

Influence of *UGT2B7* polymorphism on varenicline clearance in a cohort of smokers from the general population

Anaïs Glatard^{1,2}, Monia Guidi^{2,3}, Maria Dobrinas¹, Jacques Cornuz⁴, Chantal Csajka^{2,3*} and Chin B. Eap^{1,3*}



(1) Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Hospital of Cery, Prilly, Switzerland
(2) Division of Clinical Pharmacology, Service of Biomedicine, Department of Laboratory, Lausanne University Hospital, Lausanne, Switzerland
(3) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland
(4) Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland
*joint corresponding authors



Objectives

- Varenicline is a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor used at the dose of 1 mg twice daily.
- 90% of the dose is eliminated unchanged in urine, notably via OCT2 transporters and the most abundant metabolite is obtained by glucuronidation via *UGT2B7*¹.
- Smoking quitting rate¹ is variable and might be linked to inter-individual variability in varenicline blood concentrations.
- The aim of this work was to assess whether genetics factors can explain part of the variability in varenicline blood levels and therefore its effectiveness.

Methods

- Data**
- 82 subjects received varenicline at the recommended dosage schedule (0.5 mg/day x 3 days, 0.5 mg 2/day x 4 days, 1 mg 2/day until 12 weeks).
 - 121 varenicline blood levels were collected at 2 time points (at week 1 and week 4 after beginning of the treatment), along with self-reported abstinence confirmed by expired CO levels as well as scores of cigarette withdrawal.
 - 19 single nucleotide polymorphisms of the OCT2, *UGT2B7* and nuclear receptors that regulate the genes coding for *UGT2B7* or OCT2 transporters were genotyped using the Cardio-MetaboChip (Illumina).
 - Other clinical covariates were collected: body weight (BW), age, ethnicities, sex, height, creatinine clearance.
- Data analysis:**
- Pharmacokinetic-pharmacogenetic analysis: non-linear mixed effect modelling using NONMEM® v. 7.2.
 - Model-based simulations: prediction of varenicline exposure ($AUC_{0-24,SS}$) according to significant covariates (BW and genetic polymorphism in the *UGT2B7* gene) and comparison to the extreme values of individual $AUC_{0-24,SS}$ obtained across the clinical trials supporting varenicline development² (min=60, max =460 ng*hr/mL at steady-state for a dose of 1 mg b.i.d.).
 - Exposure-response analysis: associations between varenicline exposure (AUC of the latest q.d or b.i.d dose, cumulated AUC from the beginning of the treatment to the blood sample time (AUC_{cum}), maximal concentration (C_{max}), average concentration (C_{av}) and abstinence or withdrawal scores were evaluated by analysis of mean in R v.3.2.3).

Results

- A one-compartment model with first order absorption and elimination appropriately described varenicline concentrations.
- Varenicline population pharmacokinetic parameters are presented in Table 1.

Table 1: Final varenicline population pharmacokinetic parameter estimates and their bootstrap evaluations.

Parameter	Final population parameter		Bootstrap evaluation (n=2000 samples)	
	Estimate	RSE ^a (%)	Median	CI _{95%}
CL ₀ (l/h)	$8.5 \cdot (BW/70)^{0.75}$	4	$8.5 \cdot (BW/70)^{0.75}$	(7.9; 9.2)
$\theta^b_{UGT2B7 \text{ rs7439366 CC}}$ (%)	21	49	21	(0.4; 44)
V (l)	228	8	229	(192; 275)
k _a (h ⁻¹)	0.98	--	0.98	--
IIV ^c _{CL} (CV%)	19	22	18	(9; 26)
σ^d (CV%)	23	18	23	(19; 27)

CL₀, typical apparent clearance for *UGT2B7* rs7439366 TT or TC carrier, function of patients' body weight (BW); V, typical apparent volume of distribution; k_a, typical absorption rate constant.
^aRelative standard errors of the estimates (SE); ^bRelative deviation of CL due to *UGT2B7* rs7439366 CC carriers expressed as percentage; ^cInterpatient variability defined as CVs (%); ^dResidual inpatient variability expressed as CVs(%)

- Among the tested covariates:
 - Varenicline CL increased by 68% upon BW doubling (14% of the variability on CL explained)
 - UGT2B7* rs7439366 C/C carriers were found to have 21% higher CL than T/T and C/T carriers (9% of the variability on CL explained).
- Model-based simulations showed that all the individuals were within the targeted range of varenicline exposure except 0.6% and 3% of individuals in the low BW group (45 kg) carrying the CC/CT variant or the CC variant, respectively (Figure 2).
- No significant association was found between varenicline exposure and abstinence nor cigarette withdrawal scores.

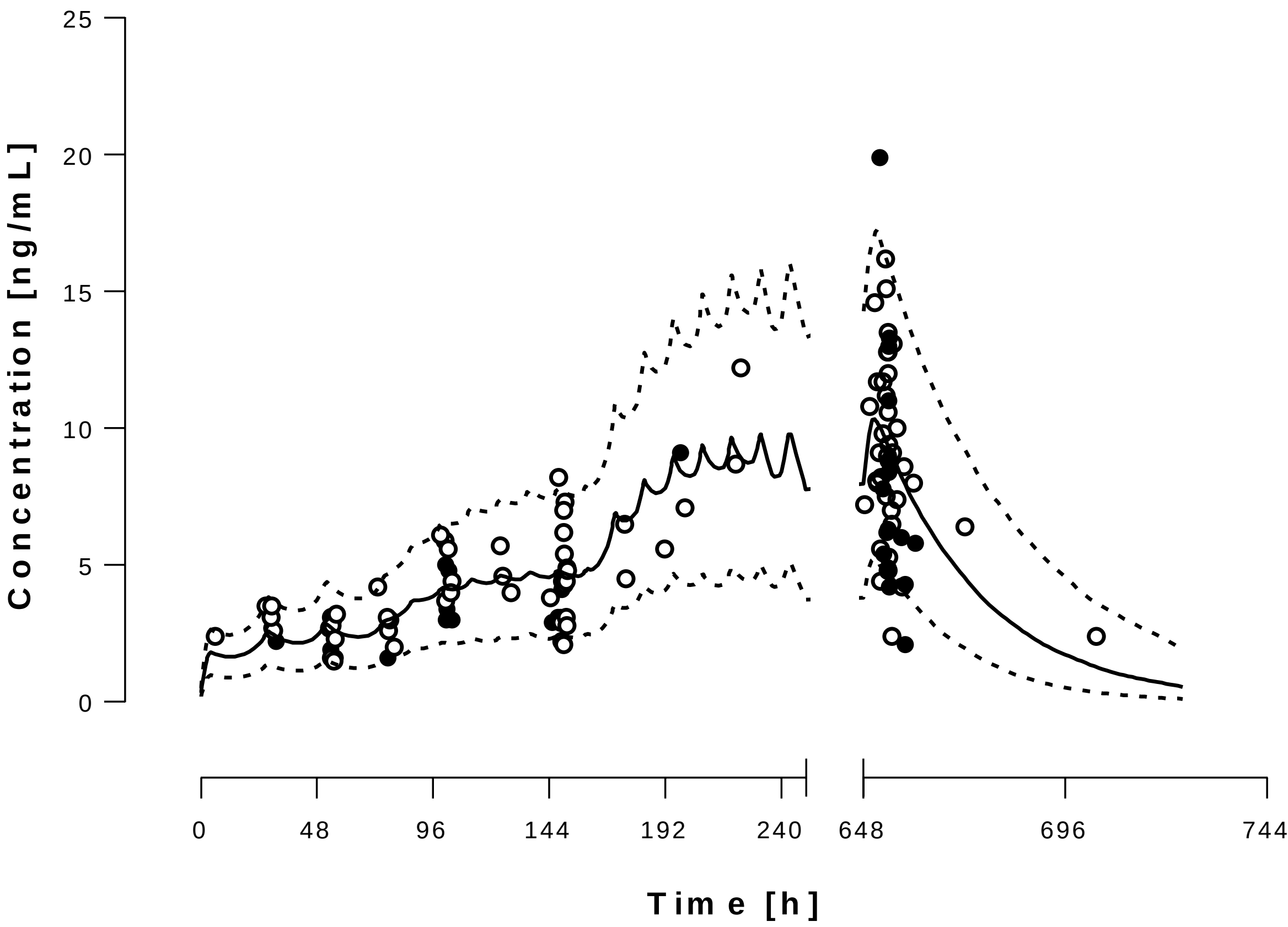


Figure 1: Observed dose-normalized varenicline plasma concentrations after administration of 0.5 mg q.d. during days 1-3, 0.5 mg b.i.d. during days 4-7 and 1 mg b.i.d. until 12 weeks, with mean population prediction (solid lines) and 95% prediction intervals (dotted lines) computed for a *UGT2B7* rs7439366 TT or TC carrier weighting 77 kg (mean population body weight). Empty and full circles represent respectively TT or TC and CC subjects.

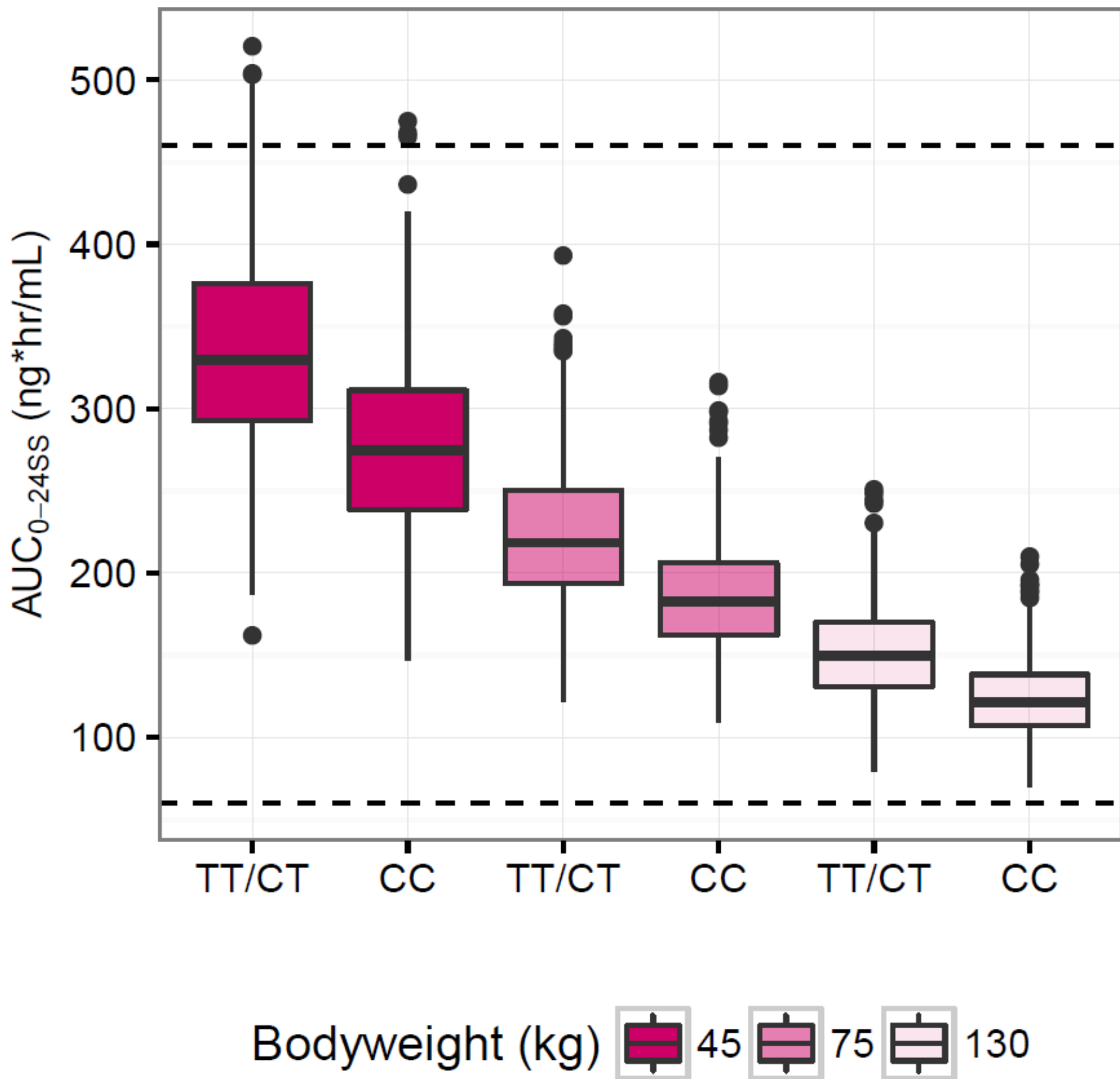


Figure 2: Distribution of the predicted area under the concentration-time curve simulated in 500 subjects per strata of bodyweight value and *UGT2B7* 802T>C genotype after administration of varenicline 1 mg b.i.d. Dashed lines represent the extreme values of individual $AUC_{0-24,SS}$ obtained during varenicline development².

Conclusions

- Body weight and a genetic polymorphism of *UGT2B7* significantly contribute to varenicline plasma concentrations variability.
- The threefold difference in varenicline exposure does not seem to be related to treatment success.

References

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- P Ravva, MR Gastonguay, JL French et al. Quantitative Assessment of Exposure-Response Relationships for the Efficacy and Tolerability of Varenicline for Smoking Cessation. Clin Pharmacol Ther. 2010 Mar;87(3):336-44.