# An exposure-response model relating nicotine plasma concentration to momentary craving across different nicotine replacement therapy formulations

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## Background and objectives

Tobacco use causes >7 million avoidable deaths yearly [1]. It is therefore vital to reduce its use. Nicotine replacement therapy (NRT) medications can facilitate smoking cessation [2] by reducing craving for nicotine. Our aim was to improve the understanding of and quantify the relationship between nicotine plasma concentrations and momentary craving. Additionally, since craving was assessed using two different scales (i.e. a 4-category scale and a 100-mm visual analogue scale (VAS) consisting of 101 categories), we also aimed to link results from both scales.

## Methods

Data were collected in 17 different studies and included four NRT formulations: mouth spray, lozenge, gum and patch. Subjects in the studies were instructed not to smoke. Existing formulation-specific population pharmacokinetic (PK) models and individual PK parameter estimates were used to obtain individual nicotine PK profiles.

NONMEM 7.3 with the Laplace approximation was used, and linear and non-linear direct and indirect-effect models were tested to relate nicotine plasma concentration to craving. The effect of released nicotine amount, predicted to be in the 'mouth', was also explored, to see if just tasting nicotine can already affect craving (reduction). Additionally, since tolerance to nicotine is known to develop (even in a single day) [2], different approaches of including the development of tolerance were investigated: model A (stepwise (0-1h, >1-2h, >2-4h, >4-8h, >8h) time-dependent $C_{50}$), and model B (tolerance compartment [3]) (Eqs. 1 and 2, respectively).

$$\hat{z} = BASE - \frac{E_{max} \cdot CONC}{CONC + C_{50}}, \qquad \text{Eq. 1}$$

$$\hat{z} = BASE - \frac{E_{max} \cdot CONC}{CONC + C_{50} \cdot \left(1 + \frac{CTOL}{C_{50,tol}}\right)}, \qquad \text{Eq. 2}$$

where *BASE* is baseline, $E_{max}$ is maximal effect, $C_{50}$ is the concentration at 50% maximal effect, *CONC* is the sum of nicotine plasma concentration and the scaled (by $\theta_{mouth}$) released nicotine amount in the 'mouth', *CTOL* is the amount in the tolerance 'effect compartment' [3], $C_{50,tol}$ is the concentration needed for 50% of tolerance to develop.

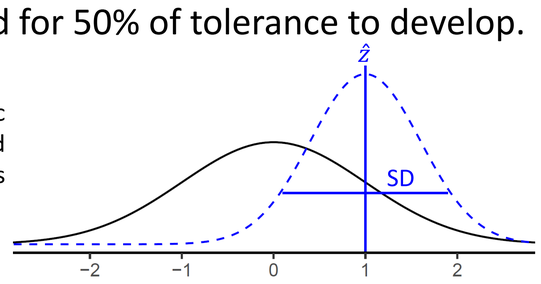



Figure 1 (right): Schematic representation of the bounded integer model with parameters $\hat{z}$ and SD.

To link the observations from the two scales, a joint model was developed, based on a bounded integer model [4, 5] (Figure 1), where a probit-based approach provides the probability of each observation from VAS. Probabilities for the scores from the 4-category scale were estimated as VAS cutoffs.

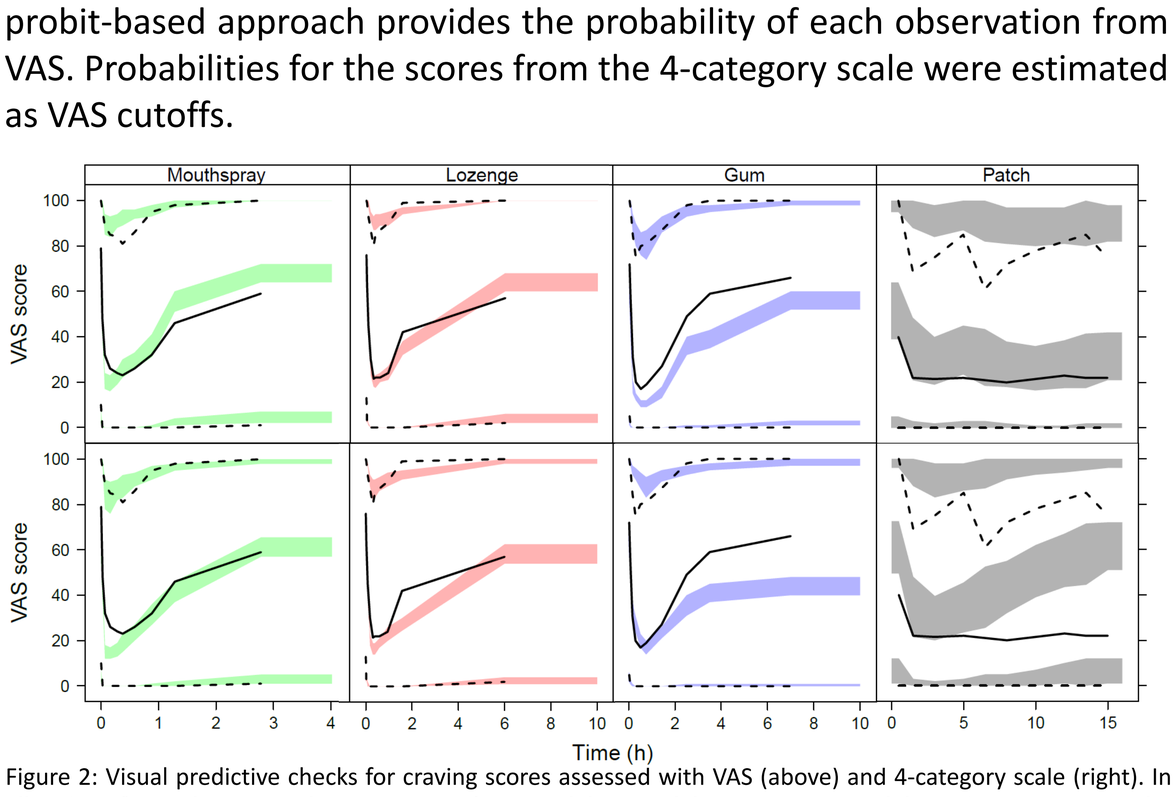



Figure 2: Visual predictive checks for craving scores assessed with VAS (above) and 4-category scale (right). In all pairs of panels top 4 plots correspond to model A, and bottom 4 to model B. Lines represent the observations (either the 2.5th, 50th and 97.5th percentiles (above) or proportions (right)) and the areas are the corresponding 95% confidence intervals from 1,000 simulations using both models' parameter estimates.

## Conclusions

- Two non-linear direct-effect pharmacokinetic-pharmacodynamic (PKPD) models with a distinct way to describe the development of tolerance were developed and related nicotine plasma concentrations to momentary craving from four different NRT formulations.
- A new methodology, the bounded integer model was for the first time applied to link observations from two separate PD endpoint scales.
- Future work will include assessing the influence of covariates (such as gender, body weight, markers of nicotine dependence).

## Results

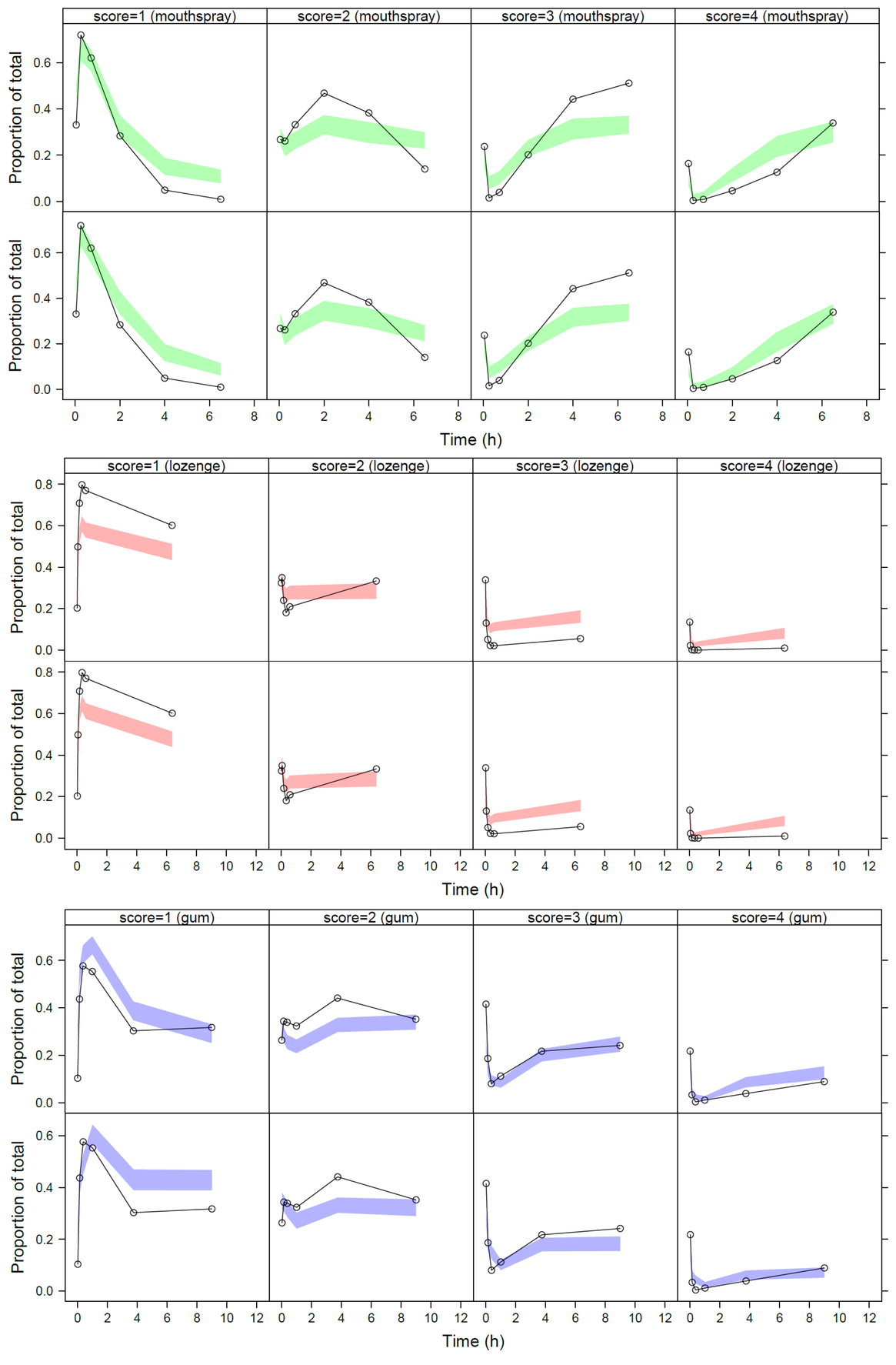
The data included 1,077 adult subjects smoking median (range) 20 (5-50) cigarettes per day for 12 (1-45) years. The subjects provided 40,347 momentary craving observations, the majority (25,922) measured with the VAS.

Results of the two models are presented in Table 1 and Figure 2.

Table 1: Comparison of results[a] from model A and model B.

| | OFV | Score=1 | Score=2 | Score=3 | Score=4 | $E_{max}$ | $C_{50}$ | Baseline (IIV) | $\theta_{mouth}$ | SD |
|---|---|---|---|---|---|---|---|---|---|---|
| Model A | 240724 | 0-32[b] | 33-71[b] | 72-94[b] | 95-100[b] | 3.32 | 4.42, 6.99, 10.5, 16.9, 14.4 | 1.11 (0.664) | 3.72 | 0.705 |
| Model B[c] | 242041 | 0-35[b] | 36-74[b] | 75-95[b] | 96-100[b] | 5.21 | 0.072 | 3.61 (0.622) | 1.11 | 0.726 |

[a] all relative standard errors were ≤11% (except $C_{50}$ (35%) and $C_{50,tol}$ (33%) in model B), [b] what a score from the 4-category scale was estimated to represent on the VAS, [c] $C_{50,tol}$ was estimated as 0.13 and KT0 as 0.194. OFV is the objective function value. IIV is the interindividual variability on the variance scale.

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**Disclosures**: EG, MCK and MOK declare no conflicts of interest; AH, JJPR, ÅW, PS and AV are (former) employees of subsidiary companies of Johnson & Johnson.

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