

Quantification of Metabolite Contribution to Esketamine Subjective Effects after Oral and Intravenous Administration in Healthy Volunteers

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INTRODUCTION

Oral (PO) esketamine administration is more clinically feasible as antidepressant treatment compared to intravenous (IV) or nasal administration

Extensive oral first-pass metabolism results in low esketamine concentrations but high metabolite exposure, including esnorketamine [1,2]

To what extent the parent and pharmacologically active metabolite each contribute to the antidepressant effects remains to be determined

Aim: to quantify the PK/PD relationship of esketamine and potential contribution of esnorketamine as measured on the visual analogue scale (VAS) 'Feeling High' in healthy volunteers receiving both PO and IV esketamine.

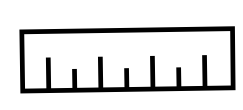
METHODS

Data

Placebo controlled cross-over clinical trial

17 healthy volunteers

0.4 mg/kg IV in 40 min (t: 0 min)
0.2 mg/kg (t:+15 min)
0.45 mg/kg (t:+15 min)

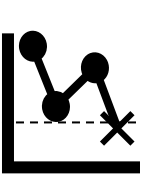


VAS

'Feeling High'

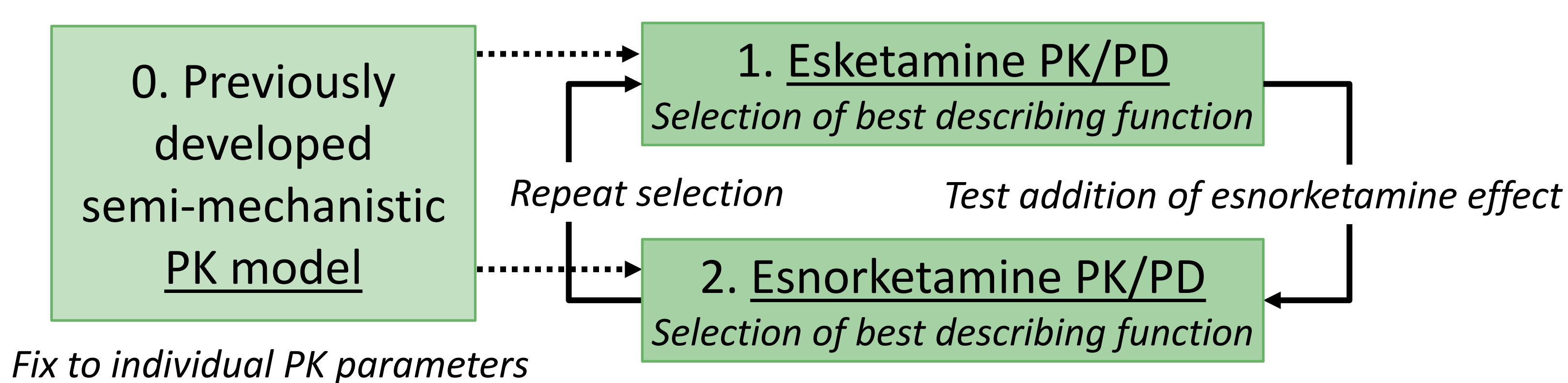


pre-dose, 31 m, 1h 10m, 1h 33m, 2h 13m, 4h 13m, 6h 13m, 25h 40m, 2w



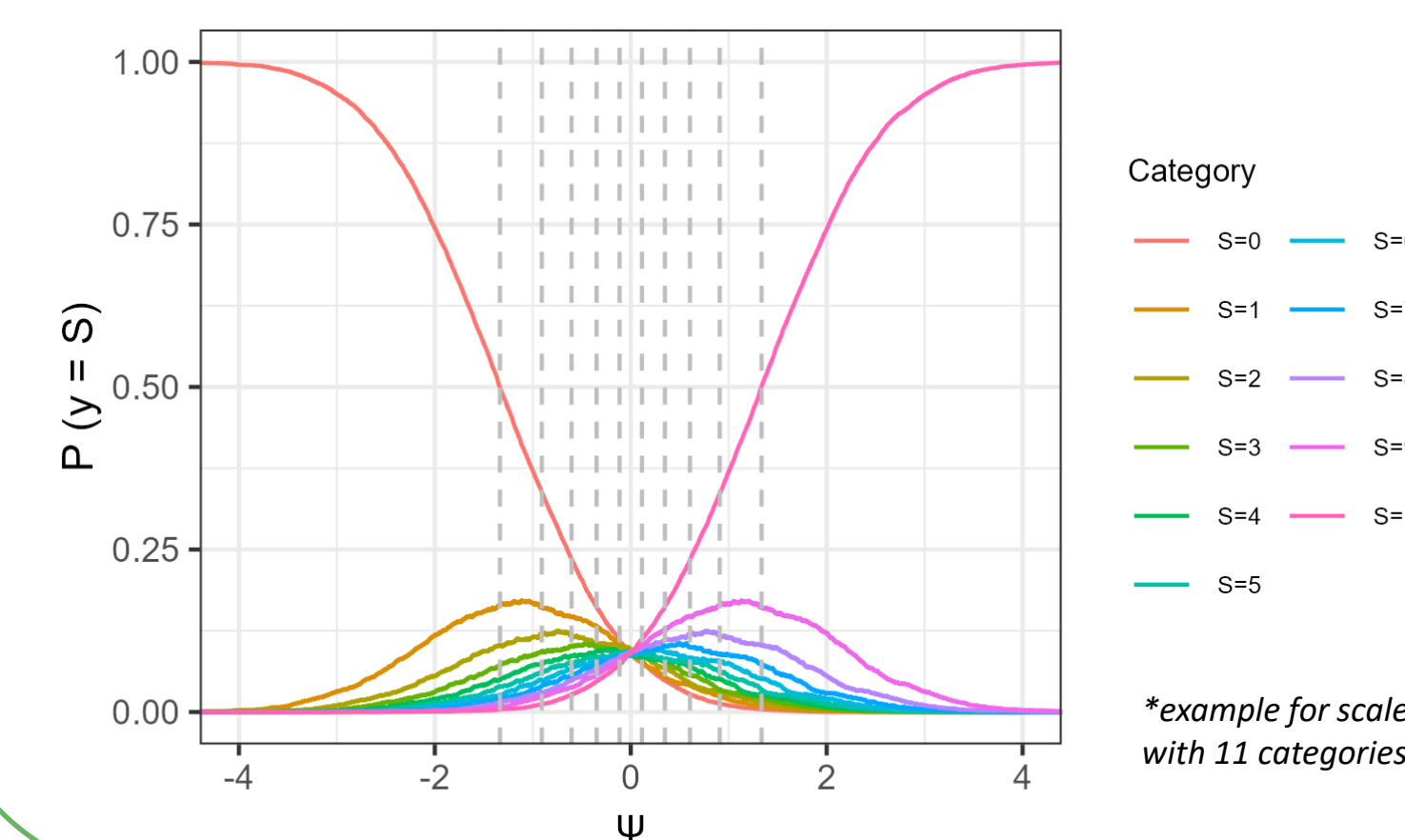
374 post-dose samples, 75% at value of 0

Model development



Bounded Integer modeling approach:

A) Link probability for certain VAS category (discrete) to underlying latent variable ϕ (continuous)



B) Test PK/PD relationship where the change in ϕ is linked to drug concentration

Tested PK/PD relationships

Linear: $\phi = \text{base} + \text{slope} * C_k$

Exponential: $\phi = \text{base} + \text{slope}^{C_k}$

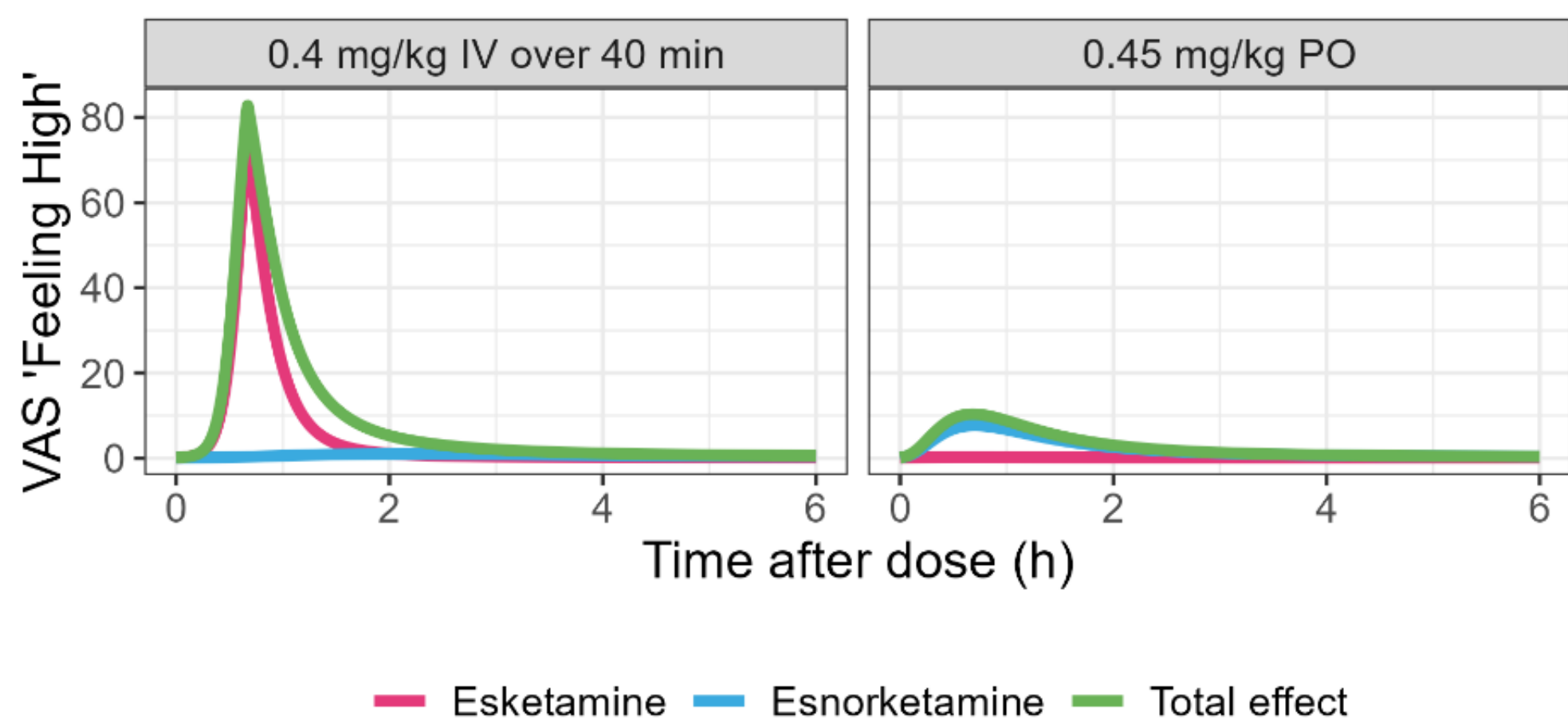
Power: $\phi = \text{base} + \left(\frac{C_k}{\text{slope}}\right)^{\text{power}}$

RESULTS

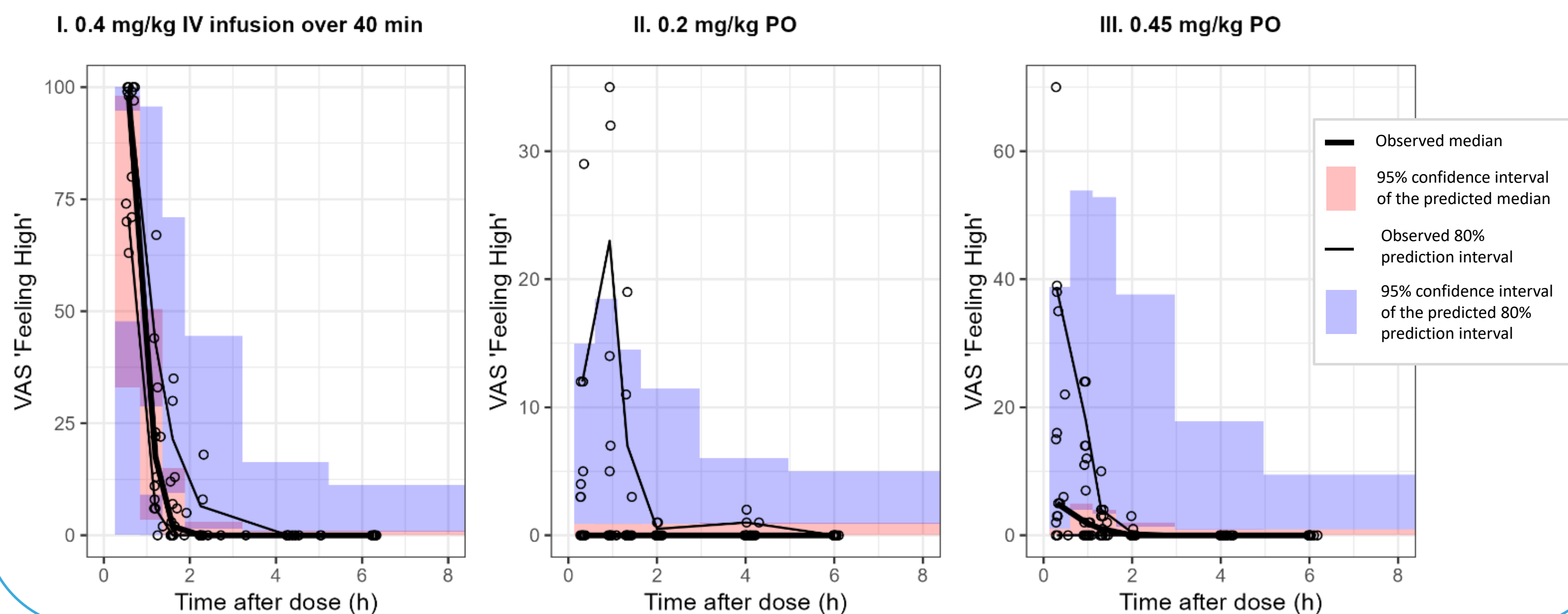
Addition of esnorketamine effect was significant during model development

Parameter	Estimate (RSE%)
Baseline (ϕ)	-5.47 (5.5)
Corrected for esketamine exponential base of 1	-4.47
Standard deviation (ϕ)	1.15 (8.4)
Esketamine exponential slope	1.013(3.1)
Esnorketamine linear slope ($\phi \cdot (\text{ng/mL})^{-1}$)	0.019 (17.1)
Inter-individual variability baseline (Var)	0.38 (48.5)

Esketamine drives IV effects, but esnorketamine drives PO effects



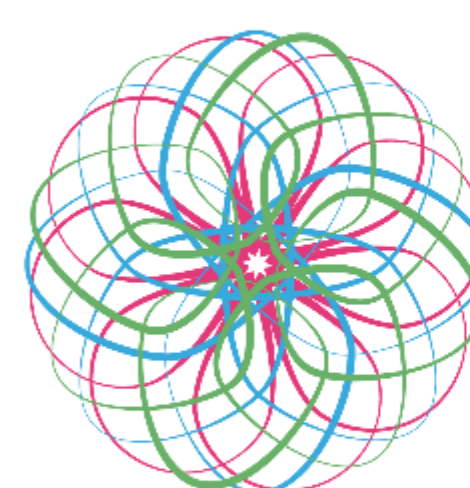
Accurate prediction of IV effects, but underprediction of early effects especially for PO dosing



CONCLUSION

- VAS 'Feeling High' effects attributed to both esketamine and esnorketamine could be quantified.
- Esketamine drives effects observed after IV dosing, while esnorketamine drives effects after PO dosing.
- High variability and underpredicted early effects indicates the esnorketamine contribution may be over-estimated. It could represent other drivers, such as other metabolites or anticipation/placebo effects.
- These results may inform study designs of future clinical trials investigating PO esketamine or administration of newly developed es(nor)ketamine analogues.

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