Development of a Longitudinal Model for Characterizing Adverse Events of Psychiatric Drugs in Routine Clinical Care

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Background and Objective

In routine clinical care of psychiatric patients, the early treatment is important because adverse events (AEs) in this period often lead to noncompliance to a drug and lowering the therapeutic effect. This study aimed to develop a longitudinal model to describe early-phase AEs in Korean psychiatric patients in an effort to be used as a guide to improve medication compliance and drug efficacy.

Methods

DATA

Patients who had been seen at the Department of Psychiatry, Severance Hospital, in Seoul, Korea, between January 2007 and June 2010 were reviewed retrospectively. Data were obtained from the medical records of outpatients, particularly those treated with anxiolytics or antidepressants. Patients who had no previous psychiatric diagnosis were included in the analysis. To find the characteristics of early-phase AEs, data were censored on Day 60 from the patient's first visit. The treatment information, treatment history, AEs history, hospital visit day and demographics were collected for the analysis.

Table. Patient demographics from routine clinical data

Characteristic	Group		Pooled data
	GAD (n= 25)	MDD (n=125)	(n=150)
Age, year			
Mean (SD)	48.64 (18.75)	51.06 (17.99)	50.66 (18.14)
Range	21-88	20-84	20-88
Sex, N(%)			
Male	17 (68)	61 (48.8)	78 (52)
Female	8 (32)	64 (51.2)	72 (48)
Comorbidity, N(%)	11 (44)	69 (55.2)	80 (53.3)
Smoking, N(%)	7 (28)	42 (33.6)	49 (32.7)
Alcohol, N(%)	14 (56)	46 (36.8)	60 (40)
Drug Class (%)			
Anxiolytics	53	26.4	30.7
Antidepressant	14.8	66.7	58.2
Other CNS	32.2	6.9	11.1

Model building

Using NONMEM 7, three different longitudinal models were developed within a mixed-effect model framework to describe the incidence, the time-to-event (TTE), and the count of AEs.

Treatment medications were grouped into three categories: "1" for the BZD class drugs, "2" for the SSRI class drugs and "3" for the other class drugs acting in the central nervous system (CNS).

After the basic model was selected, a further development of the model, achieved by finding possible covariate effects, was tested.

To evaluate the predictive ability of the model, VPCs were implemented and one hundred datasets for each final model were simulated. For incidence and count model, the results were then compared to the observed data. TTE model simulation results were compared graphically to Kaplan-Meier (non-parametric) estimates of survival probabilities. The 95% prediction intervals (PIs) of the simulated data were compared with the observed data with VPC.

AE-incidence model
- 5 non-equispaced time intervals
- Mixed effects logistic regression model
- First order Markov element
- Time-effect function for the disease progression

Time-to-event model
- Time-to-first AE and Time-to-dropout (loss of follow up)
- Discrete time survival models
- Several types of hazard models were tested
  : Time constant hazard : exponential distribution functions
  : Time varying hazard : linear exponential and Weibull functions

Count model
- Number of AE occurrences during the observation period
- Poisson distribution function
- Stirling's approximation for factorial approximation in NONMEM

Influence of covariates
- Demographics : Age, Sex, Alcohol consumption, Smoking habits
- Medical statuses : Past medical history, Concomitant medications, Comorbidities
- The goodness-of fit between different models and the data was evaluated using Akaike's information criterion (AIC)

Model evaluation
- 100 datasets were simulated from the final models
- VPC for each model
- Predicted check for the count model

Results

The most frequently observed AE was drowsiness. About 70% of the patients reported AE more than once during the observation period.

AE-incidence model
- A Markov element added in the baseline logit adequately described the data. Incorporating a mono-exponential function as a time effect further improved the model, dropping OFV by 135.96

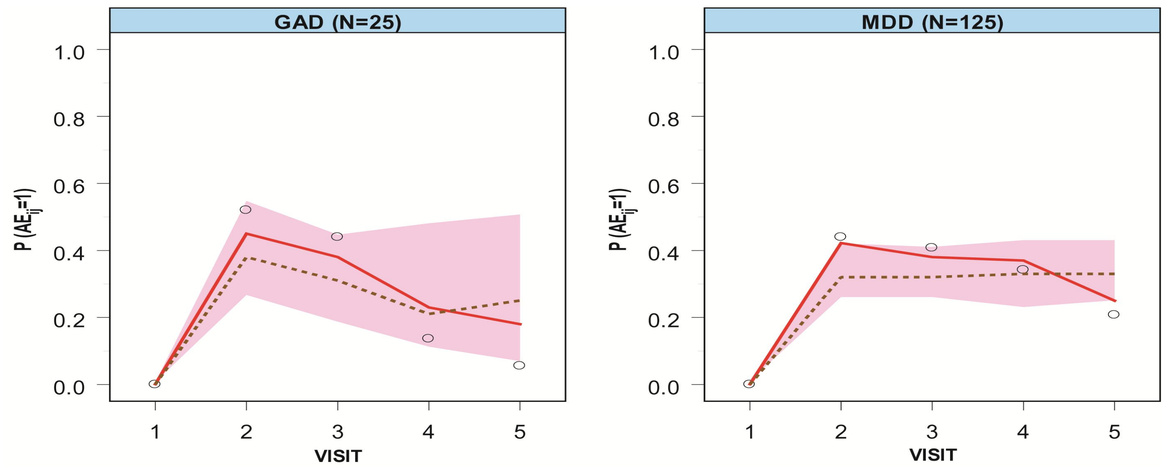

Figure. Visual predictive check for the final incidence model by diagnosis

Symbols denote the observed AEs rate, solid lines are predicted AEs rate (PRED), shaded areas are the 90% Prediction intervals, and dotted lines are median from 100 simulations

TTE model
- The Weibull hazard model best described the data, and both hazards were decreasing with time
  - First AE - Shape parameter of hazard : 0.00147 and median time to first AE : day 20 from patients' first visit
  - Dropout (loss of follow-up)- Shape parameter of hazard 0.001

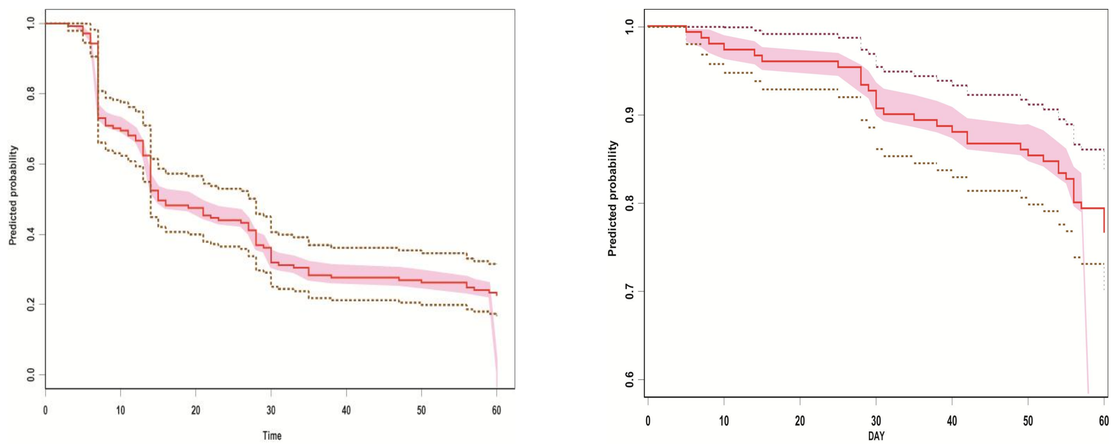

Figure. Visual predictive check for the time-to-first AEs (left) and dropout (right) models

Observed Kaplan-Meier's plot for the each TTE models (Solid line) with its 95% confidence intervals (dotted lines) and shaded areas are the 95% Prediction intervals from 100 simulations

Count model
- A constant hazard model
- The predicted mean counts of AEs
  - BZD treated patients : 1.20 (14.3% of relative standard error, r.s.e)
  - SSRI treated patients : 1.28 (8.53% of r.s.e)
  - other CNS-drug treated patients : 1.21 (25.3% of r.s.e)

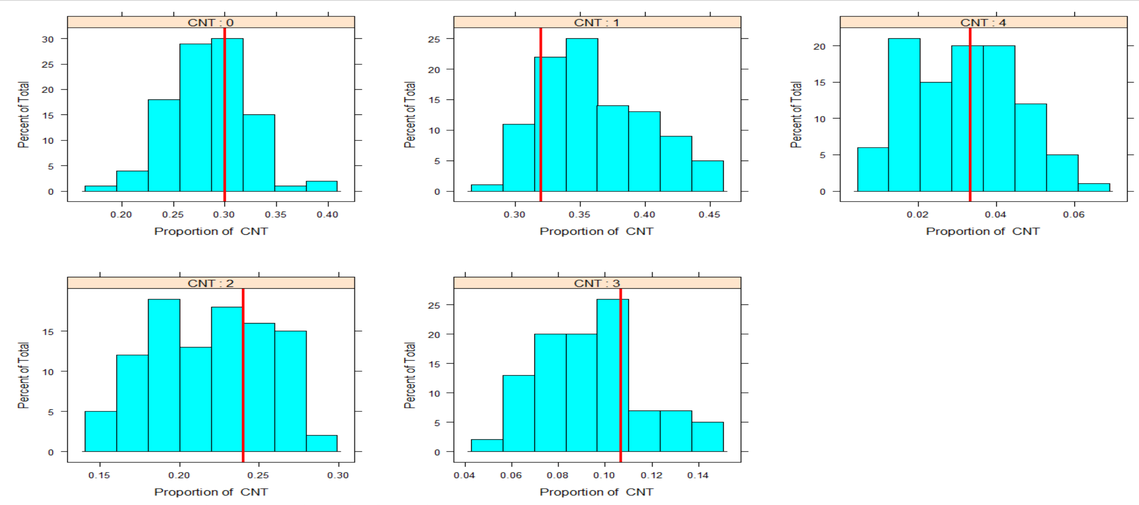

Figure. Predictive check for the count model

Distributions of the total counts of AEs from 100 simulations (bars) and the vertical line in each plot indicates the observed total counts (CNT) in the original data

Conclusion

Our preliminary results show that the incidence model described the data well whereas the TTE model needs to be further developed. To generalize our results, more work will be necessary, including assessing covariate influence on AEs with more patients. Including severity into the model will further improve the applicability of the model if such information is available. Finally, the model developed can be validated with external data obtained from a prospective study designing with respect to dropout and AEs.

References

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