Pregabalin Exposure-Adverse Event Analysis in Patients with Neuropathic Pain, Anxiety Disorder, or Partial Epilepsy

Pfizer Global Research and Development

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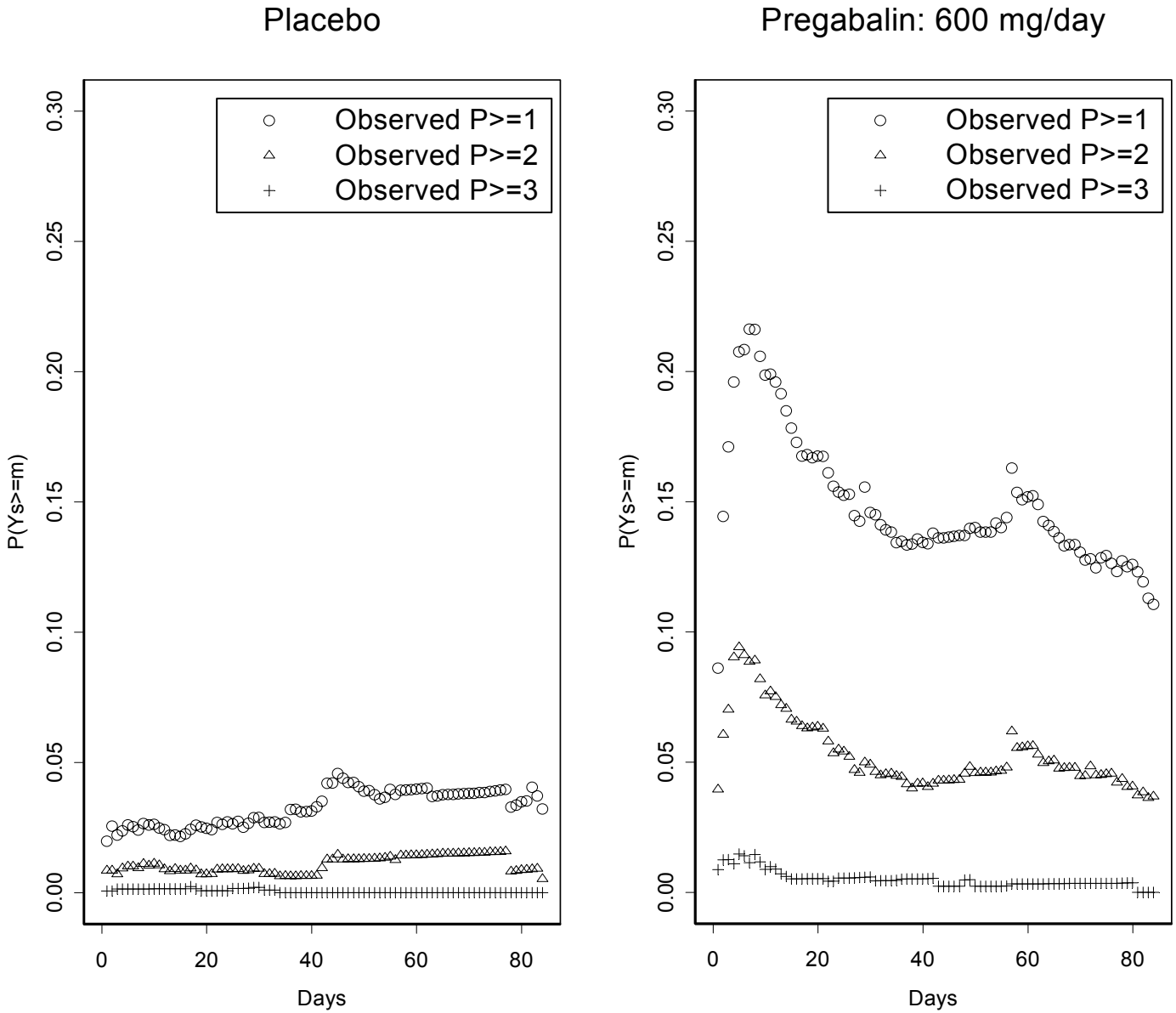
Objective

- To describe the pregabalin exposure-adverse event (dizziness) relationship.
- To present a feasible solution to modeling ordered categorical variables with biased estimates.

Data

- 194,087 observations collected in 4459 subjects from 17 studies
  - Randomized, Parallel-group, double-blind, placebo-controlled, multi-center, BID or TID
- Daily dizziness score
  - None ⇒ 0
  - Mild ⇒ 1
  - Moderate ⇒ 2
  - Severe ⇒ 3


Placebo
Pregabalin: 600 mg/day
Observed P>=1
Observed P>=2
Observed P>=3
P(Ys>=m)
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0
20
40
60
80
Days

Model building

The probability of adverse event was modeled with a proportional odds model in NONMEM.

$$g\left\{P(Y_S(t_j) \geq m)\right\} = \sum_{i=1}^{m} \beta_i + f_d + \eta_i$$

β_i = baseline set of probabilities of degrees of AE

f_d = function describing treatment effect

η_i = random individual effect assumed to be normally distributed with variance ω^2.

$g(x)$ = logit function

Drug Models

$$f(t_j) = \theta$$

$$f_d(D_{ij}, t_j) = \theta_{drg} \cdot D_{ij}$$

$$f_d(D_{ij}, t_j) = \frac{E\max \cdot D_{ij}^{\gamma}}{ED_{50}^{\gamma} + D_{ij}^{\gamma}}$$

Parameter estimates for severity of dizziness model

.Parameter Estimates For Severity of Dizziness Model

Parameter	Estimate (se)	
β_1	-12.6	(0.243)
β_2	-2.82	(0.025)
β_3	-4.63	(0.079)
E_{max}	2.51	(0.21)
ED_{50} (mg)	146.0	(9.55)
γ	5.30	(1.80)
ω^2	101.0	(6.08)

Bias Problem

- FOCE method in NONMEM calculates the mean of the impirical Bayes predictions of the ETA's and a corresponding p-value for a test that this mean (ETABAR) is zero.
- The ETABAR for this fit was 2.2 and was highly significantly different ($p<0.5x10^{-229}$) from zero.
- Model misspecification.
  - Assumption that $\eta_j \sim N_{iid}(0, \omega^2)$ is violated.

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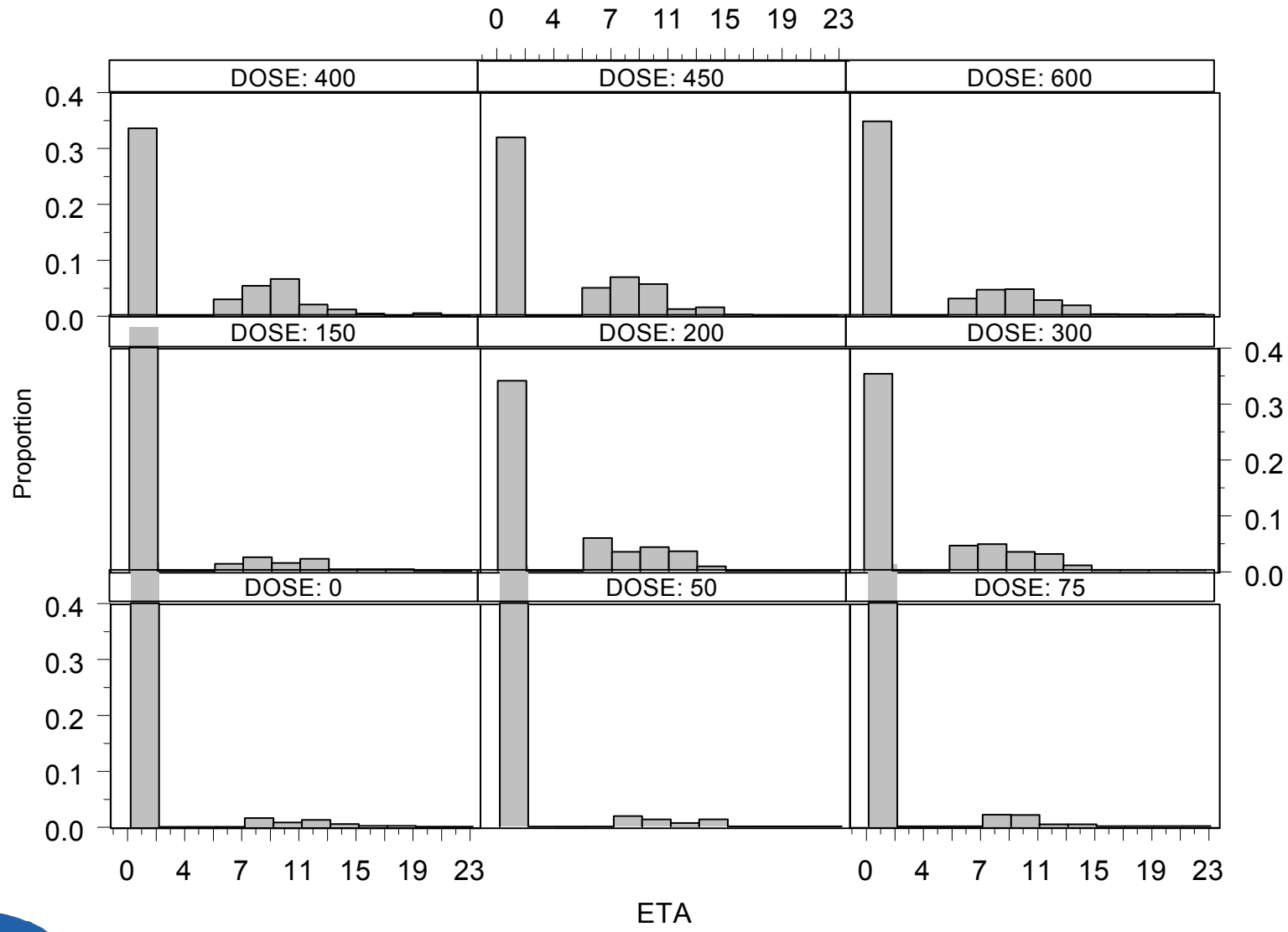
Histogram of ETA's - Dizziness



Solution

- Develop separate models (Kowalski et.al. JPP In Press)
  - Incidence of AE
    - P(AE)
  - Severity of AE given an AE has occurred
    - P(sev | AE)
- Use a two-stage model employing Baye's Rule to obtain unconditional severity probabilities.
  - $P(sev \cap AE) = P(sev \mid AE)P(AE)$
  - $P(sev) = P(sev \cap AE) + P(sev \cap \text{non-AE})$

$$P\left(Y_S(t_j)=m\right) \;=\; P\left(Y_S(t_j)=m \mid Y_{AE}=0\right)\cdot P\left(Y_{AE}=0\right) \;+\; P\left(Y_S(t_j)=m \mid Y_{AE}=1\right)\cdot P\left(Y_{AE}=1\right)$$

$$P\left(Y_S(t_j)=0 \mid Y_{AE}=0\right)=1 \qquad \textit{and} \qquad P\left(Y_S(t\ )>0 \mid Y_{AE}=0\right)=0$$

$\therefore$

$$P\left(Y_S(t_j)=0\right) \;=\; P\left(Y_{AE}=0\right)+P\left(Y_S(t_j)=0 \mid Y_{AE}=1\right)\cdot P\left(Y_{AE}=1\right)$$

$$P\left(Y_S(t_j)>0\right) \;=\; 0 \;+P\left(Y_S(t_j)>0 \mid Y_{AE}=1\right)\cdot P\left(Y_{AE}=1\right)$$

Incidence Model

- Denote indicator for AE
- Predict $P(Y_{AE}=0)$ and $P(Y_{AE}=1)$ as a function of dose and covariates

$$\log it[P(Y_{AE})] = \beta + \frac{E_{\max} \cdot D^{\gamma}}{ED_{50}^{\gamma} + D^{\gamma}}$$

Model Selection for incidence of dizziness

Base Model Description	MOF	ΔMOF
Base model (no treatment effect)	4687.756	
Linear dose dependant treatment effect	4325.286	-362.47
Emax model (i.e., $\gamma = 1$)	4273.581	-51.705
Sigmoid Emax (i.e., γ estimated)	4250.673	-22.908

MOF = minimum objective function value
ΔMOF = change in MOF relative to reference model

Full Model for Incidence of Dizziness

$$f(d)_j = \left(\frac{E_{\max} \cdot Dose^{\gamma}}{ED_{50}{}^{\gamma} + Dose^{\gamma}} \right) (1 + \theta_{SEX} \cdot SEX) \left(\frac{AGE_j}{48} \right)^{\theta_{AGE}} \left(\frac{WT_j}{78} \right)^{\theta_{WT}} (1 + \theta_{PAIN} \cdot PAIN)(1 + \theta_{EPL} \cdot EPL)(1 + \theta_{NTT}.NTT)$$

Efficient Screening of Covariates in Population Models

Using Wald's Approximation to the Likelihood Ratio Test

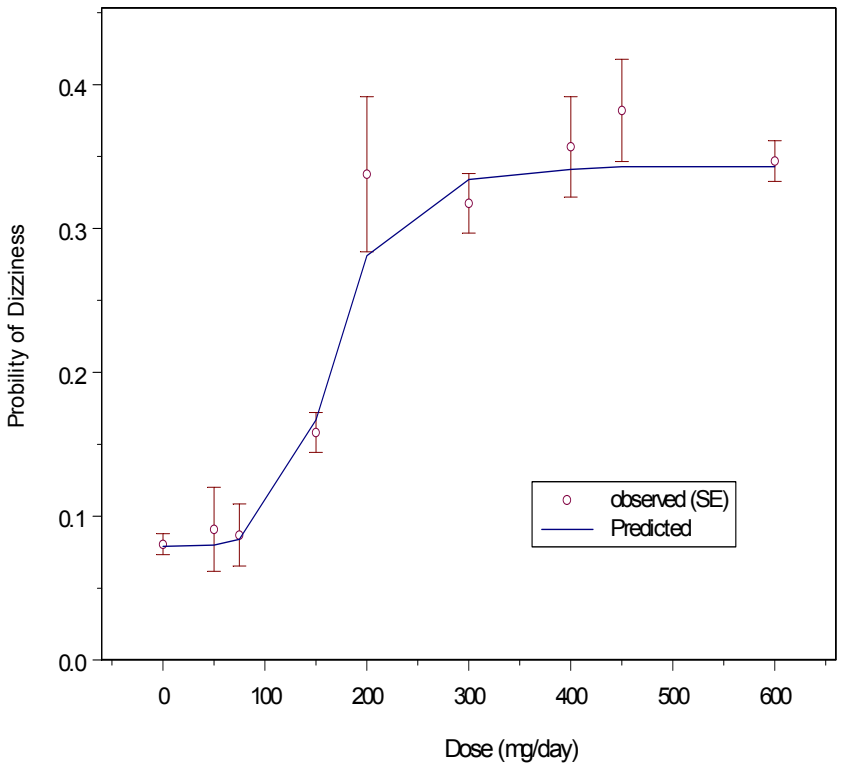
Kowalski & Hutmacher. JPP 2001;28:253-275.

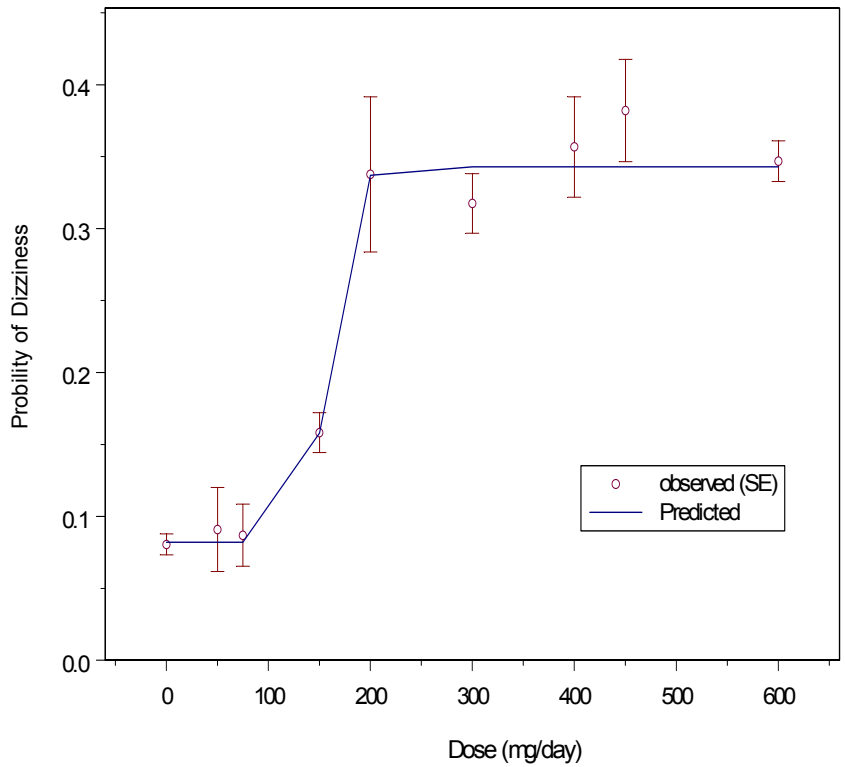
Parameter Estimates For Incidence of Dizziness

Parameters	Estimate (se)		
	Base model	Full model	Final model
MOF	4250.673	4220.269	4232.748
β	-2.42 (0.0895)	-2.45(0.096)	-2.43 (0.0894)
Emax	1.77 (0.101)	2.12 (0.18)	1.96 (0.113)
ED_{50} (mg)	153(7.35)	154 (9.75)	153 (5.56)
γ	15.3 (33.3)	4.64 (5.78)	9.08 (10.9)
θ_{SEX}	0	-0.202 (0.0467)	-0.199 (0.0441)
θ_{AGE}	0	-0.256 (0.0930)	0
θ_{WT}	0	-0.0655 (0.122)	0
θ_{PAIN}	0	-0.184 (0.065)	0
θ_{EPL}	0	0.0704 (0.0873)	0
θ_{NTT}	0	0.0671 (0.148)	0

Observed And Predicted Probabilities of Incidence For Dizziness

Base model





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The severity of adverse event was modeled with a proportional odds model in NONMEM.

$$g\left\{P(Y_S(t_j) \geq m \mid Y_{AE} = 1)\right\} = \sum_{i=1}^{m} \beta_i + f_d + \eta_i$$

β_i = baseline set of probabilities of degrees of AE

f_d = function describing treatment effect

η_i = random individual effect assumed to be normally distributed with variance ω^2.

$g(x)$ = logit function η_is

Drug Models

$$f_d\left(D_{ij}, t_j\right) = \theta_{drg} \cdot D_{ij} \qquad f_d\left(D_{ij}, t_j\right) = \frac{E\max \cdot D_{ij}^{\gamma}}{ED_{50}^{\gamma} + D_{ij}^{\gamma}}$$

$$f_d\left(D_{ij}, t_j\right) = \frac{E\,max\left[D_{ij}\left(1 - e^{-k_{eq}t_j}\right)\right]^{\gamma}}{ED_{50}^{\gamma} + \left[D_{ij}\left(1 - e^{-k_{eq}t_j}\right)\right]^{\gamma}}$$

$$f_d\left(D_{ij}, t_j\right) = \frac{E\max\left[D_{ij}\left(1 - e^{-k_{eq}t_j}\right)\right]^{\gamma}}{ED_{50}^{\gamma} + \left[D_{ij}\left(1 - e^{-k_{eq}t_j}\right)\right]^{\gamma}} \cdot \left(e^{-k_{tol}\cdot time} + \theta_{plateau}\right)$$

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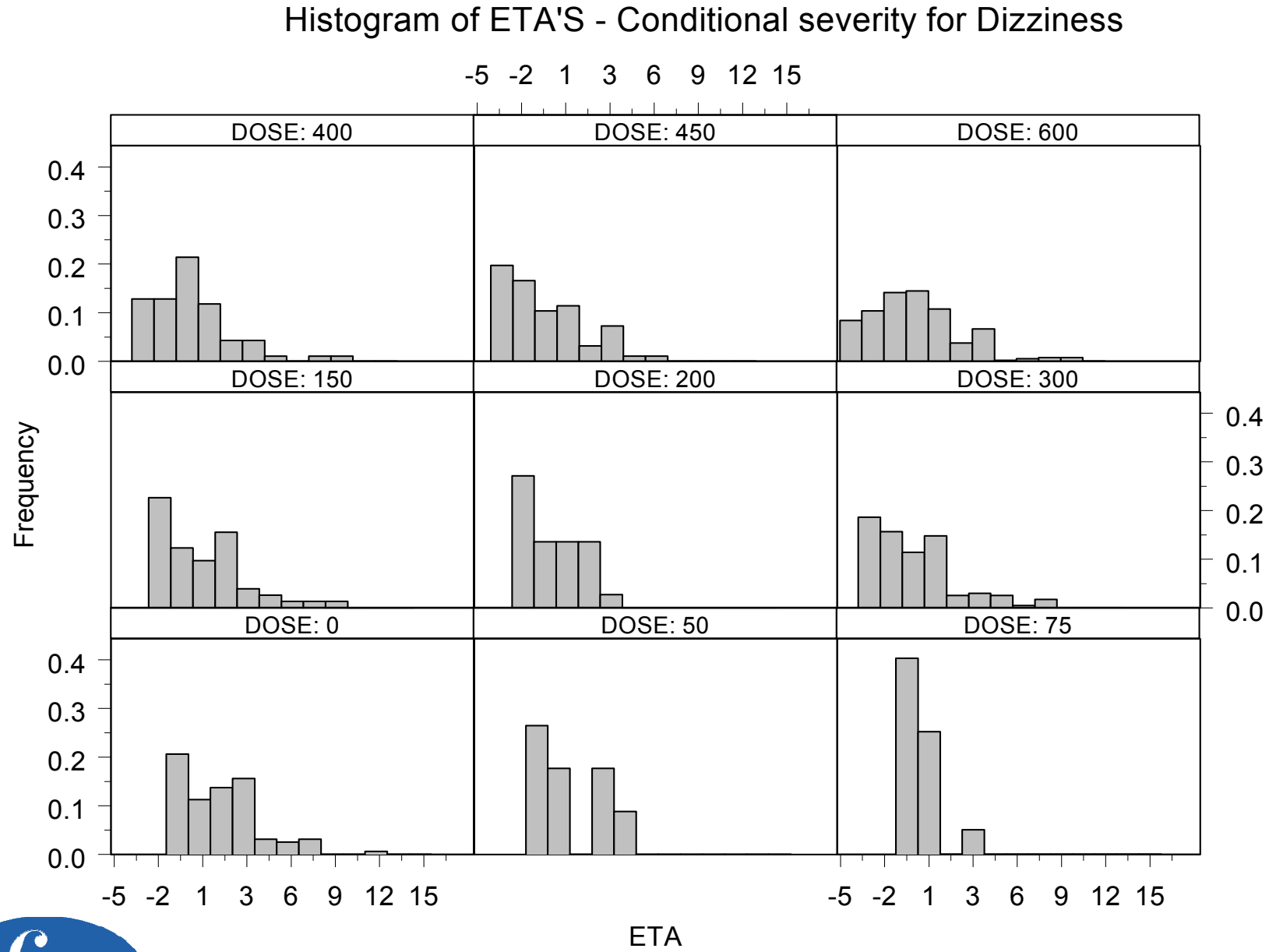
Table 1. Model Selection For Conditional Severity of Dizziness

Model Description	MOF	ΔMOF
Base Model (No Treatment Effect)	53016.946	
Linear Dose Dependent Treatment Effect	52827.611	-189.335
Emax Model (ie, $\gamma = 1$)	52724.530	-103.081
Sigmoid Emax (ie, γ Estimated)	52633.237	-91.293
Time-Dependent Exposure Effect	52622.765	-10.472
Exponential Time-Dependent Attenuation of Effect	51020.558	-1602.207
Exponential Time-Dependent Attenuation of Effect With Plateau	50802.899	-217.659

MOF = Minimum objective function value.

ΔMOF = Change in MOF relative to preceding model.


Histogram of ETA'S - Conditional severity for Dizziness
DOSE: 400
DOSE: 450
DOSE: 600
DOSE: 150
DOSE: 200
DOSE: 300
DOSE: 0
DOSE: 50
DOSE: 75
Frequency
ETA
-5 -2 1 3 6 9 12 15
0.0
0.1
0.2
0.3
0.4

Full Model for Conditional Severity of Dizziness

$$f(d)_j = \left(\frac{E_{\max} \cdot Dose^{\gamma}}{ED_{50}{}^{\gamma} + Dose^{\gamma}}\right)\left(1+\theta_{SEX}^{DRG} \cdot SEX\right)\left(\frac{AGE_j}{48}\right)^{\theta_{AGE}^{DRG}}\left(\frac{WT_j}{78}\right)^{\theta_{WT}^{DRG}}\left(1+\theta_{PAIN}^{DRG} \cdot PAIN\right)\left(1+\theta_{EPL}^{DRG} \cdot EPL\right)\left(1+\theta_{NTT}^{DRG}.NTT\right)$$

$$k_{tol\,j} = k_{tol} \cdot \left(1+\theta_{SEX}^{ktol} \cdot SEX\right)\left(\frac{AGE_j}{48}\right)^{\theta_{AGE}^{ktol}}\left(\frac{WT_j}{78}\right)^{\theta_{WT}^{ktol}}\left(1+\theta_{PAIN}^{ktol} \cdot PAIN\right)\left(1+\theta_{EPL}^{ktol} \cdot EPL\right)\left(1+\theta_{NTT}^{ktol}.NTT\right)$$

$$T_{p\,j} = Tp + \theta_{PAIN}^{Tp} \cdot PAIN + \theta_{EPL}^{Tp} \cdot EPL$$

PAIN: neuropathic pain indicator;

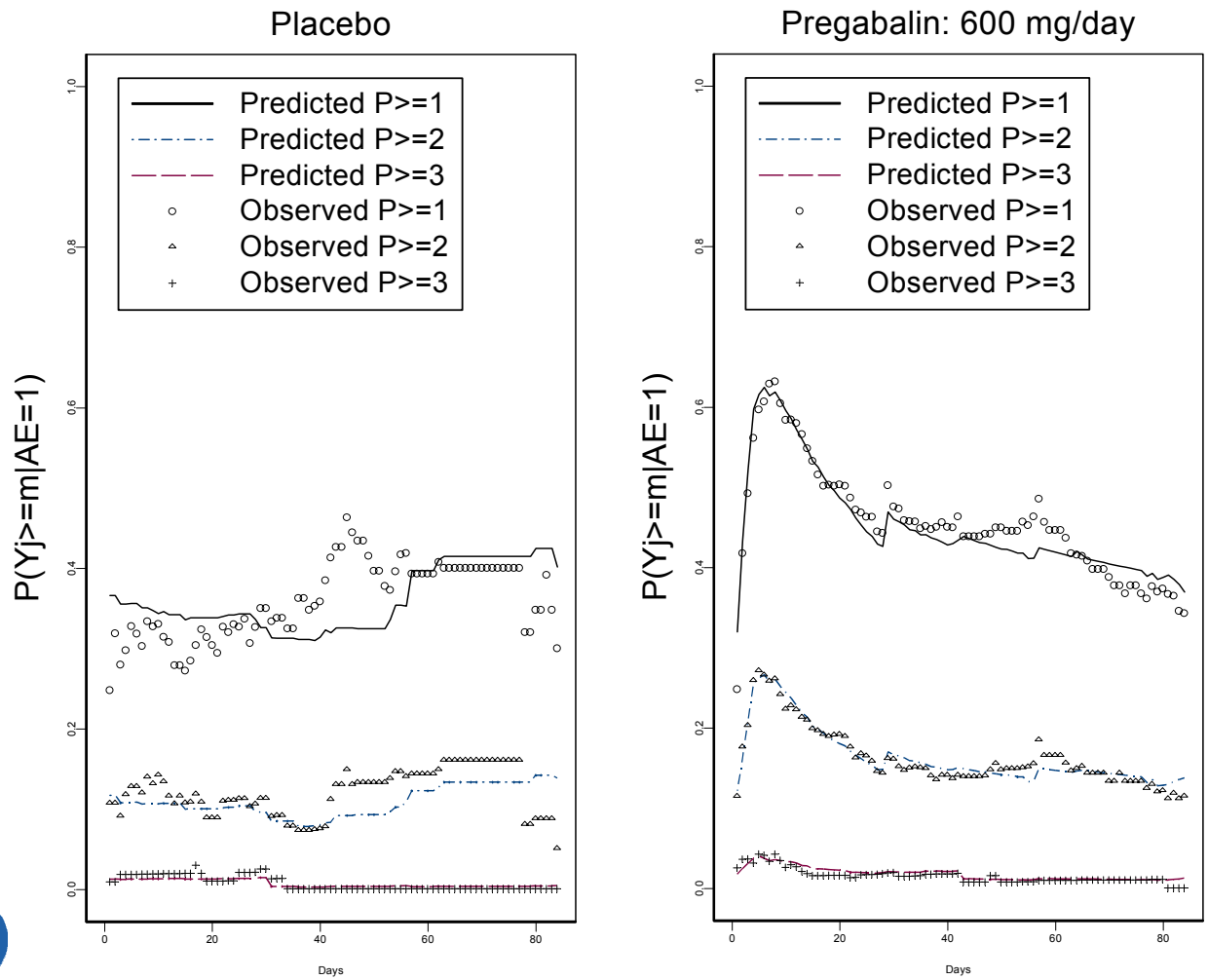
EPL: epilepsy indicator;

NTT: non-titration regimen indicator

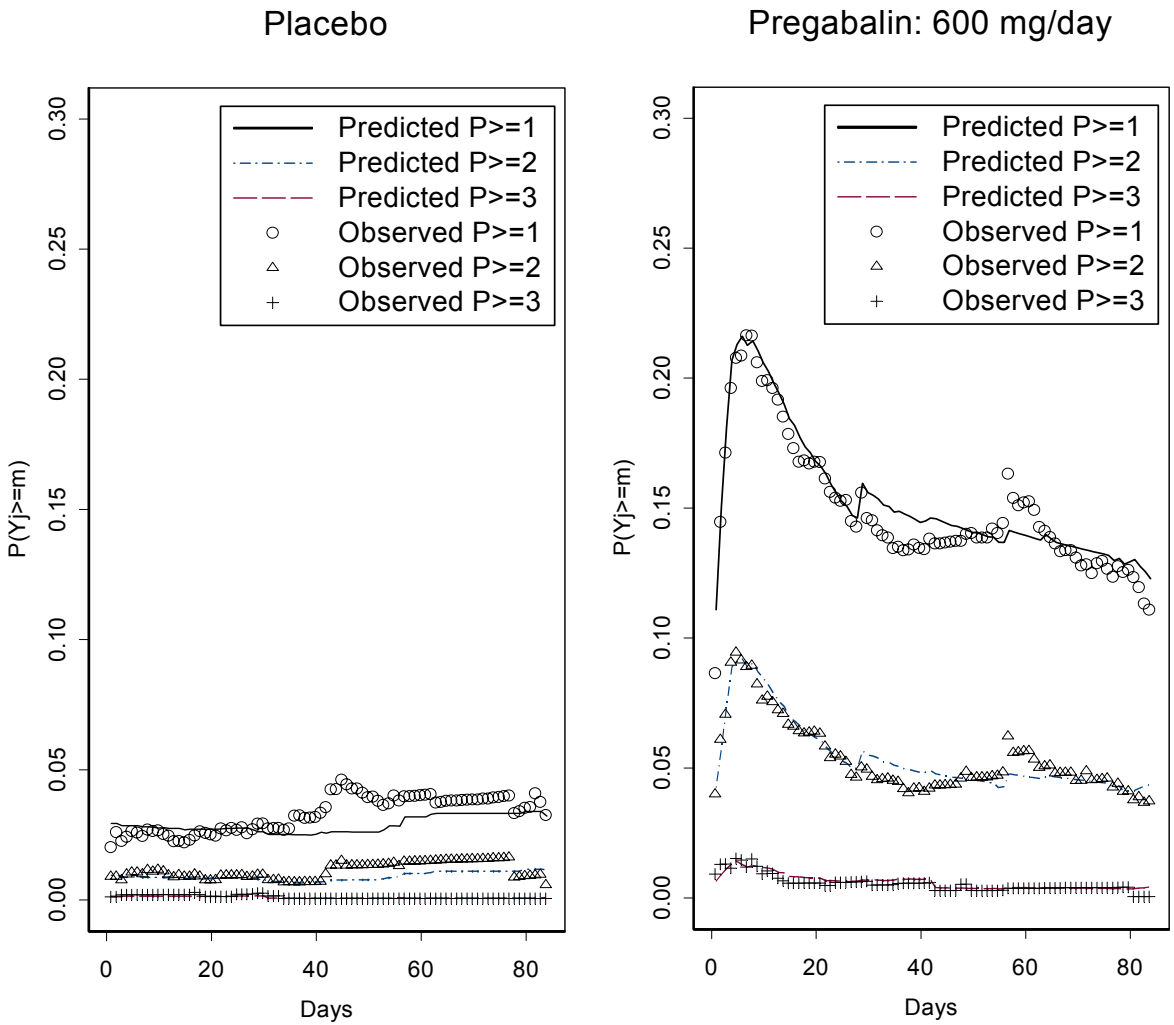
Parameter Estimates For Conditional Severity of Dizziness

Parameter	Estimate (se)		
	Base model	Full model	Final model
MOF	50799.045	49983.652	49994.926
β_1	-2.68(0.181)	-2.24(0.152)	-2.37(0.149)
β_2	-2.88(0.026)	-2.93(.0264)	-2.93(0.0264)
β_3	-4.58(0.0763)	-4.61(0.0766)	-4.61(0.0766)
Emax	5.62(0.551)	6.38(0.441)	6.17(0.412)
θ_{SEX}	0	-0.0000792(0.0384)	0
θ_{AGE}	0	-0.391(0.0615)	-0.487(0.0526)
θ_{WT}	0	0.446(0.0787)	0.416 (0.073)
θ_{PAIN}	0	-0.109(0.0691)	0
θ_{EPL}	0	-0.468(0.0305)	-0.454(0.0284)
θ_{NTT}	0	0.254(0.0725)	0.223 0.0639
ED50 (mg)	277(34.0)	187(19.2)	191(20.3)
γ	1.45(0.156)	1.50(0.162)	1.41(0.148)
Ke0 ($Days^{-1}$)	1.36(0.105)	0.700(0.0794)	0.741(0.0805)
Ktol ($Days^{-1}$)	0.0902(0.00548)	0.0378(0.00364)	0.0361(0.00282)
θ_{SEX}	0	-0.0285(0.0865)	0
θ_{AGE}	0	-0.821(0.137)	-0.828(0.126)
θ_{WT}	0	1.10(0.145)	1.06(0.131)
θ_{PAIN}	0	-0.711(0.0482)	-0.668(0.0382)
θ_{EPL}	0	-0.704(0.0388)	-0.690(0.04)
θ_{NTT}	0	3.35(0.529)	3.06(0.484)
Tp	0.651(0.0514)		
θ_{GAD}	0	0 FIX	0 FIX
θ_{PAIN}	0	-0.0980(0.0736)	0
θ_{EPL}	0	0.585(0.0957)	0.637(0.0943)
ω^2	8.70(0.453)	8.65(0.451)	8.76(0.456)

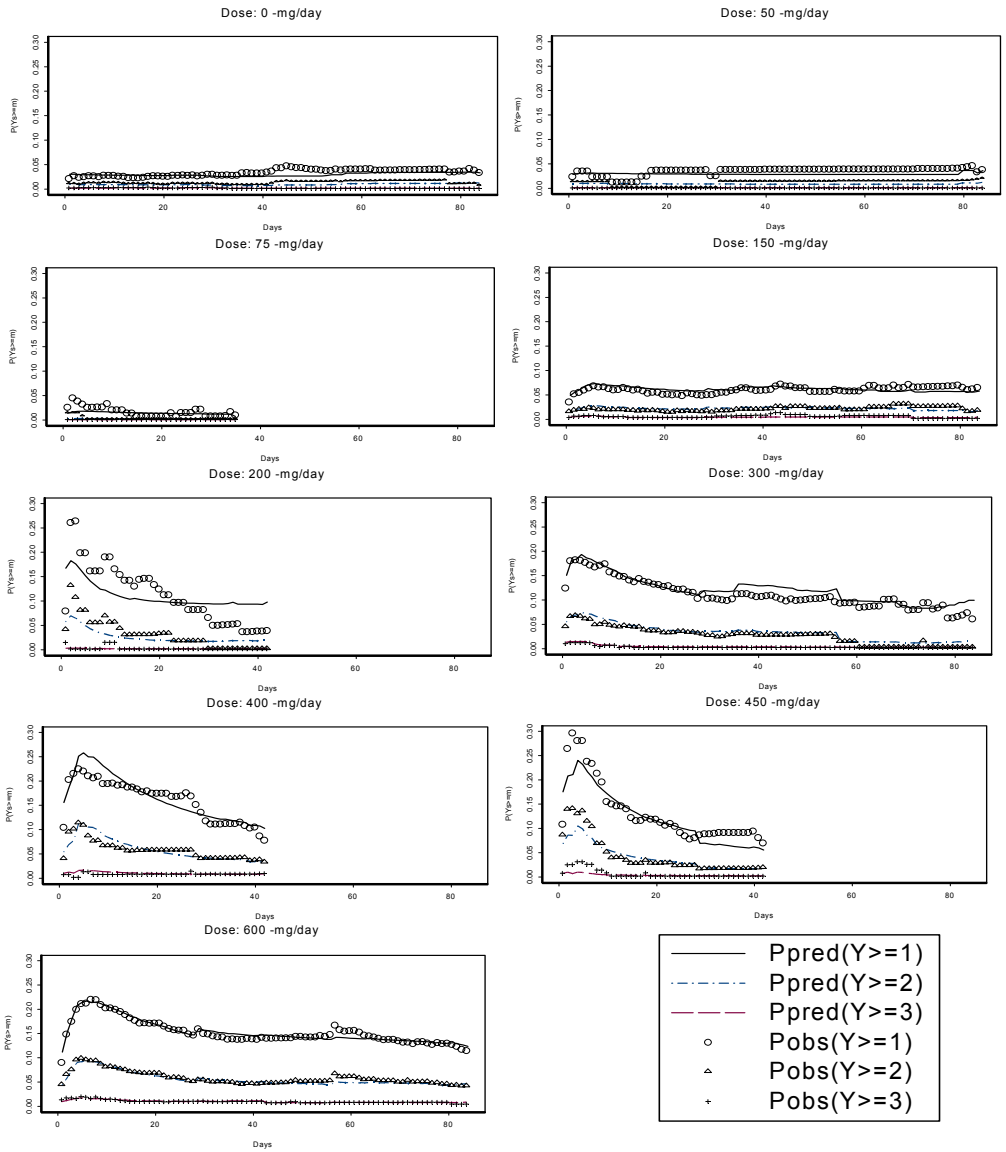
Observed And Predicted Conditional Probabilities For Dizziness



Observed And Predicted Unconditional Probabilities For Dizziness



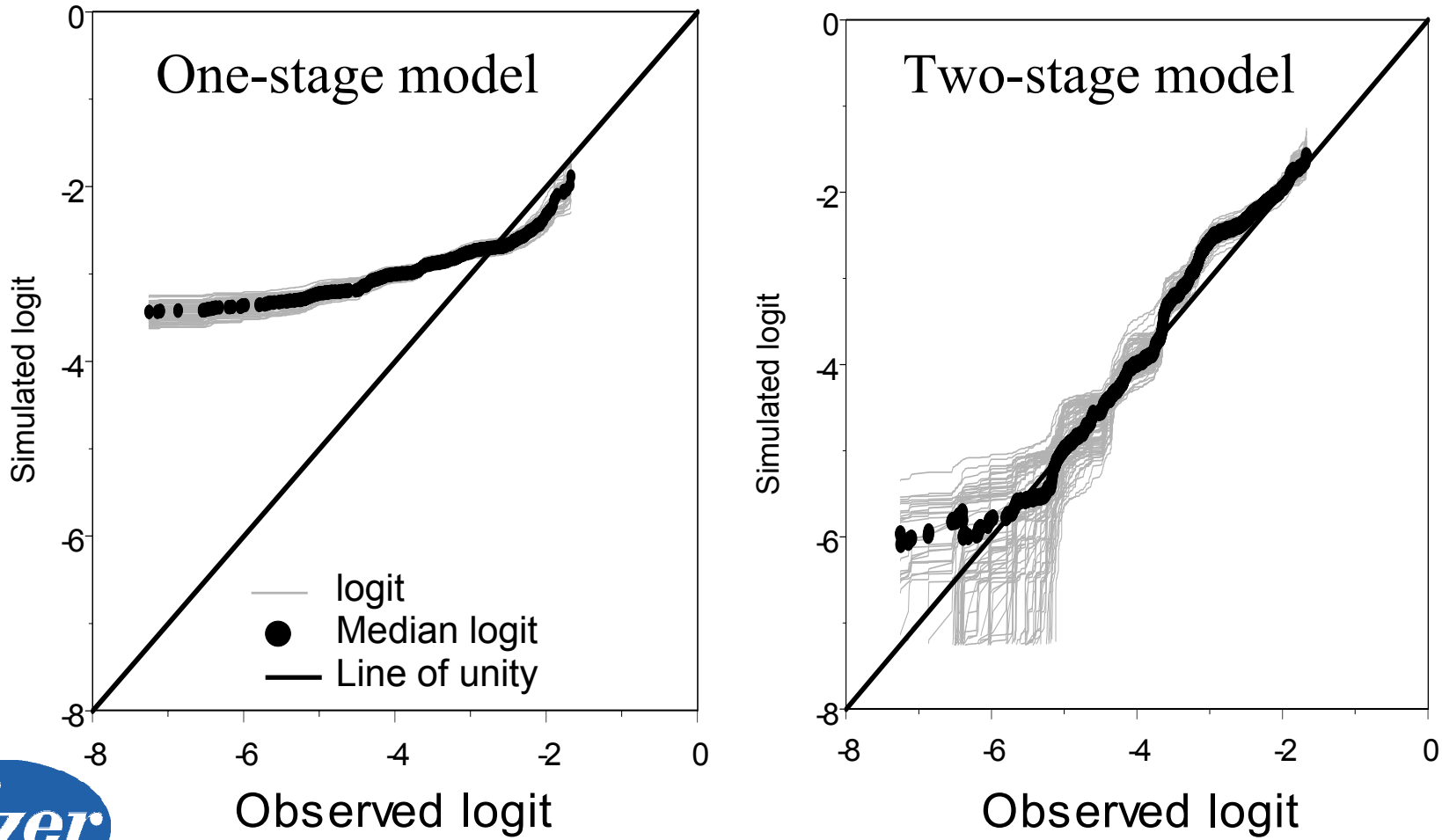
Observed And Predicted Unconditional Probabilities For Dizziness



Predictive Performance

- 100 data sets simulated for both the one stage and two stage models using their respective estimated parameters.
- Frequency based estimates of the logit for severity were calculated for the simulated and observed data sets.
- Quantile-quantile plots were constructed for each of the 100 datasets for the one stage and two stage approaches in comparison to the observed dataset.

Q-Q plots of observed and simulated logit-probability of unconditional AE



Conclusions

- Two stage model improves predictive performance.
- Increased ability to detect influential covariates