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Introduction

- Clozapine is the gold-standard treatment for treatment-resistant schizophrenia (TRS) but has a narrow therapeutic window and variable pharmacokinetics (PK)^[1-3].
- Therapeutic drug monitoring (TDM) in plasma does not reflect clozapine concentrations at its site of action in the brain^[4].
- Direct measurement of unbound clozapine in the brain extracellular fluid (brainECF) in humans is ethically constrained.
- Existing LeiCNS-PK models simulate CNS PK but previously lacked features for active transport and lipid accumulation^[5].
- This study develops and validates a mechanistic PBPK model to predict clozapine brainECF PK and/or receptor occupancy (RO) in rats and humans.

Aims

- Extending the CNS PBPK model with:
 - Active influx transport across the blood-brain barrier (BBB)
 - Accumulation in neutral lipids
 - Brain metabolism processes

And to translate and apply this LeiCNS-PK3.6 model to human data for the prediction of clozapine PK and dopamine D2 RO.

Results

- LeiCNS-PK3.6 has improved brainECF PK predictions vs. previous versions (lower SMAPE, AAFE, RA).
- In rats, incorporation of brain metabolism, active transport, and lipid accumulation improved C_{max} and T_{max} alignment with observed data.

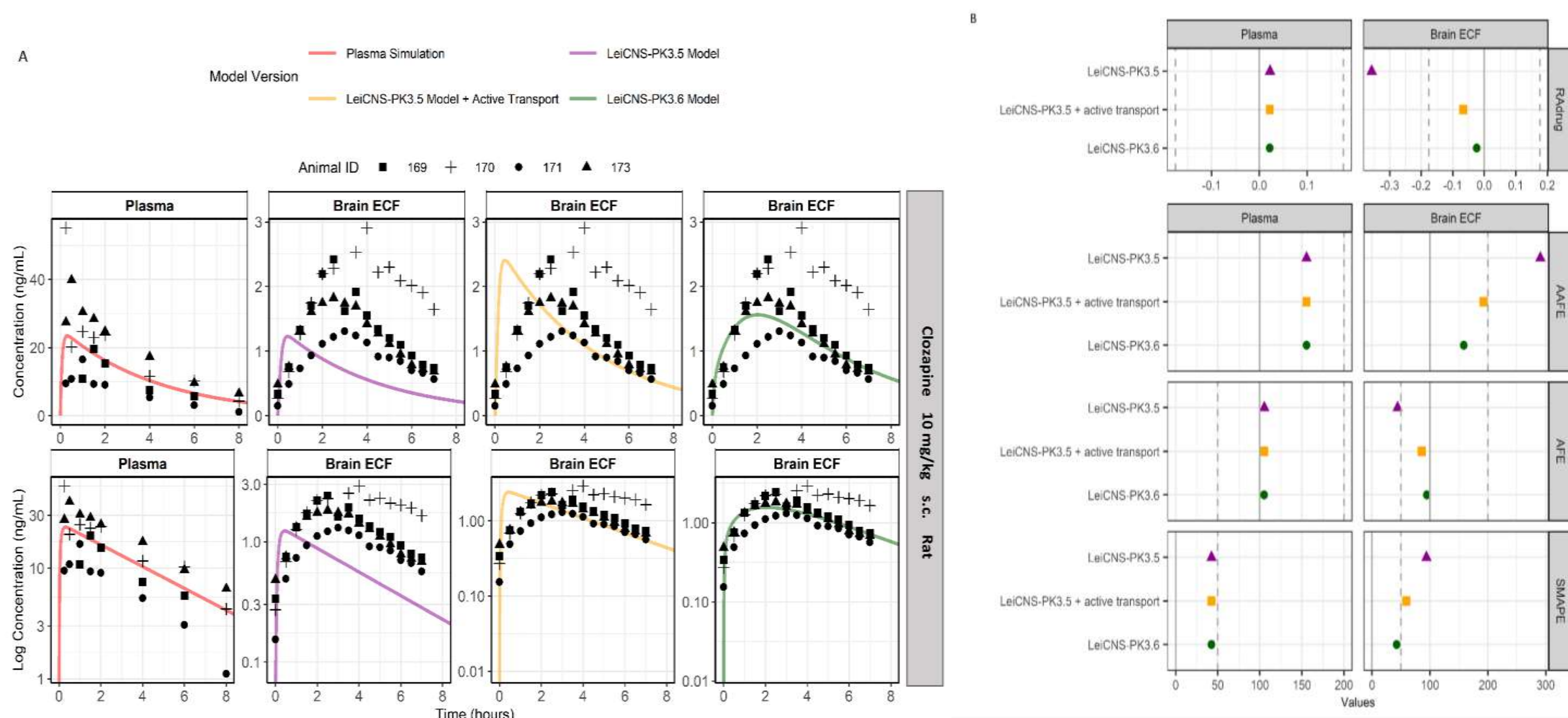


Fig 2. Rat brainECF PK predictions (left) & different model evaluations (right)

- Predicted human brainECF PK matches expected therapeutic ranges.

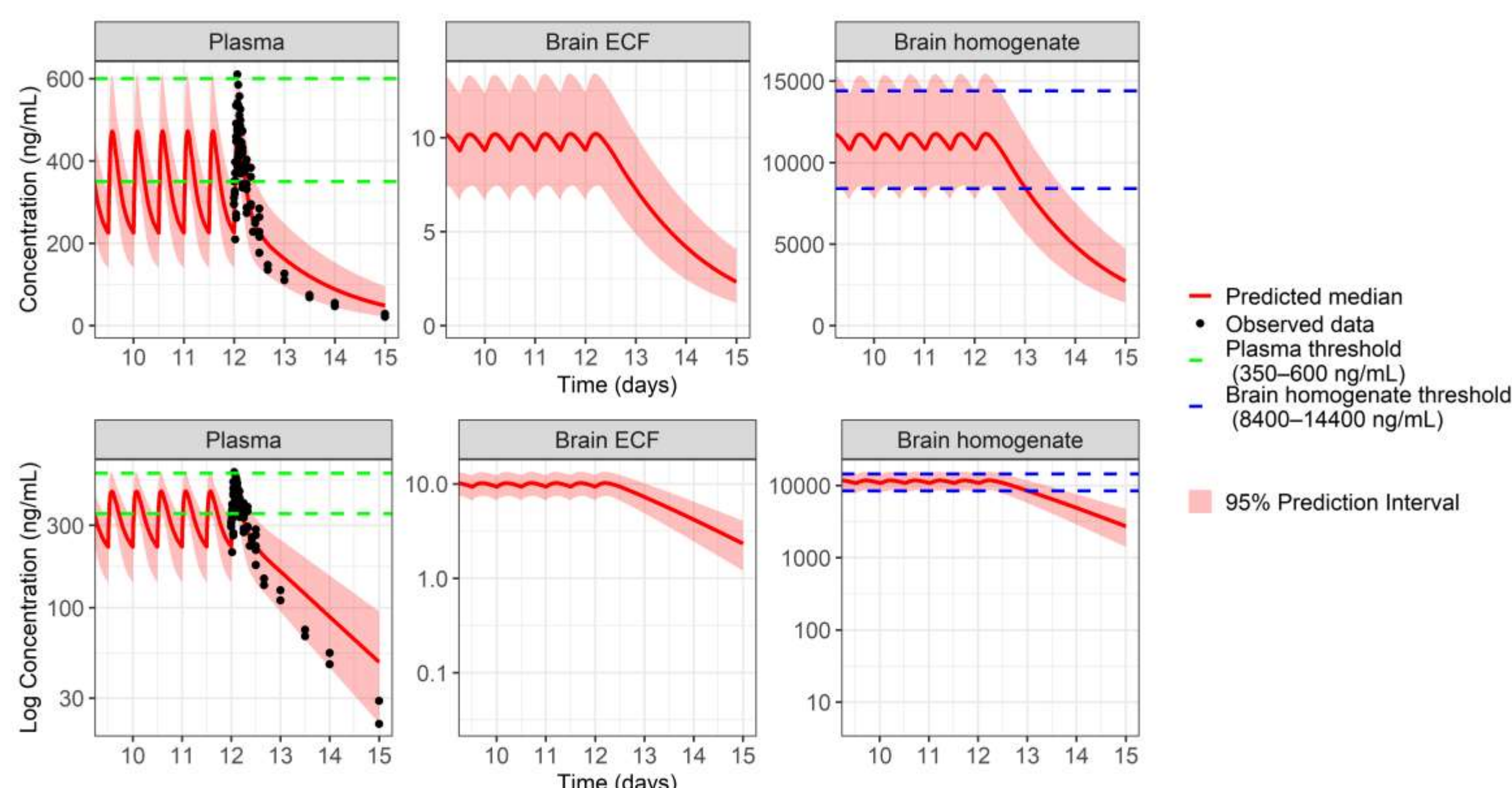


Fig 3. Human plasma & brainECF PK profiles with 95% prediction interval.

References

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Methods

- Extended the LeiCNS-PK3.5^[5] model with equations for active BBB influx and presence of neutral lipids

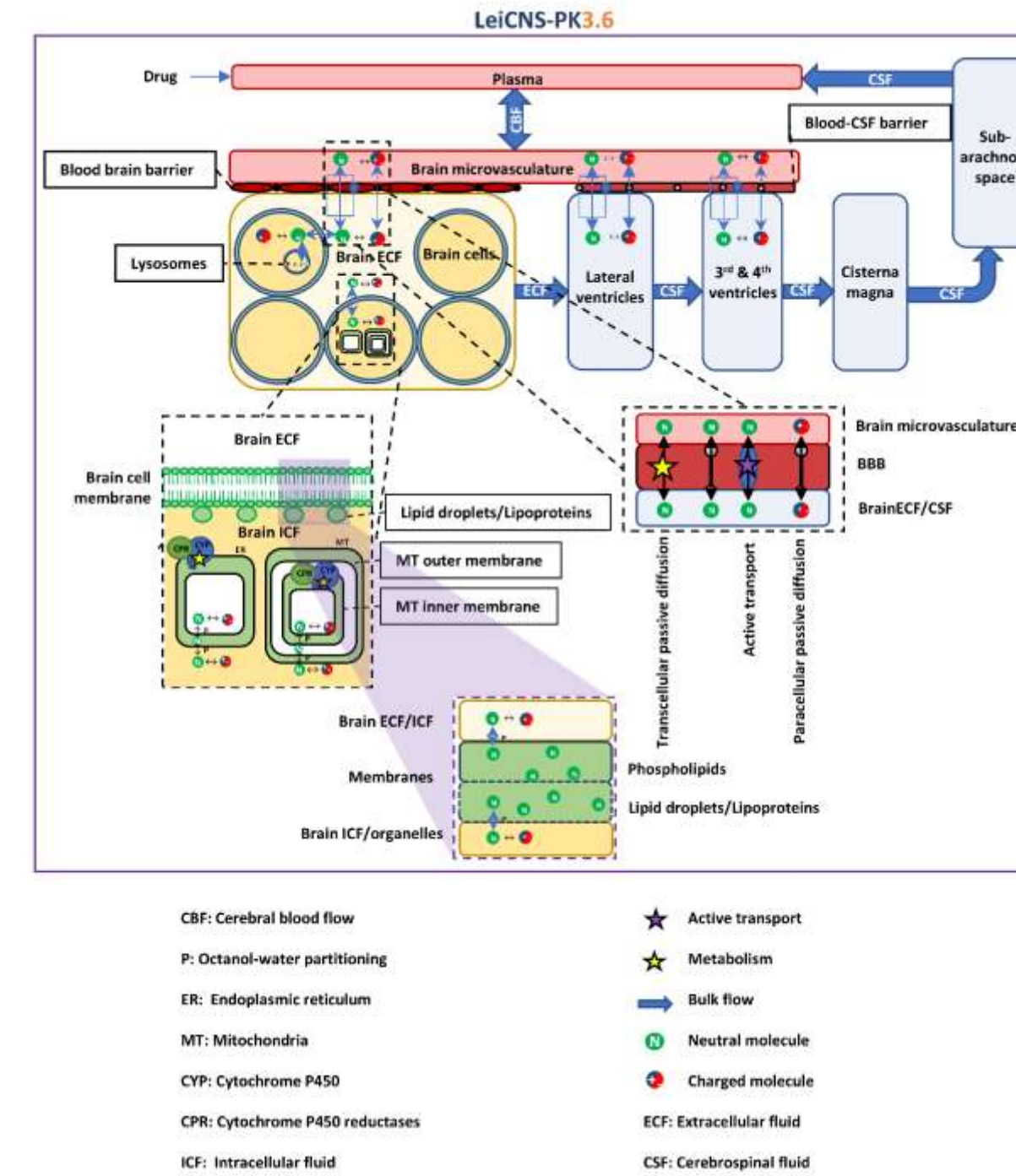


Fig 1. LeiCNS-PK3.6 Model Structure

- Used in vitro–in vivo extrapolation (IVIVE) to parameterize active transport and brain metabolism kinetics.
- Validated model using rat plasma and brainECF PK data^[6].
- Translated model to humans by adjusting physiological and plasma PK parameters.
- Predicted D2 RO in humans using kinetic receptor-ligand binding equations and clinical PET data^[7, 8].

- D2 RO predictions aligned with clinical PET data for 10/17 patients; adjustments (e.g., CYP1A2 polymorphisms, smoking) improved accuracy in others.
- Demonstrated feasibility and translatability of the model across species.

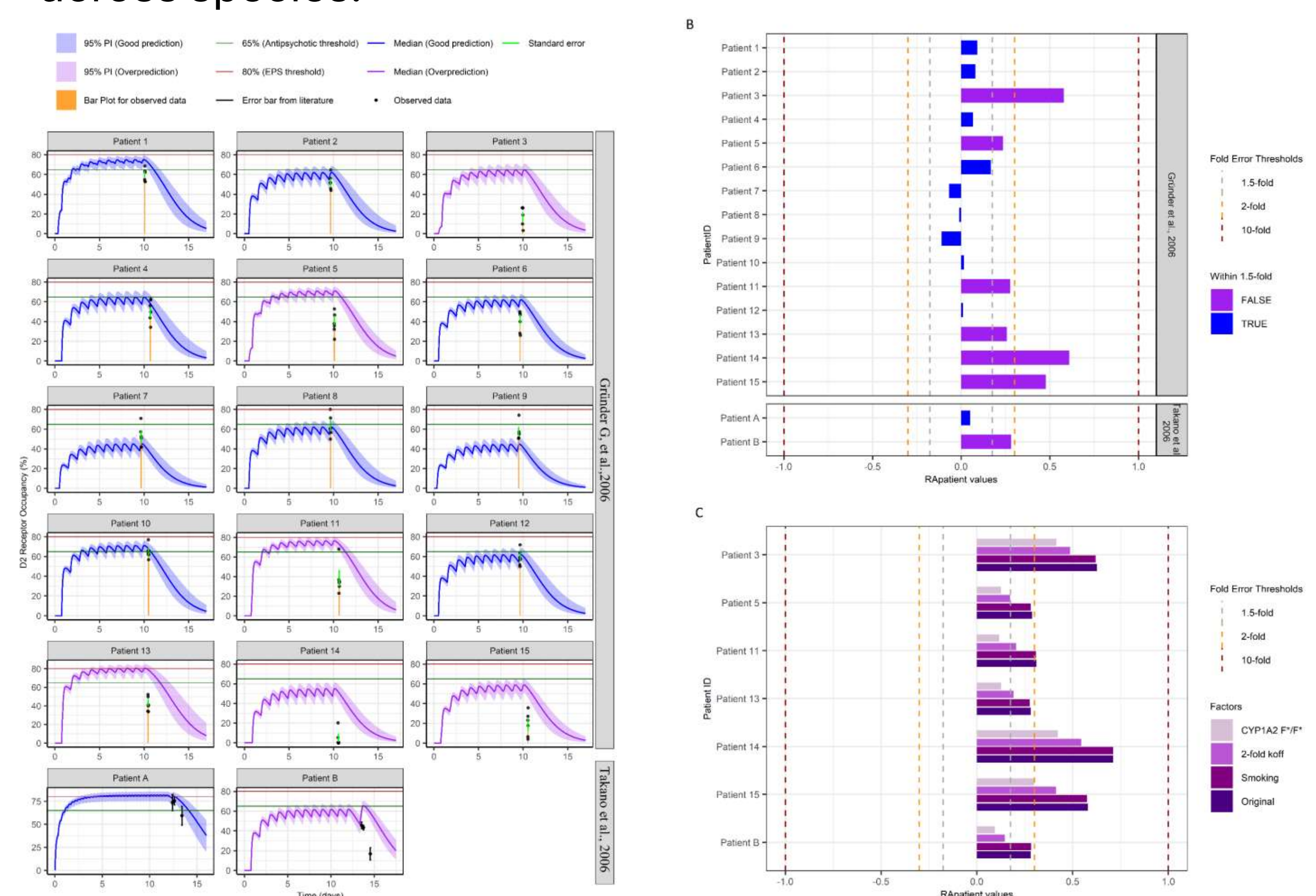


Fig 4. Predicted vs. observed D2 RO across 17 patients

Conclusions

- The LeiCNS-PK3.6 model effectively predicts clozapine brainECF PK and D2 receptor occupancy
- Active influx, brain metabolism, and lipid accumulation are essential for accurate CNS PK modeling of clozapine. PBPK modeling can complement sparse clinical data and support individualized dosing strategies
- The framework aids mechanistic understanding of inter-individual variability in CNS drug exposure