Modeling Dropout from Longitudinal Adverse Event Data

Selecting Optimal Titration Regimens

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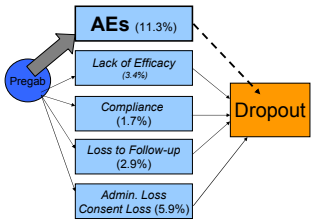
INTRODUCTION

- Pregabalin offers a new approach in the treatment of Generalized Anxiety Disorder (GAD)[1].
- Adverse events (AEs) are the predominant component of study withdrawal (dropout) contributing with at least 60% to total dropout incidence for this indication, considerably more than other dropout components/categories[2-6](Figure 1).
- Pregabalin AE incidence is dose dependent; as AEs have been modeled, we postulate a dropout model that incorporates severity of adverse effects.
- Dose was titrated based on clinical judgment; modeling approach will allow titration schedule optimization.
- Dropout analysis represents analysis of competing risk, we present a *component specific* approach, as if dropout arises from a specific risk of interest (AEs), the dose-dependent source of risk.

OBJECTIVE

- Model the dropout across the various titration schemes and evaluate the daily AE scores, a time-dependent covariate, as a predictor in the model.

Fig 1. Generalized Anxiety Disorder (GAD) Dropout Incidence (ITT)



Pregabalin Dataset-GAD Phase II studies[2-6]

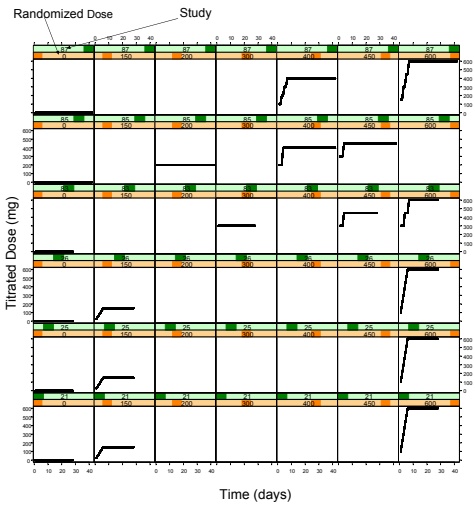
- Five comparator trials with benzodiazepines or SSRI (3 alprazolam, lorazepam and venflaxamine) and a schedule optimization study (TID vs. BID) informed the model.
- 1630 predominantly female, 18 to 64 years old subjects receiving placebo or pregabalin all reported daily subjective AE scores [no (0), mild (1), moderate (2) and severe (3)] across the 4 or 6 week trials.
- Studies employed varying dose within the first week of the protocols (Fig. 2)

Adverse Events Incidence Self-Reporting

	Placebo	150 mg/day	600 mg/day
Dizziness (%)	6-8	10-23	29-39
Somnolence (%)	11	15-29	36-50
Others* (%)		<20	<20

*Headache, Dry Mouth, Lack of Coordination, Nausea and Vomiting

Fig 2. Titrated Doses Across Study Arms (Randomized Doses)



METHODS

Discrete Survival and Conditional (Hazard) Probabilities

- Time to subject dropout (T) is modeled as discrete survival variable. S(t) is the probability that an individual survives in the study (does not drop out) beyond time t_j, where j indexes study day.

$$S(t_j) = Pr(T > t_j)$$

- Survival probability is related to hazard $h(t_j)$, the probability of the event (dropout) occurring in the time interval j, provided it has not occurred prior to j, among those "at-risk" (in study, during interval j). S(t) is also the product of conditional survival probabilities, i.e., sequential survival across each individual period t_j.

$$h(t_j) = Pr(T = t_j | T \geq t_j) = \frac{Pr(T = t_j)}{Pr(T \geq t_j)} = 1 - \frac{S(t_j)}{S(t_{j-1})} = 1 - e^{\left(-\int_{t-1}^{t} g(t_j)dt\right)}$$

- Assuming that the probability of dropout (likelihood) is only dependent on the covariate (AE score) in a particular time interval, it is:

$$Pr(T = t_j) = h(t_j)\prod_{i=1}^{t_{j-1}}(1 - h(t_i))$$

Conditional Probability Cumulative Hazard Model

- A discrete-time survival model was fit to GAD dropout time, assuming that the hazard depends on the current self-reported AE score and time since first study day.

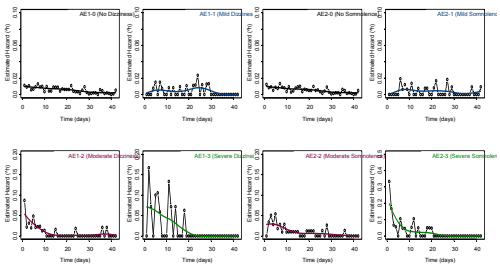
$$h(t_j) = Pr(T = t_j | T \geq t_j, AE_{MAXj} = m) = 1 - exp^{\left(-\int_{t-1}^{t_j} g(t_j, AEMAXj=m)dt\right)}$$

- T is the time of dropout, AE_{MAX_j} the maximum AE score for the patient at time t_j and $g(t_j, AE_{MAX_j}=m)$ the hazard probabilities conditioned on the last observed AE_{MAX} score (a parsimonious severity covariate).
- Nonparametric examination of risk (see Figure 3) guided the selection of the (parametric) hazard model

Fig 3. Nonparametric Estimates of the Dropout Risk- Regression of Hazard Probabilities vs. Time Given Dizziness and Somnolence, Time-Dependent AE Covariates

$$\hat{h}(t)\Big|_{AE\ max} = \frac{df_j}{n_j}$$

(df_j: number of observed subjects withdrawn within t_j; n_j: number of subjects "at risk" (remaining in study))



- Linear (exponential) and several time-dependent hazard probability models including the Weibull, loglogistic, linear-exponential and Gompertz were considered.
- Gompertz model (exponentially decreasing hazard with time) where λ is a hazard intercept and γ the slope with time, was selected based on visual inspection of the fitted vs. observed hazard plots, NONMEM OFV, predictive check model simulations and bootstrap confidence intervals. (Figures 4 and 5)

$$g(t_j, AE_{MAXj} = m) = exp^{(\lambda m + \gamma m \cdot t)}$$

- The LAPLACIAN method as implemented in NONMEM V (Icon Corp., Ellicott City, MD) provided the maximum likelihood (-2LL)) parameter estimates for the hazard parameters[7-8].

Fig 4. Fitted Hazard Probability Distribution Models to the Observed Conditional Probabilities

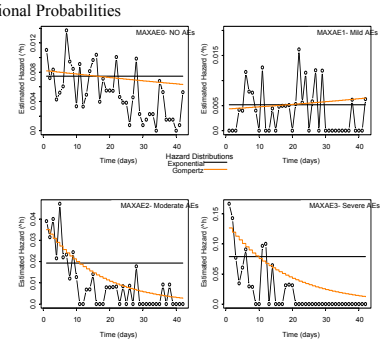
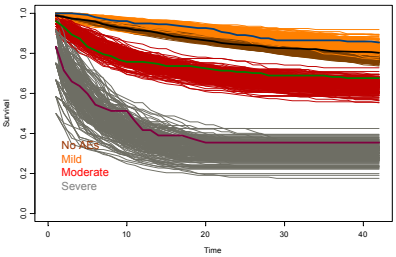


Fig 5. Simulation of Dropout (Gompertz Hazard Model) using Observed MaxAEs- Predictive Check (200 Simulations) with KM Nonparametric Survival Estimates (thick lines)



Prospective Simulations

- To generate prospective titration schemes AE data were simulated according to a 2-part incidence and severity AE model[9]. Simulated AEs and resulting dropouts are depicted below.

Fig 6. Dropout from Simulated AEs (3 Part Model) for Placebo, 450-600 mg Dose Groups/Titration Schemes. Blue line depicts the observed Kaplan-Meier dropout estimates.

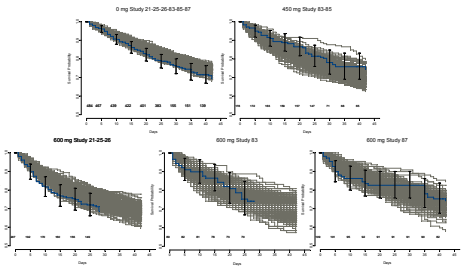
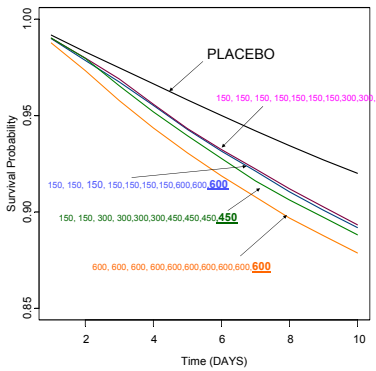


Fig 7. Mean Dropout from Prospective 7-day Titration Schemes (300 Simulations) using the ***3-Part AE-Dropout Model***



RESULTS

- Exponentially decreasing dropout risk (hazard) probability model (Gompertz) adequately described the dropout across GAD studies.
- Hazard was highest with high severity of either dizziness and somnolence (AE_{MAX}) decreasing with time for individuals with moderate or severe AEs; subjects reporting severe dizziness or somnolence on day 1 exhibit a 21% per day chance of dropout, which decreases to 9% and 1% per day on days 10 and 30 respectively.
- Patients reporting mild or no adverse events were estimated to exhibit a constant but low dropout risk, <1% per day at all times.
- Prospective studies can be planned/optimized in respect to AE and dropout across other indications.

REFERENCES

[1] Frampton JE, Foster RH. Pregabalin in the Treatment of Generalized Anxiety Disorder. CNS Drugs 2006; 20 (8): 685-693. [2] Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol 2003 Jun; 23 (3): 240-9.
[3] Pohl RB, Feltner DE, Fieve RR, et al. Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. J Clin Psychopharmacol 2005; 25: 151-8.
[4] Rickels K, Pollack MH, Feltner DE, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry 2005; 62: 1022-30.
[5] Montgomery SA, Tobias K, Zornberg GL, et al. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind,placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry 2006; 67: 771-82.
[6] Pande AC, Crockatt JG, Feltner DE, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry 2003 Mar; 160 (3): 533-40.
[7] Sheiner LB, Beal SL, Dunn A. Analysis of Nonrandomly Censored Ordered Categorical Longitudinal Data from Analgesic Trials. J Am Stat Assoc 1997 Dec; 92(440) 1235-44.
[8] Mandema JW, Stanski DR. Population pharmacodynamics model for ketorolac analgesia. Clin Pharmacol Ther 1996 Dec; 60 (6) 619-35.
[9] Kowalski KG, McFadyen L, Hutmacher MM, Frame B and Miller R. J Pharmacokinet Pharmacodynam. 2003 Oct;30(5):315-36