Exposure-Response Analysis of Longitudinal Adverse Event Data

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INTRODUCTION

Pregabalin is an alpha-2 delta (α2δ) ligand that has analgesic, anxiolytic, and anticonvulsant activity.

Exposure-response analyses play an important role in understanding efficacy as well as adverse events of a new chemical entity (NCE) in clinical development. In clinical studies conducted with pregabalin in patients with Generalized Anxiety Disorder (GAD), the 2 most prevalent adverse events (AE) reported by patients have been dizziness and somnolence.

OBJECTIVE

To develop a model to describe the pregabalin exposure-adverse event (dizziness) relationship (incidence and longitudinal response) in patients with Generalized Anxiety Disorder (GAD).

METHODS

Data

- 6 studies in patients with GAD.
- Randomized, double-blind, multiple dose (TID or BID regimens), placebo controlled, parallel-group multicenter studies.
- Durations ranged from 5 to 7 weeks including a 1 week titration and a 1 week taper phase.
- Individual dizziness scores recorded by patient diary on a daily basis using a 4-point ordered categorical scale (0=none, 1=mild, 2=moderate, 3=severe) were used for the analysis.

Two-Stage Model

A two-stage mixed effect logistic regression model was used[1] to fit the four-point ordered categorical AE scores. The first step modeled the probability of AE incidence, P(AE). The second step modeled the probability of each AE severity grade given that the patient had an AE, P(Y|AE). The unconditional probability of AE [P(Y)] were calculated by merging the incidence and severity probability predictions.

Incidence Model

The incidence of dizziness was modeled using a nonlinear logistic regression model given by the expression:

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

where AE_i takes a value of 1 if patient i has adverse event Y_{ij} at some time point during the study (ie, Y_{ij} >0 for some time t_j) and 0 otherwise. The parameter β denotes the logit for patients not on drug (placebo). The function f_d represents the function describing the exposure response relationship and can take linear or Emax forms.

Conditional Severity Model

The probability of severity was modeled with a proportional odds model given by the expression:

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

where

- Y_{ij} denotes the AE severity score for the i^{th} individual at time t_j.
- g[P(Y_{ij} m|AE_i=1, η_i)] denotes the logit function of the cumulative probability that the AE severity score is m = 1, 2, or 3 for patient i at time t_j given the patient has an AE at some time point during the study (ie, AE_i = 1),
- β_k specifies the baseline set of logit probabilities of the various degrees of adverse event severity,
- f_p is a function describing placebo effect,
- f_d is a function describing treatment effect which may take on various structures as describe for the proportional odds model,
- η_i is a random individual effect determining the individual sensitivity assumed to be normally distributed with variance ω^2 and mean zero.
- Drug exposure was based on the titrated daily dose of pregabalin.

Time Dependent Effects

- **Placebo**

$$PCB=BSL\cdot\left(1-e^{-k_{pbo}\cdot t}\right)$$

BSL = baseline
k_{pbo} = rate constant for time-course of placebo effect.

- **Drug Exposure**

$$TDE=D_{ij}\cdot\left(1-e^{-k_{eo}\cdot t_j}\right)$$

D_{ij} = actual dose that i^{th} patient received at t_j.
k_{eo} = rate constant at which the probability of dizziness reaches its maximum.

- **Attenuation of Response**

$$TOL_j+T_p$$

where $TOL_j=e^{-k_{toi}\cdot t_j}$,
k_{toi} = rate constant of AE decline
T_p = plateau of tolerance effect.

Markov Element

A Markov transition model was used to account for correlation between neighboring AE observations. The model estimates the cumulative probabilities of having a certain adverse event score given the preceding observation.

Unconditional Severity Probability Distribution

The unconditional adverse event probabilities can be obtained by integrating the joint likelihood over the possible outcomes for AE status. Since AE status is a dichotomous variable the marginal (unconditional) severity probability distribution is obtained by summing the joint probabilities:

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

These unconditional severity probabilities permit one to make inference to the whole population regardless of AE status. The unconditional cumulative probabilities can be obtained by summing the individual severity probabilities defined by Equation above to obtain:

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

Model Evaluation/Predictive Check

- The performance of the final model was evaluated by simulating data (n=100) using its parameter estimates (fixed and random effects). The AE incidence was simulated for each subject using the incidence parameters from incidence model, then the time-course of unconditional severity probability by dose was calculated from the simulated conditional severity data with/without Markov element and compared with observed data (Fig 4).
- The distribution of the number of the different transitions was also counted from the simulated data to evaluate the model performance with/without Markov element (Fig 5).

CONCLUSION

- The probability of experiencing dizziness during any day increases with pregabalin daily dose. The predicted mean incidence of dizziness was around 14.2 % at daily doses of 150 mg/day, which was at least 2 fold lower than at doses of 200 mg/day.
- The most frequently reported severity of dizziness was mild to moderate. For doses exceeding 200 mg/day, the risk for mild or moderate dizziness plateaus at 25 % within 1 week, and declines to around 7 % over 3 to 4 weeks.
- The proportional odds model incorporating a Markov element could well describe the time-course of probability of dizziness and well predict the time-course of probability of dizziness.

RESULTS

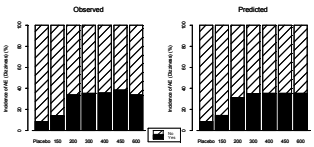
Incidence Model

Table 1. Final Parameter Estimates

Parameter Estimates	Estimate (se)	
β	-2.38	(0.2)
Emax	1.77	(0.193)
ED_{50} (mg)	159	(10.5)
γ	14.0	(13.6)

Sigmoid Emax model best describes the dose-AE response relationship although the parameter estimate for sigmoidicity was relatively large and not precisely estimated (14 ± 13.6: mean ± standard error).

Fig 1. Mean Incidence of Dizziness (Observed and Predicted)



Daily Dose (mg/day)	Dizziness Incidence (%)	
	Observed	Predicted (Mean and 95%CI*)
Placebo	8.5	8.2 (6.8-10.9)
150	13.8	14.2 (9.6-19.1)
200	33.8	31.3 (22.7-37.3)
300	35.2	35.0 (31.7-38.2)
400	35.7	35.2 (32.9-38.5)
450	38.2	35.3 (32.9-38.7)
600	33.8	35.3 (33.0-38.7)

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

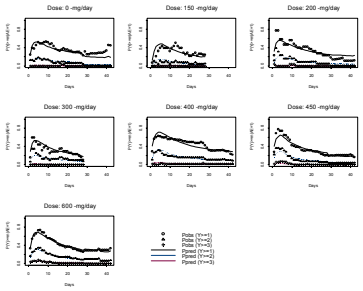
Conditional Severity Model

Table 2. Parameter Estimates for Conditional Severity

Parameter	Estimate (se)	
β_1	-6.44	(0.176)
β_2	-2.66	(0.026)
β_3	-4.56	(0.076)
Emax	1.97	(0.332)
ED_{50} (mg)	126	(45.5)
γ	1 (fix)	
BSL	3.21	(0.52)
K_{pbo} ($Days^{-1}$)	0.85	(0.129)
K_{eo} ($Days^{-1}$)	0.0625	(0.00777)
T_p	0.975	(0.208)
ω^2	6.61	(0.551)

Emax model was selected with placebo time-course effect and a component that allows for an exponential attenuation of the AE severity.

Fig 2. Observed and Predicted Conditional Probabilities for Dizziness

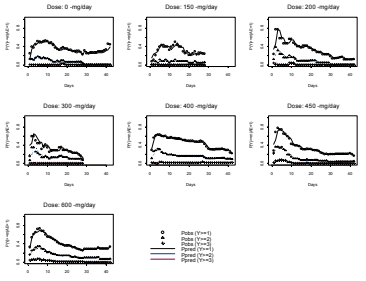


Markov Model

Table 3. Parameter Estimates for Conditional Severity (Markov)

Parameter	Estimate (se)	
$\beta_{1,\ psn=0}$	-3.02	(0.289)
$\beta_{2,\ psn=0}$	-1.06	(0.0652)
$\beta_{3,\ psn=0}$	-2.05	(0.185)
$Emax_{\ psn=0}$	6.21	1.91
$\beta_{1,\ psn=1}$	2.64	(0.0872)
$\beta_{2,\ psn=1}$	-9.81	(0.586)
$\beta_{3,\ psn=1}$	-20 (fix)	
$Emax_{\ psn=1}$	-6.00	(1.87)
$\beta_{1,\ psn=2}$	2.5	(0.132)
$\beta_{2,\ psn=2}$	-0.128	(0.0368)
$\beta_{3,\ psn=2}$	-9.94	1.01
$Emax_{\ psn=2}$	-6.17	(1.96)
$\beta_{1,\ psn=3}$	2.49	(0.349)
$\beta_{2,\ psn=3}$	0 (fix)	
$\beta_{3,\ psn=3}$	-0.0961	(0.0957)
$Emax_{\ psn=3}$	-4.74	(2.68)
ED_{50} (mg)	226	(148)
γ	1 (fix)	
BSL	2.72	(0.568)
K_{pbo} ($Days^{-1}$)	1.36	(0.412)
K_{eo} ($Days^{-1}$)	0.0778	(0.0164)
T_p	-0.443	(0.0901)
ω^2	0.129	(0.0814)

Fig 3. Observed and Predicted Conditional Probabilities for Dizziness with Markov Element

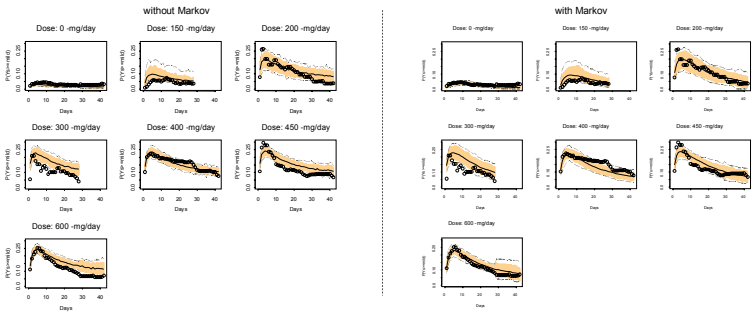


Markov element was introduced to account for the correlation between neighboring observations, and it improved the model fit and the predictability of the time-course of probability of dizziness.

Note) Emax $_{psn=k}$ specifies the magnitude of the maximum exposure effect which depended on the previously observed severity. ED_{50} the pregabalin dose (mg) producing 50 % of maximum effect. The rate constant for placebo effect (K_{pbo}) describing the appearance of dizziness with initiation of treatment was 1.36 day^{-1} which corresponds to a half life of appearance of 0.51 day. The rate constant for attenuation of dizziness (K_{eo}) was 0.0778 $days^{-1}$ which corresponds to a half-life of 8.9 days.

Simulations

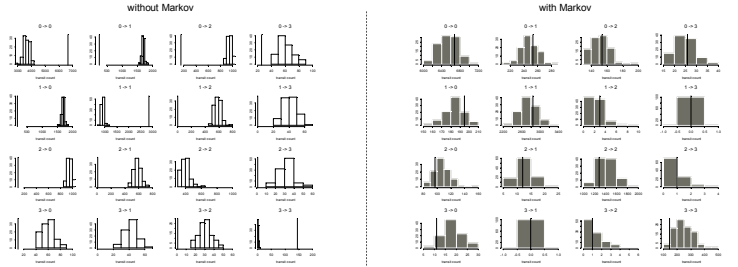
Fig 4. Observed vs Simulated Probabilities of Unconditional Severity of Dizziness (≥mild)



The mean probabilities of dizziness (≥mild) with and without Markov model confidence intervals (80% CI shaded, 95% CI dash line) were compared with the observed data. The simulation of unconditional severity of dizziness well described the observed data across doses with both models, although there was a trend to slightly overestimate with the model without Markov element . The simulation results for ≥moderate and ≥severe dizziness also demonstrated a good performance.

Predictive Check

Fig 5. Distributions of the Number of the Different Transitions



The vertical line in each plot represents the observed number of transition in the original dataset.

The numbers of observed transitions for all combinations were contained within the predictive check distributions from the Markov model, indicating that that the model with Markov element is able to describe the spontaneously reported adverse event scores over time accurately on the individual levels as well as on the population level.

REFERENCES

1. Kowalski KG, McFadyen L, Hutmacher MM, Frame B, Miller R. *A two-part mixture model for longitudinal adverse event severity data.* J Pharmacokinet Pharmacodyn, 2003. **30**(5): p. 315-36.
2. Ito K, Hutmacher MM, Liu J, Qiu R, Frame B, Miller R. *Exposure-response Analysis for Spontaneously Reported Dizziness in Pregabalin-treated Patient With Generalized Anxiety Disorder.* Clin Pharmacol Ther 2008; advance online publication, February 6, 2008