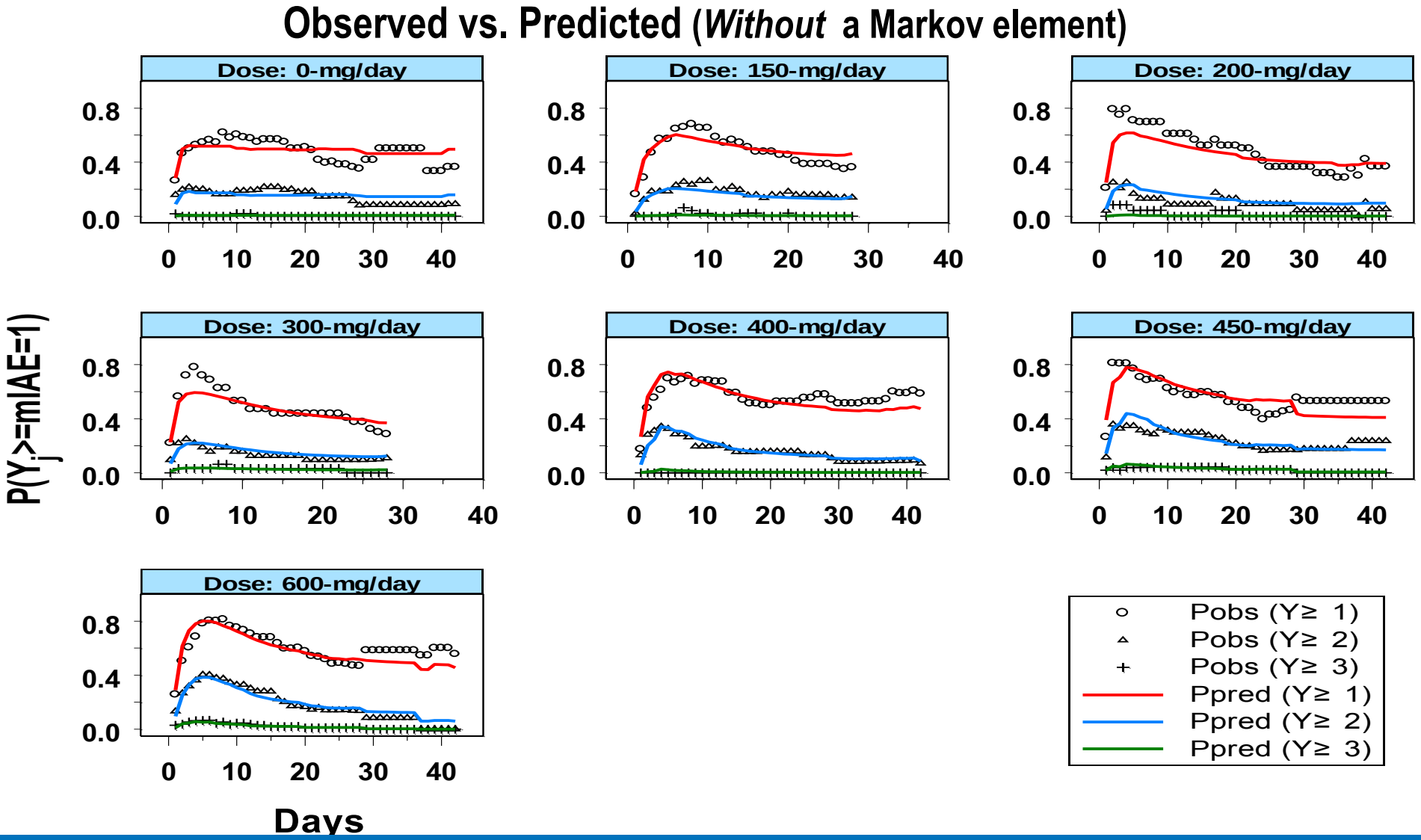
	E_{max} model
β	-2.01
E_{max}	1.48
ED_{50} (mg)	99.5

$$g[p(AE=1)] = \beta + \frac{E_{\max} \cdot D_i}{ED_{50} + D_i}$$

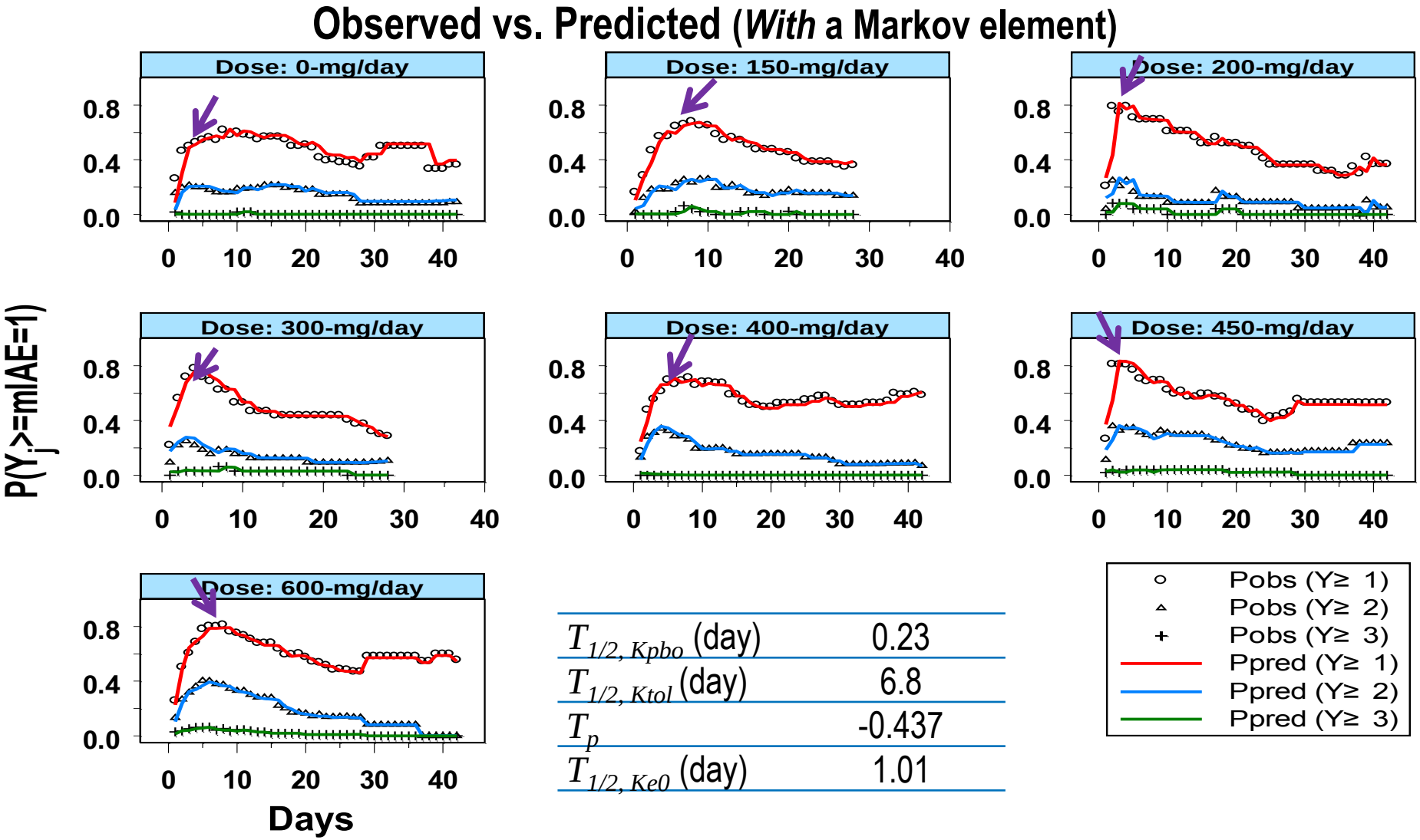
Results - *Incidence model*

- The **E_{max} model** adequately described the incidence of AE
- The predicted mean incidence of 24.6% at the dose of 150 mg/day, and 11.8% for the placebo group
- The predicted incidence tended to increase with dose, reaching 32.4% at the dose of 600 mg/day

Results - *Conditional severity model*



Results - *Conditional severity model*



$T_{1/2,\,Kpbo}$ (day)	0.23
$T_{1/2,\,Ktol}$ (day)	6.8
T_p	-0.437
$T_{1/2,\,Ke0}$ (day)	1.01

Results - *Conditional severity model*

- **Final parameters** (***With*** **a Markov element**)

Parameter	Estimates
$\beta_{1,h=0}$	-5.500
$\beta_{2,h=0}$	-6.460
$\beta_{3,h=0}$	-3.050
$E_{max,h=0}$	12.200
$\beta_{1,h=1}$	-0.034
$\beta_{2,h=1}$	-9.814
$\beta_{3,h=1}$	-11.030
$E_{max,h=1}$	-2.040
$\beta_{1,h=2}$	-0.041
$\beta_{2,h=2}$	-0.274
$\beta_{3,h=2}$	-9.743
$E_{max,h=2}$	-0.023

Parameter	Estimates
$\beta_{1h=3}$	2.650
$\beta_{2,h=3}$	2.243
$\beta_{3,h=3}$	-3.407
$E_{max,h=3}$	-0.626
ED_{50} (mg)	300
γ	1 (fix)
BSL	3.190
$T_{1/2,\ Kpbo}$ (day)	0.23
$T_{1/2,\ Ktol}$ (day)	6.8
T_p	-0.437
$T_{1/2,\ Ke0}$ (day)	1.01
ω^2	0.142

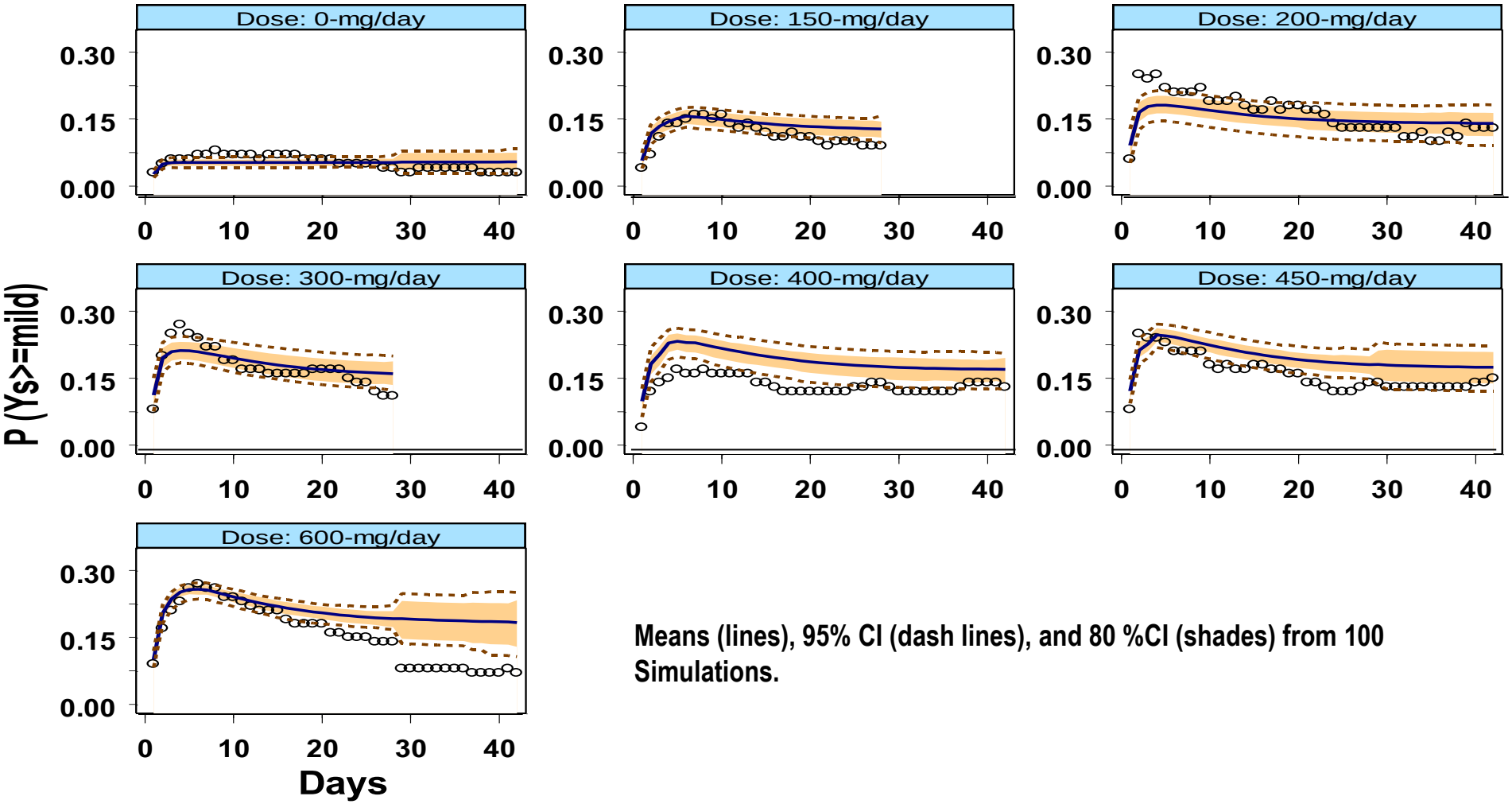
$$g[\,p(Y_{ij} \geq k \mid AE_i = 1, Y_{i,j-1} = h, \eta_i)] = \beta_{k,h} + f_p + f_d + \eta_i$$

$$f_p = PL \cdot (1 - e^{-k_{pbo} \cdot t}), \qquad f_d = \frac{E_{\max} \cdot TDE}{ED_{50} + TDE} \cdot TOL$$

$$TDE = D_{ij} \cdot (1 - e^{-k_{keo} \cdot t}), \qquad TOL = e^{-k_{tol} \cdot t} + T_p$$

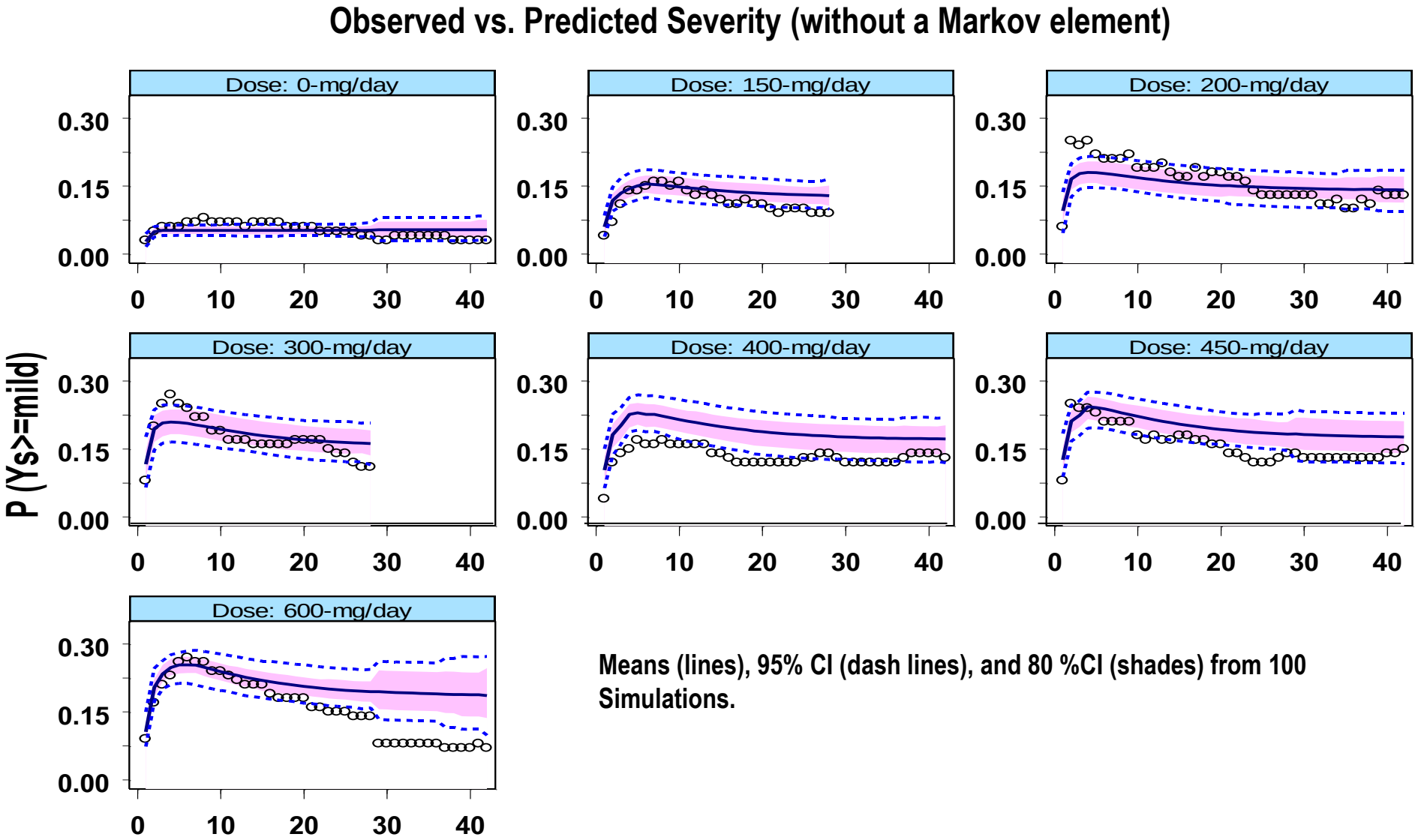
Results – *Visual predictive check*

Observed vs. Predicted (*Without* a Markov element)



Means (lines), 95% CI (dash lines), and 80 %CI (shades) from 100 Simulations.

Results - *Posterior predictive check*



Means (lines), 95% CI (dash lines), and 80 %CI (shades) from 100 Simulations.

Results - *Severity of somnolence*

- A mono-exponential function used for the placebo effect, and an E_{max} model for the drug effect
- The Model fit significantly improved by time-dependent effects of drug exposure and AE attenuation
- A Markov component further improved the model, yielding estimated parameters
  - ✓ ED_{50} : **300 mg/day**
  - ✓ $T_{1/2}$ for placebo effect : **0.23 day**
  - ✓ $T_{1/2}$ for time-dependent drug exposure effect: **1 .01 days**
  - ✓ $T_{1/2}$ for attenuated AE effect : **6.8 days**

Results – *Dropout events*

- Incidence-dropout
  - ✓ Placebo and drug effect parameters being almost identical to the case not modeling dropout events
- Conditional severity-dropout
  - ✓ Predicted dropout rate lowest for no AE and abruptly increased for severe somnolence group
  - ✓ Dropout probability for no AE as high as for mild AE group
  - ✓ No significant improvement in model fit by adding a dropout model

Conclusions

- Probability of somnolence incidence increased with the dose
- Significant time-dependent effects of drug exposure and AE attenuation
- The Markov model well described the time course of AE rates
- No significant dropout effect was found

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