



# Pharmacodynamic Comparison of Pregabalin and Gabapentin

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## Background

- Pregabalin was recently approved by the FDA
  - Adjunctive therapy for adult patients with partial-onset seizures
  - Management of neuropathic pain associated with diabetic peripheral neuropathy
  - Postherpetic neuralgia
- Gabapentin originally approved in the UK in 1993; marketed in >100 countries for use in
  - Epilepsy
  - Neuropathic pain disorders
- Pregabalin and gabapentin bind to the  $\alpha_2\text{-}\delta$  protein, an auxiliary subunit of voltage-gated  $\text{Ca}^{++}$  channels in CNS neuronal tissues<sup>1</sup>

<sup>1</sup>Gee NS, et al. *J Biol Chem.* 1996;271:5768-5776.

## Objective

- In animal models, selective binding to the  $\alpha_2\text{-}\delta$  subunit is necessary for pregabalin- and gabapentin-induced anticonvulsant, antinociceptive, and anxiolytic-like effects<sup>1</sup>
- Pregabalin and gabapentin bind qualitatively to the same  $\alpha_2\text{-}\delta$  binding site<sup>2</sup>; however, they differ in  $\alpha_2\text{-}\delta$  binding affinity, potency, physical chemistry, and PK/PD properties
- The purpose of this presentation is to compare the dose-response (seizure frequency) relationship of pregabalin and gabapentin add-on treatment in patients with refractory partial epilepsy.

<sup>1</sup>Belliotti TR, et al. *J Med Chem.* 2005;48:2294-2307.

<sup>2</sup>Dooley DJ, et al. *Synapse.* 2002;45:171-190.

## Methods

Data were analyzed using a nonlinear mixed-effects model (NONMEM) to characterize the relationship between seizure frequency and pregabalin and gabapentin dose.

3 pregabalin clinical trials (1042 patients)

6 gabapentin trials (551 patients)

The mean number of seizure episodes per month ( $\lambda$ ) was modeled as a function of drug dose, placebo, baseline and subject specific random effects in NONMEM using a Poisson probability distribution .

$$P(Y_i = x) = e^{-\lambda} \frac{\lambda^x}{x!}$$

$$\lambda = \text{Baseline} \cdot (1 + \text{drug} + \text{placebo}) \cdot e^{\eta}$$

Baseline = estimated number of seizures reported during baseline period

Placebo = function describing placebo response

Drug = function describing the drug effect

$\eta$  = random effect

## Sub-population Analysis

Some patients are refractory to any particular drug at any dose.

Interest is in dose-response in patients that respond.

Investigate the possibility of at least two sub-populations using a MIXTURE MODEL.

## Mixture Model

A model that implicitly assumes that some fraction p of the population has one set of typical values of response, and that the remaining fraction 1-p has another set of typical values

### Population A (p)

$$\lambda_1 = \text{Baseline}_1 \cdot (1 + \text{drug}_1 + \text{placebo}_1) \cdot e^{\eta_1}$$

### Population B (1-p)

$$\lambda_2 = \text{Baseline}_2 \cdot (1 + \text{drug}_2 + \text{placebo}_2) \cdot e^{\eta_2}$$

## Conclusions

A comparison of the dose-response relationship for gabapentin and pregabalin reveals that pregabalin was 2.5 times more potent, as measured by the dose that reduced seizure frequency by 50% (ED<sub>50</sub>, Table 1).

Pregabalin was more effective than gabapentin based on the magnitude of the reduction in seizure frequency (E<sub>max</sub>, Table 1)

Three hundred clinical trials for each drug were simulated conditioned on the original study designs. Each simulated trial was analyzed to estimate % median change in seizure frequency. The observed and model-predicted treatment effects of median reduction in seizure frequency for gabapentin and pregabalin are illustrated for all subjects (Figure 3a) and for responders (Figure 3b). Data points represent observed median percentage change from baseline in seizure frequency for each treatment group (including placebo). The shaded area corresponds to predicted 10<sup>th</sup> and 90<sup>th</sup> percentiles for median change from baseline in seizure frequency.

## Results

Table 1.

| Estimated population parameters for the exposure-response relationship of seizure frequency to pregabalin or gabapentin dose. |                              |                     |
|-------------------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------|
| Parameter                                                                                                                     | Parameter Estimates (95% CI) |                     |
|                                                                                                                               | Gabapentin                   | Pregabalin          |
| Base <sub>seiz</sub> (seizures/month)                                                                                         | 14.0 (12.4,15.6)             | 11.1 (10.2,12.0)    |
| Base <sub>seiz</sub> (seizures/month)                                                                                         | 16.8 (8.8,24.8)              | 15.1 (12.3,17.9)    |
| E <sub>maxA</sub> (maximal fractional change)                                                                                 | -0.25 (-0.31,-0.18)          | -1.0 FIXED          |
| E <sub>maxB</sub> (maximal fractional change)                                                                                 | 2.34 (0.20,4.48)             | 0.26(-0.15,0.66)    |
| Placebo <sub>A</sub> (maximal fractional change)                                                                              | -0.15 (-0.29,-0.009)         | -0.11 (-0.18,-0.03) |
| Placebo <sub>B</sub> (maximal fractional change)                                                                              | 4.34 (-0.80,9.47)            | 1.44 (0.66,2.22)    |
| ED <sub>50</sub> (mg)                                                                                                         | 463.0 (161.3,764.7)          | 186.0 (91.4,280.6)  |
| Proportion <sub>A</sub>                                                                                                       | 0.95 (0.93,0.98)             | 0.75(0.61,0.88)     |
| Interindividual variability in A (%CV)                                                                                        | 93.4 (84.5,101.6)            | 100.1 (95.5,105.6)  |
| Interindividual variability in B (%CV)                                                                                        | 86.7 (58.3,107.8)            | 100.1 (95.5,105.6)  |

## Goodness of Fit

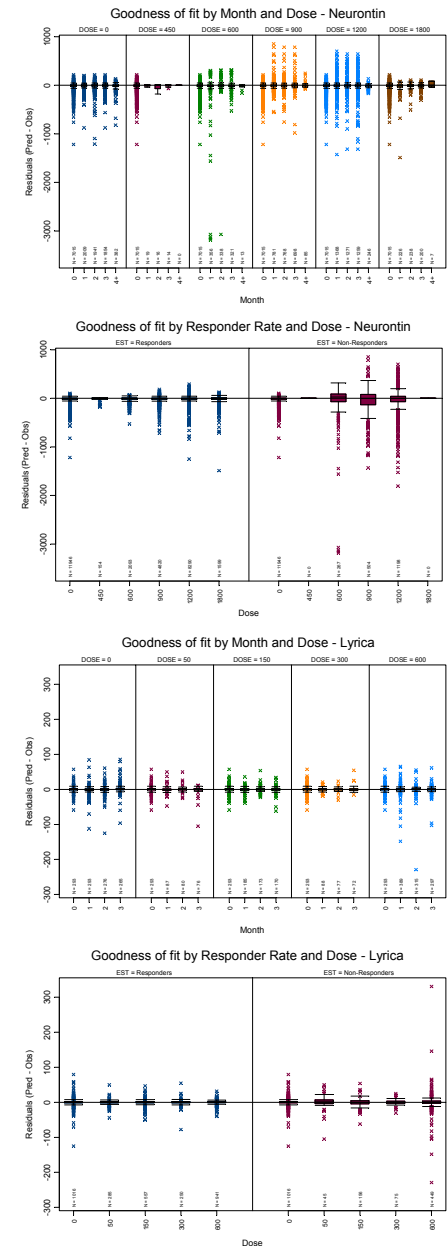


Figure 3a. Relationship Between %Change in Seizure Frequency (Relative to Baseline) and Daily Dosage of Gabapentin and Pregabalin

Figure 3b. Relationship Between %Change in Seizure Frequency (Relative to Baseline) and Daily Dosage of Gabapentin and Pregabalin in Responders to Treatment

