

Modeling of pain scores from a flexible titration study using ordered categorical approach

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Introduction

Context

- In clinical pain studies, the primary endpoint is an 11-point Numeric Rating Scale (NRS): 0: no pain, 10: worst pain imagined. Data Type: ordinal, categorical and bounded data
- Studies with controlled adjustment of dose: subjects have their study drug titrated upwards or onwards if needed depending on the degree of pain experienced and reported adverse events
 - Potential bias in the dose-response analysis of the data according to the sensitivity of each subject
 - The dose received over the maintenance period (modal dose) could be a surrogate for each subject's sensitivity
 - Methodological answers: Linear mixed effect model with parameter estimates depending on dose (Dunne 2012) Dynamic linear mixed-effect model (Xu 2012), Marginal structural model (Xu 2012)

Objective:

Modeling of pain score data coming from a study with controlled adjustment of dose with an ordered categorical approach

Data:

Study drug: drug A: agonistic activity at the mu-opioid receptor + inhibitor of noradrenaline reuptake

Study: phase III study with controlled adjustment of dose : patients receiving drug A vs patients receiving placebo

- Titration phase followed by a maintenance phase (dose controlled in patient) in OA (from D1 to D5 with D1<D2<D3...)
- NRS recorded twice a day

Material and methods

Approach described by Plan et al (Plan, PAGE 2011): modeling the cumulative frequencies to have a score $\leq 0, 1, 2, 3 \dots$

$$\text{logit}(P[Y_t \leq m/\eta_Y]) = f_p(m, t) + f_d(\text{Dose}) + f_{cov}(cov) + \eta_Y$$

With m being 0, 1, ..., 10, f_p : function describing the natural time course of pain score, f_d : function describing the time course of the drug effect depending on the received dose (placebo or drug A), f_{cov} : function describing the covariate effect, η_Y : random individual effect

Extract of Nonmem Code

```
;Baseline values
B0 =THETA(1)
B1 =THETA(2)...

;Logits for Y<=1, Y<=2, Y<=3
LGEPO =B0+DEF+BSL+MEF+DF+ETA(1)
LGEPI =B0+B1+DEF+BSL+MEF+DF+ETA(1)
...

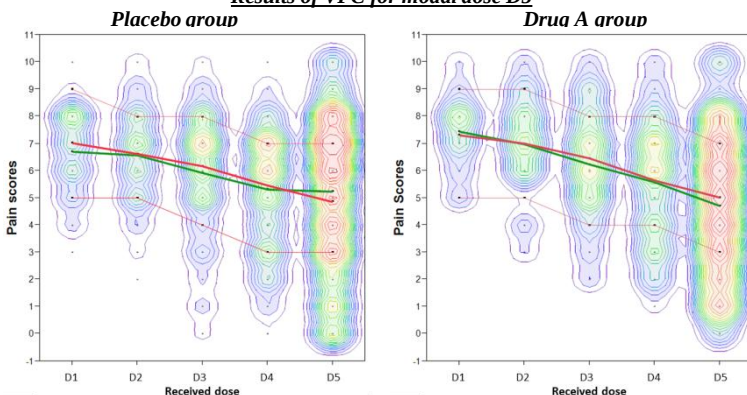
;Probabilities for Y<=2, Y<=3
PGEPO =EXP(LGEPO)/(1+EXP(LGEPO))
PGEPI =EXP(LGEPI)/(1+EXP(LGEPI))
...
PGEPI0 =1

;Select appropriate P(Y=m)
IF(DV.EQ.0) Y=P0
IF(DV.EQ.1) Y=P1
...

;predicted pain scores
IF(CALL.EQ.4) THEN
CALL RANDOM(2,R)
UNIF1=R
PAIN2=0
IF (UNIF1.LE.PGEPO) PAIN=0
IF (UNIF1.GT.PGEPO.AND.UNIF1.LE.PGEPI) PAIN=1
...
IF (UNIF1.GT.PGEPI) PAIN=10
PNS=PAIN
ENDIF
```

- Dataset:** all the pain scores for patient (2 records per day)
- Dose effect (DEF):** Linear relationship between effect and **received dose** (=dose received at each intake). This relationship changes with each **modal dose** (=most received dose over the maintenance period)
- Covariates:**
 - Baseline effect (BSL)
 - Morning/Evening intake effect (MEF)
 - Day effect (during titration phase) (DF)
 - Opioid experience and gender tested but not included in the model

Results of VPC for modal dose D5



Results of VPC for Placebo and Drug A

- The model correctly predicts the pain scores
- Lower predicted than observed variability
- Dose effect not visible when all the modal doses are considered together (data not shown) but dose effect clearly visible when each modal dose is considered separately for both placebo and drug A.

Predicted Pain Score Observed Pain score

Solid line: Mean ,Dotted lines: 2.5 and 97.5 percentiles of predictions

Results and Discussion

- The model correctly fitted the data
- Placebo showed a robust dose-response relationship
- Trend of lowering Pain score similar between PBO and Drug A groups
- Dose effect** modeled for placebo and drug A:
 - Not clear when all modal dose are considered together (data not shown)
 - Clear when each modal dose is considered separately for placebo and drug A group
- Predicted pain scores **variability** lower than observed pain scores variability:
 - Two populations in the D5 modal dose subsets?
 - Use of another distribution or of a mixture of distribution for improving the predictions
 - Use of exposure parameters instead of dose in the drug A group