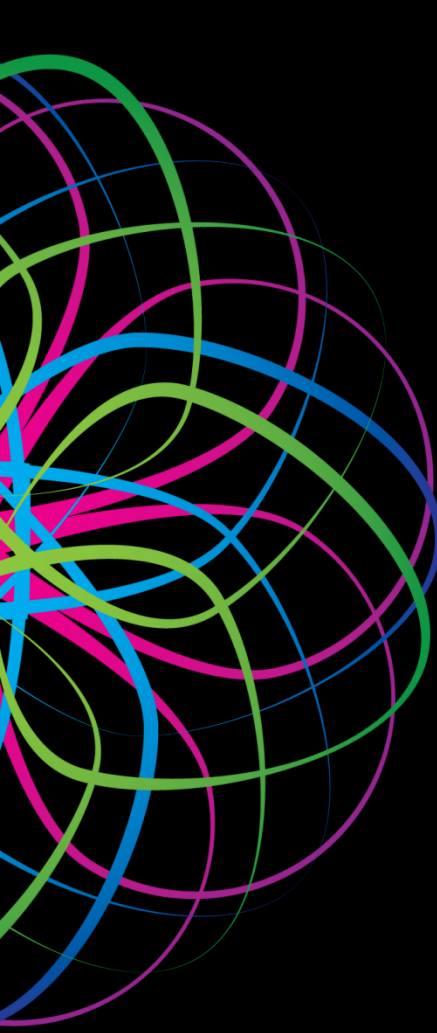




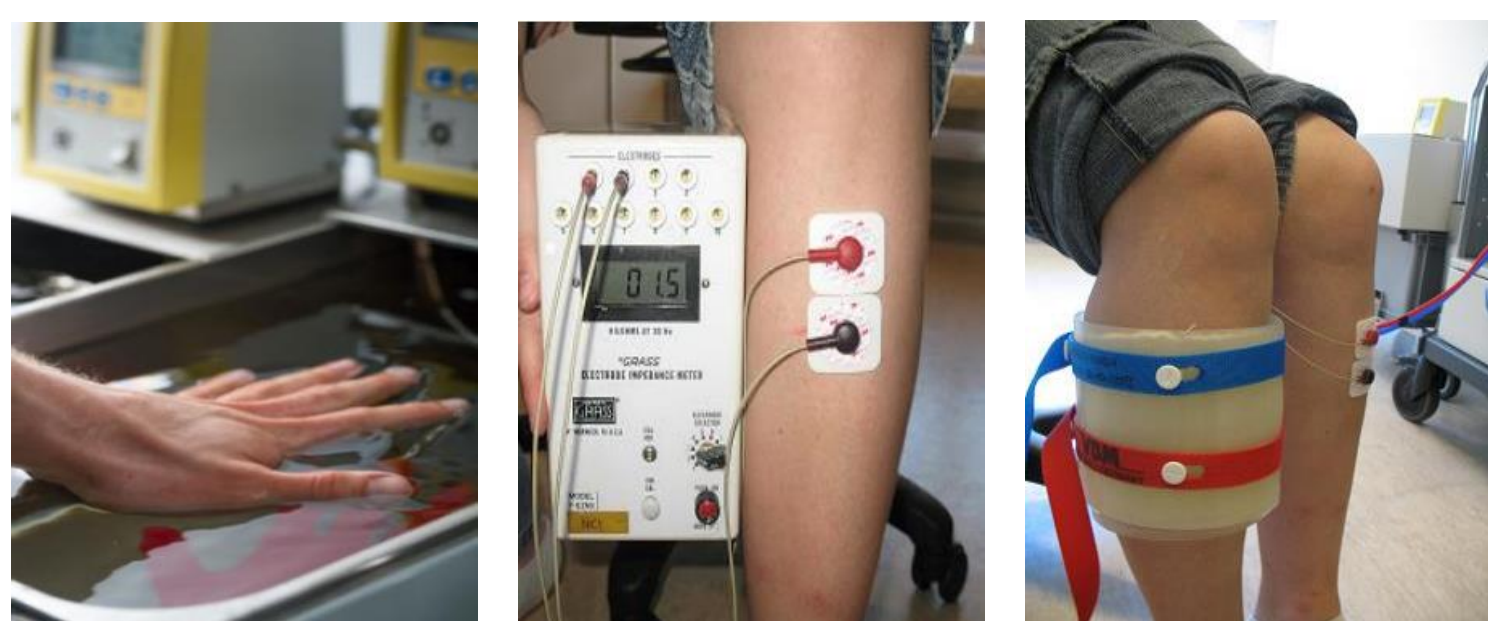
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INTRODUCTION

- Pain tests are an objective way to study analgesic effects in addition to the commonly used pain questionnaires in clinical trials.
- The use of a battery of pain tests enables the quantification of a concentration-effect relationship in phase 1 clinical trials
- The analgesic effect of a single dose of 300 mg pregabalin on 4 pain tests was quantified

- Cold pressor
- Electrical stimulation
- Pressure stimulation
- Heat detection



RESULTS

- Pregabalin gave a significant improvement in two pain tests: cold pressor and electrical stimulation
- A decrease in the cold pressor response over time in the placebo occasion was identified
- Pharmacokinetic and pharmacodynamic models were able to describe the data (**Figure 1 & 2**)
- Linear effect on cold pressor, on/off effect on electrical stimulation
- Significant between occasion variability on the baseline response was estimated (**Table 1**)

Table 1: Population parameter estimates of the pharmacodynamic models for the cold pressor pain tolerance threshold (PTT) and the electrical stimulation PTT. BOV = between occasion variability, CV = coefficient of variation, RSE = relative standard error, CI = confidence interval.

Parameter	Cold pressor PTT		Electrical stimulation PTT	
	Population parameters (RSE)	Bootstrap result mean [95%-CI]	Population parameters (RSE)	Bootstrap result mean [95%-CI]
Baseline	16.9 sec (16.8%)	17.0 [12.6 – 22.6]	19.1 mA (7%)	19.2 [16.36 – 22.06]
k _{out}	0.39 /h (21%)	0.39 [0.18 – 0.64]	0.494 /h (24%)	0.50 [0.28 – 0.77]
Slope over time	-0.07 s/h (57.8%)	-0.08 [-0.16 – -0.04]	-	-
Slope pregabalin	0.135 1/mg/L (16.7%)	0.143 [0.09 – 0.20]	-	-
Effect pregabalin	-	-	0.322 (18%)	0.326 [0.215 – 0.450]
Inter-individual variability (CV, shrinkage)			Inter-individual variability (CV, shrinkage)	
ω ² BOV baseline	0.057 (24.2%, 27%)	0.060 [0.01 – 0.15]	0.122 (22%, 2%)	0.116 [0.070 – 0.172]
ω ² baseline	0.283 (57.2%, 2%)	0.267 [0.056 – 0.50]	-	-
ω ² k _{out}	0.738 (105%, 19%)	0.715 [0.01 – 2.46]	-	-
ω ² Effect	-	-	0.187 (70, 25%)	0.20 [0.02 – 0.60]
Residual error (shrinkage)			Residual error (shrinkage)	
σ ² proportional	0.041 (6%)	0.041 [0.032 – 0.050]	0.0143 (6%)	0.0144 [0.010 – 0.019]

METHODS

Study design

- Single oral dose of 300 mg pregabalin
- 16 healthy subjects (8 male/8 female)
- Placebo controlled, randomized, 4 way cross-over study
- Battery of pain tests as PD outcome

Pharmacokinetic model

- 1-, 2-, 3-compartment
- Lag time or transit compartments for absorption
- Linear and non-linear elimination kinetics

Placebo model

- Linear
- E_{MAX}
- Gompertz
- Bateman

Pharmacodynamic model

- (In)direct effects
- Linear
- Sigmoid E_{MAX}

CONCLUSIONS

- Pregabalin showed a significant effect on two pain tests, no concentration-effect relationship could be established on the pressure stimulation and heat detection thresholds.
- High levels of variability in PD responses were observed
- Additional dosing regimens would improve model parameter estimation

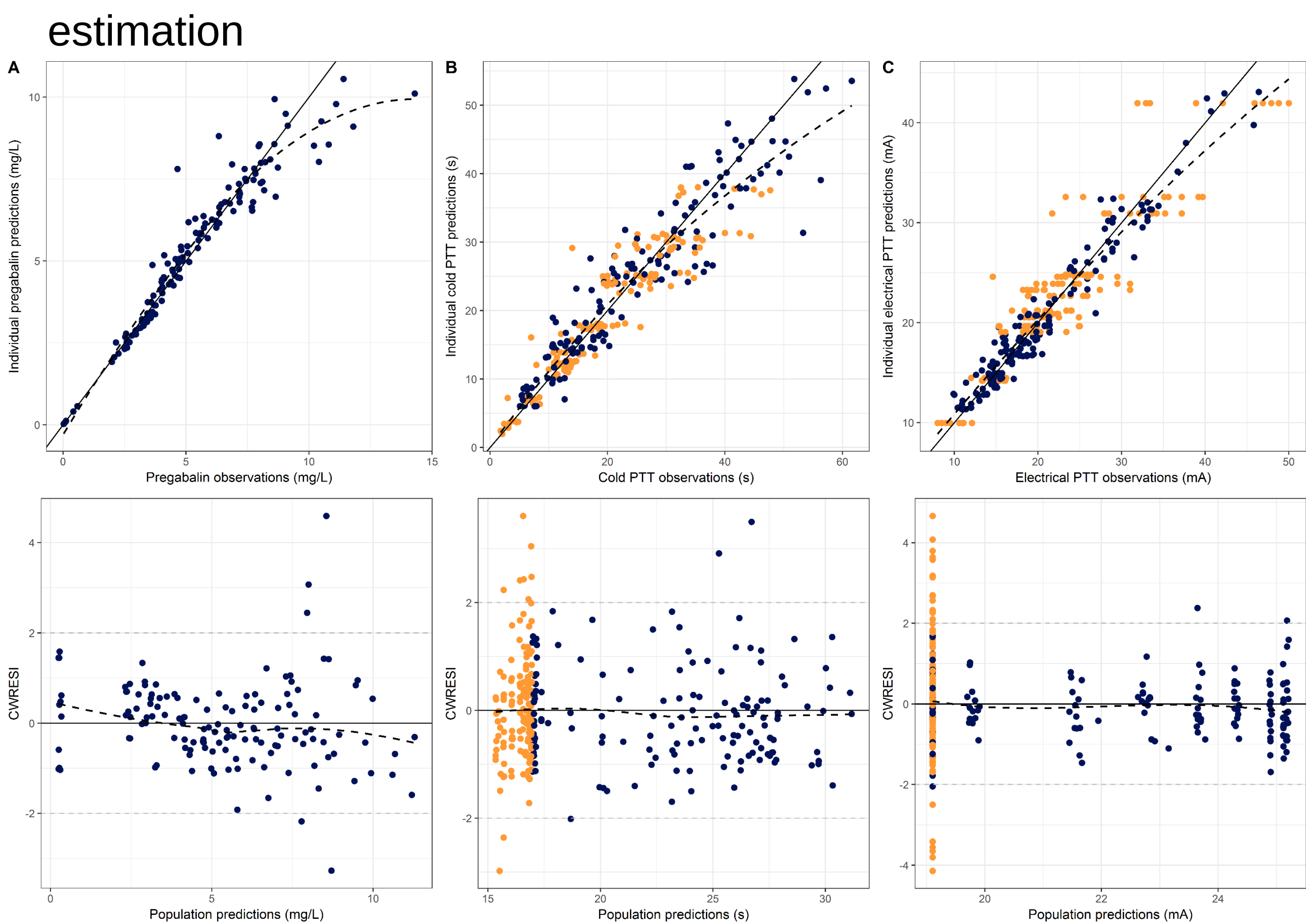


Figure 1: Individual model predictions vs observations for the final model of pregabalin (A), cold pressor pain tolerance threshold (PTT) (B) and electrical stimulation PTT (C). Blue dots = pregabalin visit measurements, orange dots = placebo visit measurements, CWRESI = conditional weighted residuals with interaction, black solid line = line of unity, grey dashed line = [-2, 2] interval, black dashed line = loess fit.

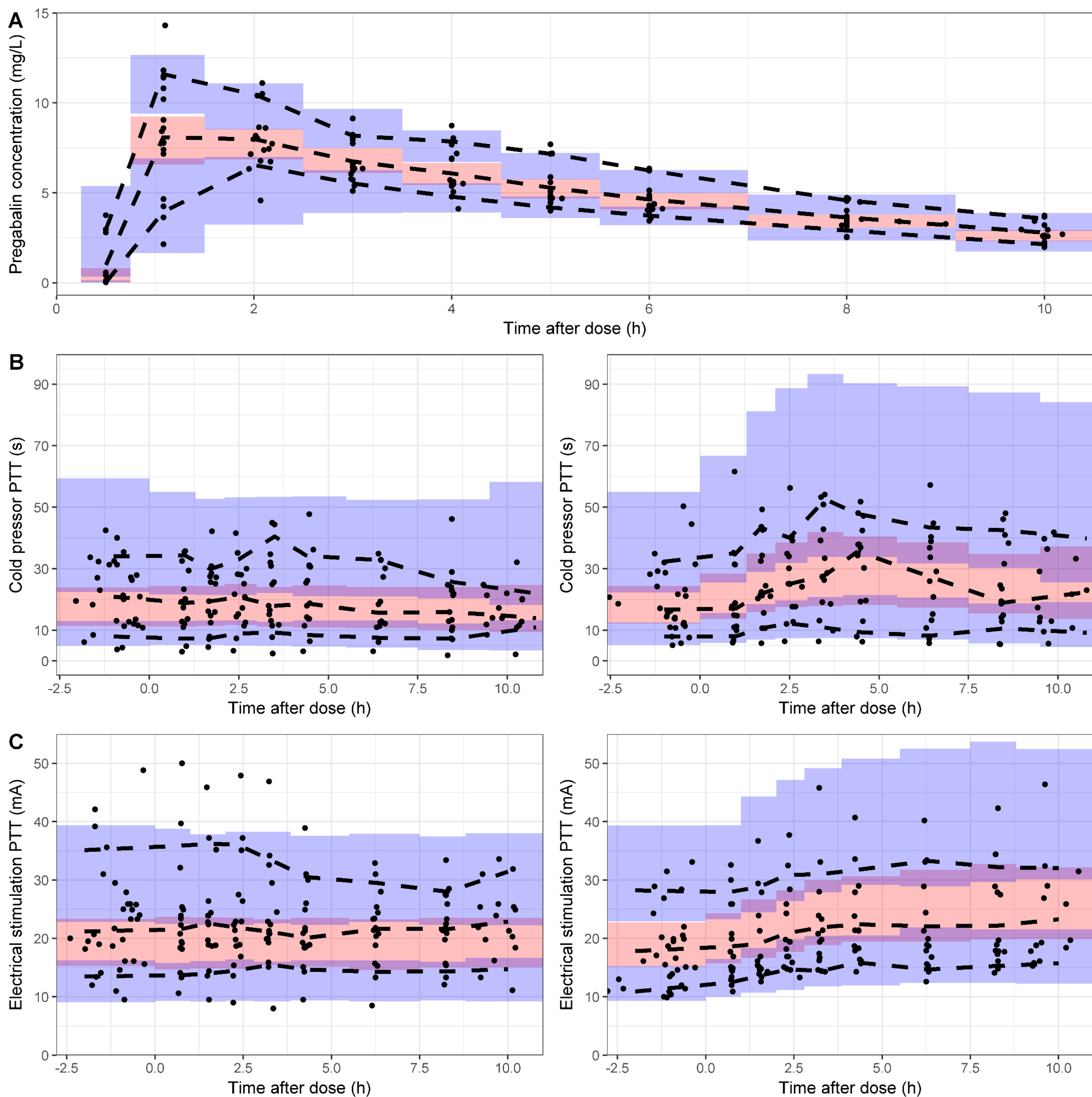


Figure 2: Visual predictive checks of 500 samples of the population PK (A), the cold pressor pain tolerance threshold (PTT) (B) and the electrical stimulation PTT (C) after administration of a single oral dose of 300 mg pregabalin. For the pharmacodynamic outcomes, the left figure indicates the placebo occasion, the right figure indicates the pregabalin treated occasion.