

Amisulpride: Real-World Evidence of Dose Adaptation and Effect on Prolactin Concentrations

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Introduction & Objectives

- Amisulpride is used at a wide range of daily doses (100-800 mg). Therapeutic drug monitoring of amisulpride is strongly recommended with a therapeutic reference range of 100-320 ng/mL for trough concentrations.^{1,2}
- Hyperprolactinemia is reported in more than 90% of patients³ frequently resulting in fast onset sexual dysfunction and other adverse effects at long-term.
- The objectives of this work were:
 - To characterize the PK profile and to detect sources of variability in order to suggest optimal dosage regimens for reference range achievement.
 - To develop a PK/PD model describing the relationship between amisulpride concentrations and prolactin data.

Methods

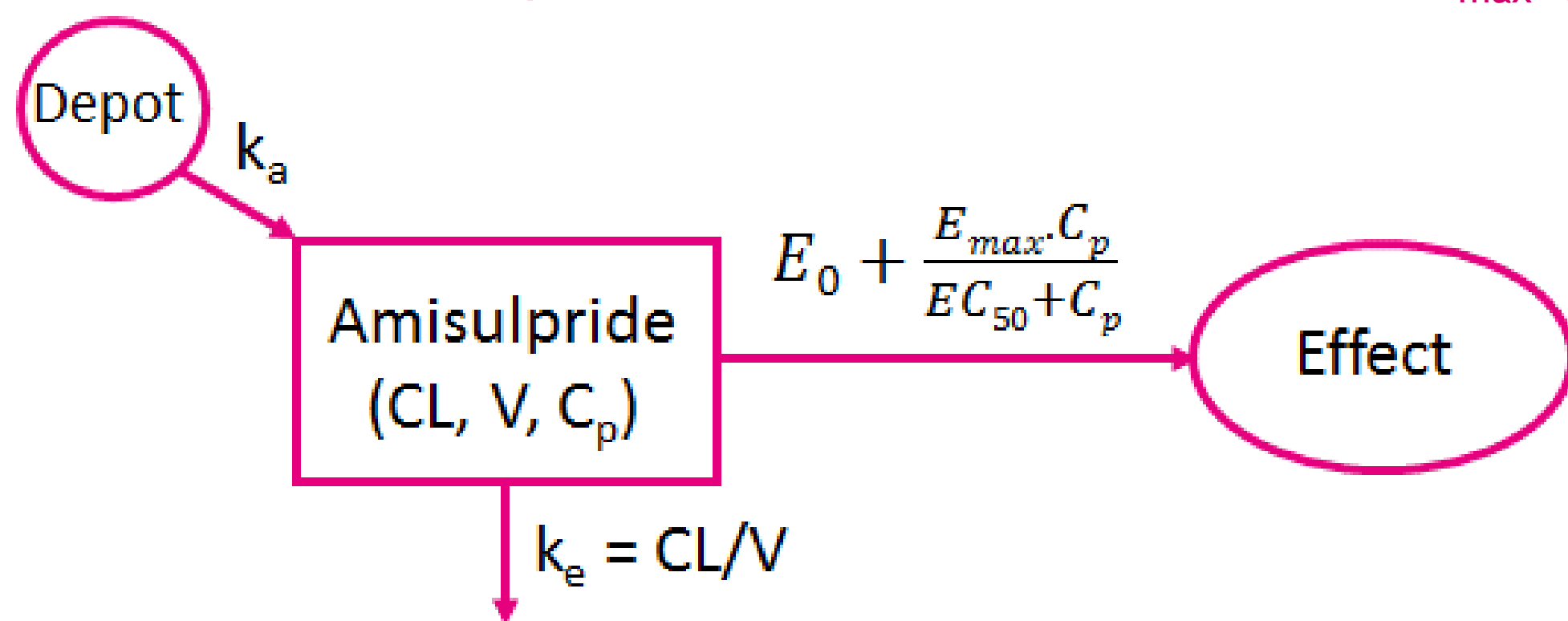
PK model: Data were obtained from patients from the Lausanne University Hospital.

- Influence of age, sex, body weight (BW), lean body weight (LBW) estimated by the Janmahasatian formula⁵, body mass index, creatinine clearance estimated by the Cockcroft-Gault formula using BW if BMI < 25 kg/m² and LBW if BMI ≥ 25 kg/m²,⁶ single nucleotide polymorphisms of the OCT1/2, P-gp and nuclear receptors and comedications (P-gp inhibitors and lithium) were quantified on amisulpride clearance (CL) and volume of distribution (V).
- Simulations of trough concentrations at steady-state (C_{min,ss}) based on the final PK model in 500 individuals per strata of age and LBW and after administration of daily doses of 300 and 800 mg in adults; 200 and 400 mg in elderly patients.

PK-Prolactin model: the final PK model was combined with an E_{max} model. The gender effect on E_{max} was directly included in the structural model development.

- Influence of age, menopause, BW, LBW, season and concomitant antipsychotics that might have increased prolactin levels were quantified on E_{max}.
- Prolactin levels were predicted by using the final PK/PD model at time of trough amisulpride concentrations.

Figure 1: PKPD model: 1 compartment PK model with a direct E_{max} (NONMEM)



Results

- Data available: 513 amisulpride concentrations from a cohort of 242 patients and 101 prolactin concentrations from a subset of 68 patients

Table 1: Demographic and clinical characteristics of the study population

Characteristics	Value	% missing data
Sex (male), n (%)	132 (55%)	0
Age (years), median (range)	37 (18-91)	0
Body weight (kg), median (range)	75 (43-185)	5.6
Lean body weight (kg), median (range) ^a	52 (29-98)	14.2
Body mass index (kg/m ²), median (range)	25 (15-59)	14.2

- Only age and LBW significantly influenced amisulpride clearance:
 - CL decreased by 50 % in a 80-year individual as compared to a 40-year patient (LBW=50 kg)
 - CL increased by 50 % in a 40-year individual with a LBW=100 kg vs. LBW=50 kg.
- When C_{min,ss} are in 100-320 ng/mL, model-predicted prolactin levels were over the normal values (model-predicted median = 71 ng/mL, range = 41-135 ng/mL and 138 ng/mL, 75-309 ng/mL in males and females respectively).
- E_{max} parameter was decreased by 53% in males as compared to females and by 21% in postmenopausal women compared to premenopausal women (p= 0.2).

References:
1. Hiemke, C., et al. Pharmacopsychiatry. 2017
3. Holt RI et al. Clin Endocrinol. 2011
5. Janmahasatian S et al. Clin Pharmacokinet. 2005.

2. Muller, M. J., et al. J Psychiatr Res. 2007
4. Bergemann N, et al. Eur Neuropsychopharmacol. 2004
6. Pai MP. Adv Chronic Kidney Dis. 2010.

Table 2: Final population PK/PD parameter estimates and their bootstrap evaluations.

Parameter	Final population parameter		Bootstrap evaluation (n=2000 samples)	
	Estimate	RSE ^a (%)	Median	CI _{95%}
CL (L/h)	44	4	44	41; 48
V (L)	956	11	961	705; 1258
k _a (h ⁻¹)	0.9 fix	-	-	-
Bioavailability ⁴	0.48 fix	-	-	-
θ _{AGE_CL}	-0.46	10	-0.47	-0.54; -0.36
θ _{LBW_CL}	0.54	36	0.54	0.27; 0.85
IIV _{CL} (CV%)	33	12	33	24; 42
IIV _V (CV%)	65	24	63	35; 92
proportional residual error (%) ^c	53	4	53	46; 60
E ₀ (ng/mL)	16	35	16	11; 20
E _{max} (ng/mL)	141	13	142	116; 182
EC ₅₀ (ng/mL)	42	34	43	4.6; 110
θ _{MALE_EMAX}	-0.53	13	-0.54	-0.65; -0.38
IIV _{E_{max}} (CV%) ^b	50	16	49	36; 62
Additive residual error (ng/mL)	15	13	15	10; 20

Final model:

CL (L) = 44 x (1 - 0.46 x ((age - median age)/median age)) x (1 + 0.54 x ((LBW - median LBW)/median LBW))

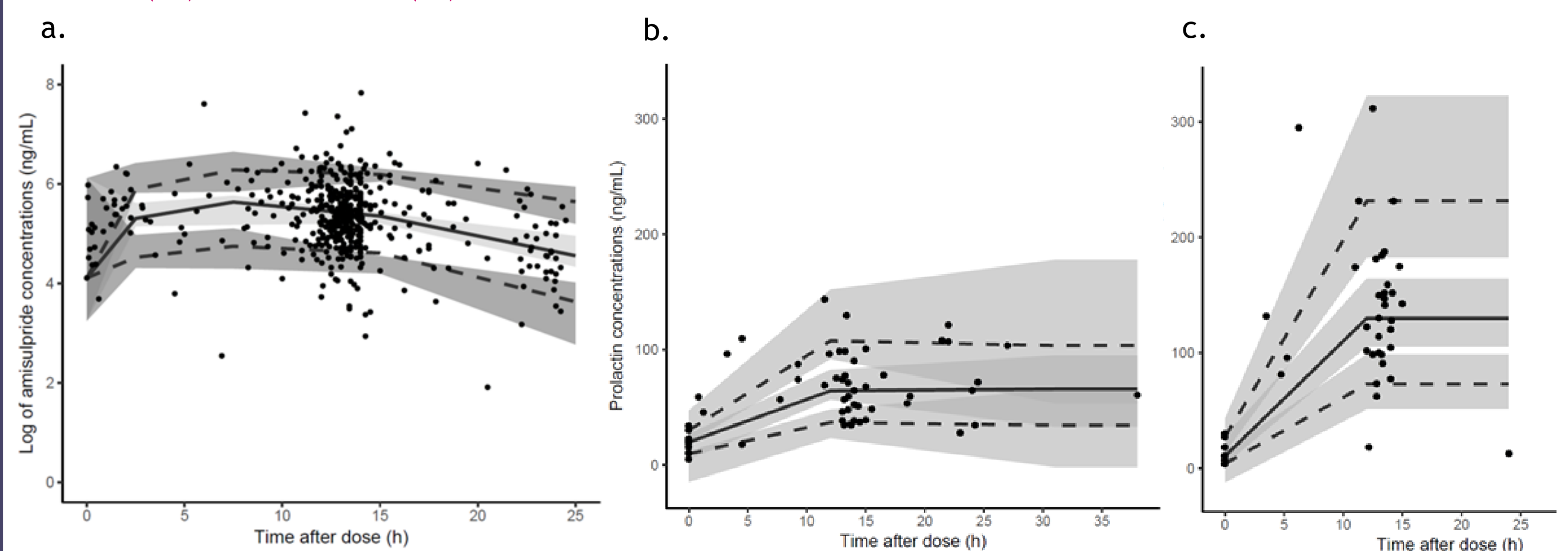
E_{max} (ng/mL) = 141 x (1 - 0.53 * MALE) with MALE=1 if male patients and MALE=0 if female patients.

a. Relative standard errors of the estimates (SE) defined as SE/estimate directly retrieved from NONMEM®.

b. Interindividual variability defined as CVs (%).

c. Proportional residual error as percentage on the linear scale derived from the additive residual error on the log scale

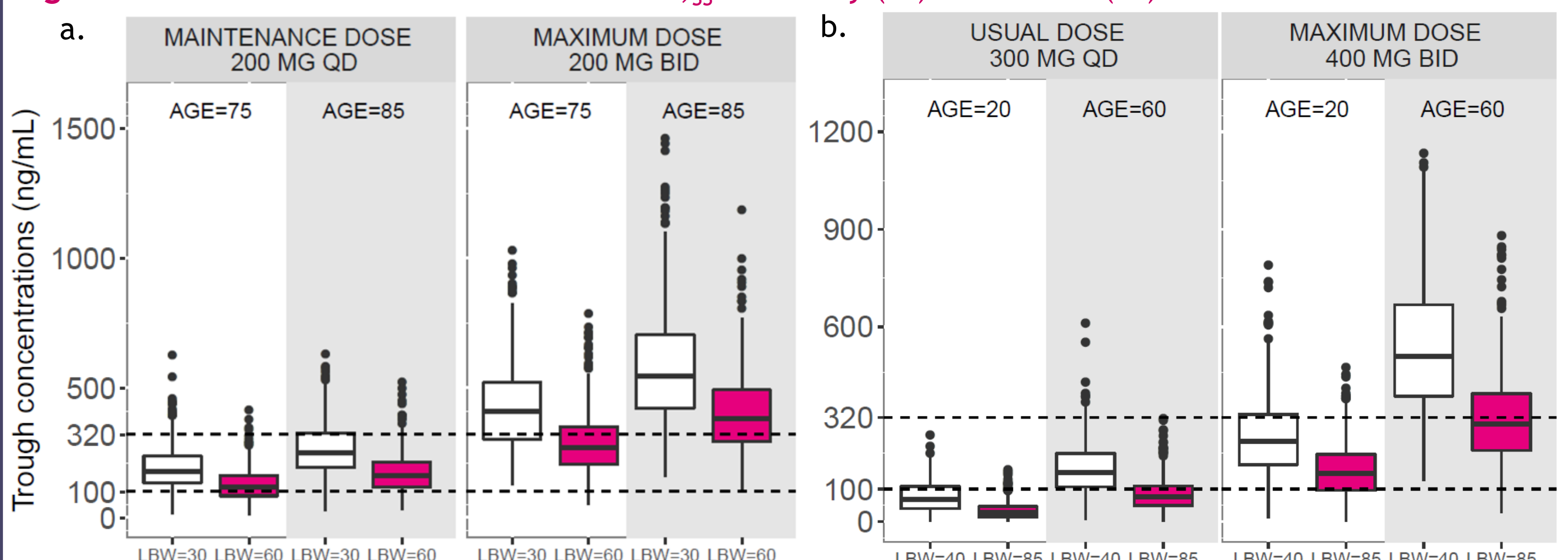
Figure 2: Prediction-corrected visual predictive checks (VPC) of the final PK (a.), the PK-Prolactin in females (b.) and in males (c.) models.



a. Circles represent amisulpride plasma concentrations. b. Black dots represent prolactin plasma concentrations.

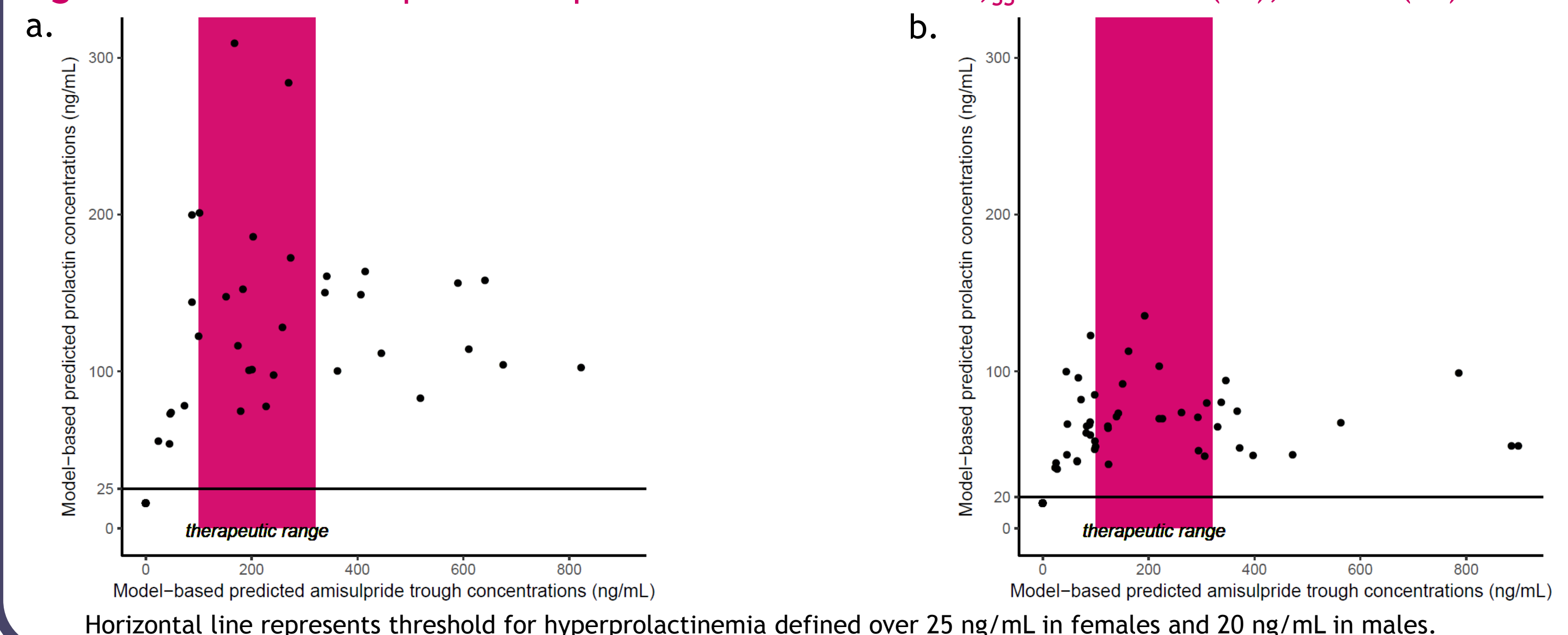
a., b., c. The continuous line represents the median observed plasma concentration and the dashed lines represent the observed 5% and 95% percentiles. Shaded areas represent a simulation-based 95% confidence interval for the median, the 5% and 95% percentiles.

Figure 3: Distribution of the simulated C_{min,ss} in elderly (a.) and adults (b.).



Dashed lines represent the reference range of trough concentrations

Figure 4: Model-based predicted prolactin levels vs. C_{min,ss} in females (a.), males (b.).



Conclusion

- LBW had a more significant effect on CL than BW supposedly because LBW better estimates body size in overweight or obese patients.
- Amisulpride dose adaptation with age and LBW seems essential in order to reach the recommended C_{min,ss} range in patients.
- When amisulpride C_{min,ss} are in the recommended range, amisulpride dose reduction is not appropriate to reduce prolactin levels.