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

Lay Ahyoung Lim¹, Raymond Miller²,³, Kyungsoo Park¹

¹ College of Medicine, Yonsei University, Seoul, Korea
² Pfizer Global R&D, New London, CT, USA
³ Current affiliation: Daiichi Sankyo Co., Ltd., Edison, NJ USA
Outline

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

- Pregabalin (LYRICA®)
  - $\alpha_2$-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

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

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

## Study Scheme

<table>
<thead>
<tr>
<th>Period</th>
<th>Pretreatment</th>
<th>Double-Blind Treatment (daily dosing)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… mg</td>
</tr>
<tr>
<td></td>
<td>All Treatment Groups</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

0 capsule

Week

0 1 2~5 6 7

6-day titration 6-day taper

AE recording: Daily (Somnolence Score)
### Study Data

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Number of Subjects</th>
<th>Number of Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>AE=0</td>
</tr>
<tr>
<td>0</td>
<td>484</td>
<td>427</td>
</tr>
<tr>
<td>150</td>
<td>210</td>
<td>161</td>
</tr>
<tr>
<td>200</td>
<td>77</td>
<td>53</td>
</tr>
<tr>
<td>300</td>
<td>91</td>
<td>59</td>
</tr>
<tr>
<td>400</td>
<td>185</td>
<td>139</td>
</tr>
<tr>
<td>450</td>
<td>178</td>
<td>125</td>
</tr>
<tr>
<td>600</td>
<td>405</td>
<td>269</td>
</tr>
<tr>
<td>total</td>
<td>1630</td>
<td>1233</td>
</tr>
</tbody>
</table>

† Numbers in parenthesis indicate dropout by adverse events
Objective

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

Dose: 0-mg/day

Dose: 150-mg/day

Dose: 200-mg/day

Dose: 300-mg/day

Dose: 400-mg/day

Dose: 450-mg/day

Dose: 600-mg/day

Days

P (Ys≥m)

Pobs (Y≥ 1)

Pobs (Y≥ 2)

Pobs (Y≥ 3)
Methods – Model building

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

- Logistic Regression

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

- \(AE_i\) : AE response for subject \(i\)
  - \(AE_i = 1\) → an AE at any time during the treatment
  - AE recorded only once for each subject (0 or 1)
    → **No inter-individual random effect**

- \(\beta\) : 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 \( E_{\text{max}} \) model
    \[
    f_d(D_i) = \frac{E_{\text{max}} \cdot D_i}{ED_{50} + D_i}
    \]
  - Sigmoid \( E_{\text{max}} \) model
    \[
    f_d(D_i) = \frac{E_{\text{max}} \cdot D_i^\gamma}{ED_{50}^\gamma + D_i^\gamma}
    \]
  - \( D_i \): 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)
- \( \beta_k \): Baseline set of logit probabilities
  \[ \begin{align*}
  \beta_1 &= \theta_1 &: Y \geq 1 \\
  \beta_2 &= \beta_1 + \theta_2 &: Y \geq 2 \\
  \beta_3 &= \beta_2 + \theta_3 &: Y \geq 3
  \end{align*} \]
- \( f_p \): Placebo effect
- \( f_d \): Treatment effect
- \( \eta \): Inter-individual random random effect
Methods - Conditional severity model

\[ f_p = PL \cdot (1 - e^{-k_{pbo}t}) \]

\[ f_d = \frac{E_{\text{max}} \cdot TDE}{ED_{50} + TDE} \cdot TOL \]

\[ TDE = \text{Time-dependent exposure effect} \]
\[ = D_{ij} \cdot (1 - e^{-k_{e0}t_j}) \]

\[ TOL = \text{Tolerance effect with plateau} \]
\[ = e^{-K_{tol}t_j} + T_p \]

\[ D_{ij} : \text{Dose at } t_j \text{ for subject } i \]
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 \( \beta_k \) given \( Y_{i,j-1} = h \) \((h = 0, 1, 2, 3)\) such that

\[ \beta_{1,h} = \theta_{1,h} \]
\[ \beta_{2,h} = \beta_{1,h} + \theta_{2,h} \]
\[ \beta_{3,h} = \beta_{2,h} + \theta_{3,h} \]
\[ E_{\text{max},h} = \theta_{4,h} \]
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, \( P_{DRP} = \theta_i \) (\( i = 0, 150, \ldots, 600 \)mg)
- \( QUIT \): 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

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

\[ P_{DRP1} = P_{DRP10} \cdot P_{DRP11} \]

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

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

- \( P_{DRP1} \): Probability of dropout (QUIT = 1) at \( t \) (days)
- \( P_{DRP10} \): Probability of no-dropout up to \( t_p \) (days) (= previous observation time)
- \( P_{DRP11} \): Probability of dropout at \( t_e \) (days) (= elapsed time since \( t_p \))
- \( P_{DRP0} \): Probability of no-dropout (QUIT = 0) up to \( t \) (days)
- \( \lambda_m \): 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*

Observed vs. Predicted

Incidence model

![Graph showing observed vs. predicted incidence rates for different dose levels (0, 150, 200, 300, 400, 450, 600 mg) for Yes and No categories.](image-url)
## Results - *Incidence model*

### Observed vs. Predicted

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

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

### Final model parameters

<table>
<thead>
<tr>
<th></th>
<th>$E_{\text{max}}$ model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>-2.01</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>1.48</td>
</tr>
<tr>
<td>$ED_{50}$ (mg)</td>
<td>99.5</td>
</tr>
</tbody>
</table>

\[
g[p(AE = 1)] = \beta + \frac{E_{\text{max}} \cdot D_i}{ED_{50} + D_i}
\]
Results - *Incidence model*

- The $E_{\text{max}}$ 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

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

- **Dose: 0-mg/day**
- **Dose: 150-mg/day**
- **Dose: 200-mg/day**
- **Dose: 300-mg/day**
- **Dose: 400-mg/day**
- **Dose: 450-mg/day**
- **Dose: 600-mg/day**

<table>
<thead>
<tr>
<th>$P(Y_j \geq \text{mlAE}=1)$</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 10 20 30 40</td>
<td>0 10 20 30 40</td>
</tr>
</tbody>
</table>

- $O_{obs}$ ($Y \geq 1$)
- $O_{obs}$ ($Y \geq 2$)
- $O_{obs}$ ($Y \geq 3$)
- $P_{pred}$ ($Y \geq 1$)
- $P_{pred}$ ($Y \geq 2$)
- $P_{pred}$ ($Y \geq 3$)

---

PAGE 2010, 06.10.2010
Results - Conditional severity model

Observed vs. Predicted (With a Markov element)

<table>
<thead>
<tr>
<th>Dose: 0-mg/day</th>
<th>Dose: 150-mg/day</th>
<th>Dose: 200-mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose: 300-mg/day</th>
<th>Dose: 400-mg/day</th>
<th>Dose: 450-mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose: 600-mg/day</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

\[
P(Y_j \geq \text{mlAE}=1)
\]

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{1/2, Kpho}$ (day)</td>
<td>0.23</td>
</tr>
<tr>
<td>$T_{1/2, Ktol}$ (day)</td>
<td>6.8</td>
</tr>
<tr>
<td>$T_p$</td>
<td>-0.437</td>
</tr>
<tr>
<td>$T_{1/2, Ke0}$ (day)</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Days
# Results - Conditional severity model

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{1,h=0}$</td>
<td>-5.500</td>
</tr>
<tr>
<td>$\beta_{2,h=0}$</td>
<td>-6.460</td>
</tr>
<tr>
<td>$\beta_{3,h=0}$</td>
<td>-3.050</td>
</tr>
<tr>
<td>$E_{\text{max},h=0}$</td>
<td>12.200</td>
</tr>
<tr>
<td>$\beta_{1,h=1}$</td>
<td>-0.034</td>
</tr>
<tr>
<td>$\beta_{2,h=1}$</td>
<td>-9.814</td>
</tr>
<tr>
<td>$\beta_{3,h=1}$</td>
<td>-11.030</td>
</tr>
<tr>
<td>$E_{\text{max},h=1}$</td>
<td>-2.040</td>
</tr>
<tr>
<td>$\beta_{1,h=2}$</td>
<td>-0.041</td>
</tr>
<tr>
<td>$\beta_{2,h=2}$</td>
<td>-0.274</td>
</tr>
<tr>
<td>$\beta_{3,h=2}$</td>
<td>-9.743</td>
</tr>
<tr>
<td>$E_{\text{max},h=2}$</td>
<td>-0.023</td>
</tr>
</tbody>
</table>

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

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

\[
TDE = D_{ij} \cdot (1 - e^{-k_{pbo}t}), \quad TOL = e^{-k_{tol}t} + T_p
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{1h=3}$</td>
<td>2.650</td>
</tr>
<tr>
<td>$\beta_{2,h=3}$</td>
<td>2.243</td>
</tr>
<tr>
<td>$\beta_{3,h=3}$</td>
<td>-3.407</td>
</tr>
<tr>
<td>$E_{\text{max},h=3}$</td>
<td>-0.626</td>
</tr>
<tr>
<td>$ED_{50}$ (mg)</td>
<td>300</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>1 (fix)</td>
</tr>
<tr>
<td>BSL</td>
<td>3.190</td>
</tr>
<tr>
<td>$T_{1/2, , \text{Kpbo}}$ (day)</td>
<td>0.23</td>
</tr>
<tr>
<td>$T_{1/2, , \text{Ktol}}$ (day)</td>
<td>6.8</td>
</tr>
<tr>
<td>$T_p$</td>
<td>-0.437</td>
</tr>
<tr>
<td>$T_{1/2, , \text{Ke0}}$ (day)</td>
<td>1.01</td>
</tr>
<tr>
<td>$\omega^2$</td>
<td>0.142</td>
</tr>
</tbody>
</table>
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*

Observed vs. Predicted Severity (without a Markov element)

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 $E_{\text{max}}$ 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
  - $ED_{50} : 300 \text{ mg/day}$
  - $T_{1/2}$ for placebo effect : $0.23 \text{ day}$
  - $T_{1/2}$ for time-dependent drug exposure effect: $1.01 \text{ days}$
  - $T_{1/2}$ for attenuated AE effect : $6.8 \text{ days}$
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
Acknowledgements

• Prof. Kyungsoo Park, Yonsei University, Seoul, Korea
• Dr. Raymond Miller, Daiichi Sankyo Co., Ltd., Edison, NJ, USA
• PMECK
  (Pfizer Modeling & Simulation Education Center in Korea)
• Department of Pharmacology, Yonsei University
• PAGE