

**Title:** Exposure-Response Analysis for Spontaneously Reported Dizziness in Pregabalin Treated Patients with Generalized Anxiety Disorder.

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**Objectives:** To describe the pregabalin exposure-adverse event (dizziness) relationship in patients with Generalized Anxiety Disorder (GAD).

**Methods:** Separate models were developed for the incidence of adverse event and for the conditional severity (0=none, 1=mild, 2=moderate, 3=severe) of adverse event given that an adverse event has occurred in 6 clinical studies in patients with GAD. The incidence component was modeled using a nonlinear logistic regression model. The conditional severity component was modeled as an ordered categorical variable with proportional odds. The exposure response relationship was evaluated as a linear or Emax relationship. To describe the time-course of severity, time-dependent effects (placebo and tolerance) were also included. A Markov element was introduced to account for the correlation between adjacent observations.

**Results:** The dataset prepared for the 6 studies consisted of 47218 observations collected in 1630 patients. For the incidence model, a sigmoid Emax model best describes the dose-AE response relationship. Figure 1 shows the mean observed and predicted incidence by dose, including a summary of observed and predicted values with 95% CI obtained from a nonparametric bootstrap. For conditional severity, the model that best described the data was an Emax model with placebo time-course effect and a component that allows for an exponential attenuation of the AE severity. To account for the correlation between adjacent observations a Markov element was added to the model to relate the probability of the current AE score to the preceding observation. Observed and predicted conditional probability plots with the Markov model are presented in Figure 2. These plots demonstrate that the model fit is dramatically improved by incorporating the Markov element. To evaluate the predictive properties of the model, a posterior predictive check was performed. One hundred data sets were simulated from the final conditional severity model with and without the Markov element and the number of transitions between each possible transition were calculated. Figure 3 shows the distribution of the number of transitions for the

simulated dataset with or without the Markov element. The numbers of observed transitions for all combinations were contained within the predictive check distributions, while the number of transitions were extremely overestimated or underestimated without the Markov element.

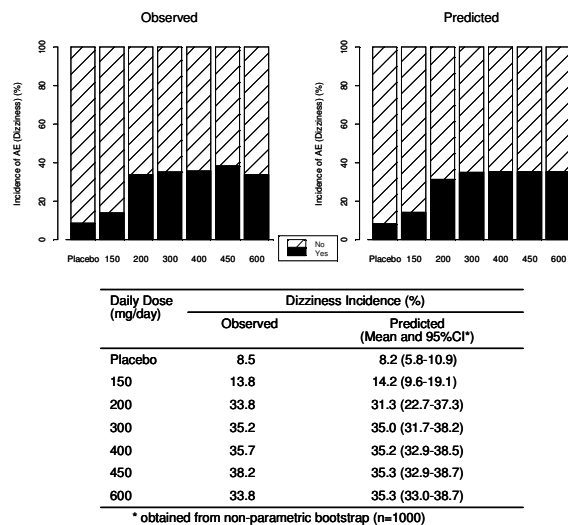


Figure 1. Mean Observed and Predicted Incidence of Dizziness

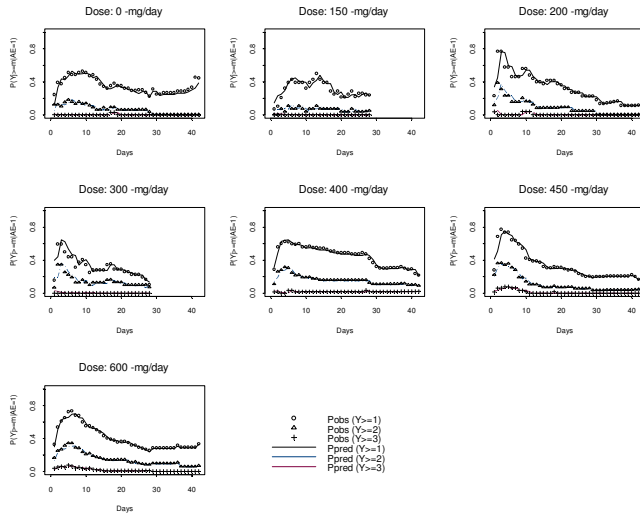
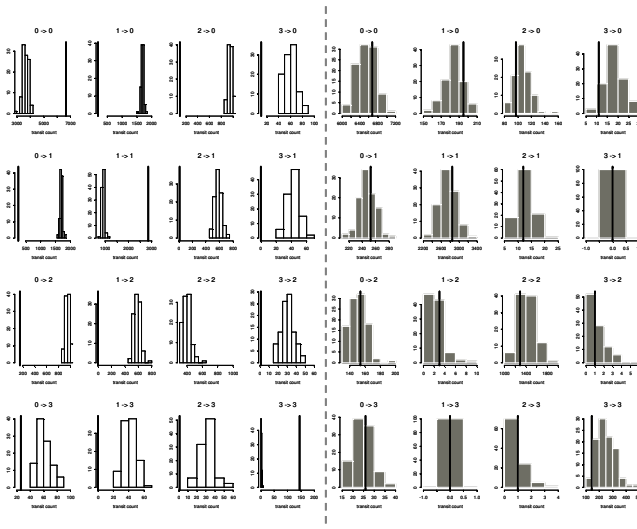


Figure 2. Observed and Predicted Conditional Probabilities for Dizziness by Dose Group (Markov)



The vertical line in each plot represents the observed number of transition in the original dataset. left side (clear): without the Markov element, right side (gray): with the Markov element

Figure 3 Distributions of the Number of the Different Transitions from the Posterior Predictive Check using 100 Simulated Datasets

**Conclusions:** The probability of experiencing dizziness during any day increases with pregabalin daily dose. The predicted mean incidence of dizziness was around 35 % at daily dose of 200 mg/day or greater, which was at least 2 fold higher compared to those at daily doses <150 mg/day. The most frequently reported severity was mild to moderate. The risk of mild or moderate dizziness increases up to 25 % within 1 week, but declines to around 7 % over 3 to 4 weeks. The proportional odds model including a time course of appearance and disappearance of adverse event could adequately describe the time-course of probability of dizziness. Incorporating a transition model including Markov elements improved the model fit and greatly improved the predictability of the time-course of probability of dizziness.