

# CYP2D6 Phenotype as a Predictor of Adverse Drug Reactions in Patients Treated with Trazodone: Insights from an Observational Pharmacogenetic Study

Christian D. Krieg<sup>1</sup>, Florine M. Wiss<sup>1,2</sup>, Samuel S. Allemann<sup>1</sup>, Henriette E. Meyer zu Schwabedissen<sup>3</sup>, and Markus L. Lampert<sup>1,2</sup>

<sup>1</sup> Pharmaceutical Care Research Group, University of Basel, Switzerland

<sup>2</sup> Institute of Hospital Pharmacy, Solothurner Spitäler, Olten, Switzerland

<sup>3</sup> Biopharmacy, University of Basel, Switzerland

## Background & Objectives

### Pharmacogenetic (PGx) panel testing in the field of depression:

- ✓ can lead to more effective antidepressant therapy [1]
- ✓ can lead to less adverse drug reactions (ADRs) [2]
- ✓ can be cost saving [3]

### But for trazodone:

- ∅ no PGx dosing guidelines exist
- ∅ only little PGx research exist
- trazodone is metabolized by CYP3A to meta-chlorophenylpiperazine (mCPP) [4] (fig. 1)
- mCPP is an active metabolite associated with many ADRs [5]
- mCPP is inactivated by CYP2D6 [6] (fig. 1)
- it's unknown whether mCPP is a Pgp-substrate

### How can we use PGx information in the context of trazodone?

Are there associations between pharmacogenetic variants in **CYP3A5**, **CYP2D6**, and **ABCB1** and the occurrence of **ADRs** during trazodone treatment?

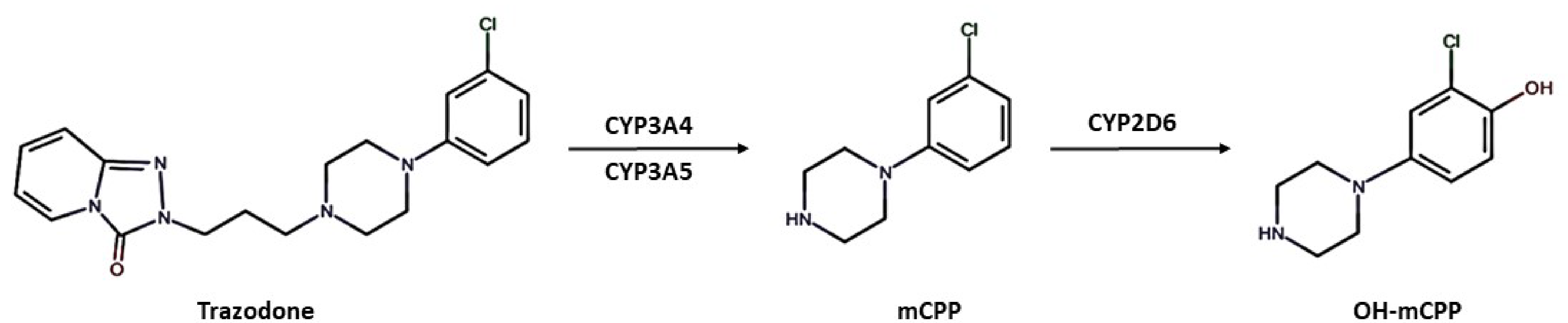


Figure 1: Hepatic metabolism of trazodone and mCPP

## Methods

### Retrospective exploratory association study:

- Data extraction from two ongoing pharmacogenetic studies

### Extracted data:

- Patient (sex, age)
- Trazodone (dose, ADR)
- Genetics (CYP2D6 and CYP3A5 phenotype, ABCB1 genotype)
- Co-medication (CYP2D6, CYP3A, and PGP inhibitors and inducers)
- Drug-drug-gene interactions (phenoconversion)
- Serum level measurements (trazodone, mCPP)

### Statistical analysis:

- $\chi^2$ -tests
- Logistic regression analysis (variables: CYP2D6 and CYP3A5 phenotype, trazodone dose, sex)

## Conclusion

- ✓ mCPP may be responsible for a significant portion of trazodone ADRs

- ✓ ADRs occur more frequently in CYP2D6 PMs

→ In clinical practice, CYP2D6 genotyping before prescribing trazodone might contribute to reduce the occurrence of ADRs

## Results

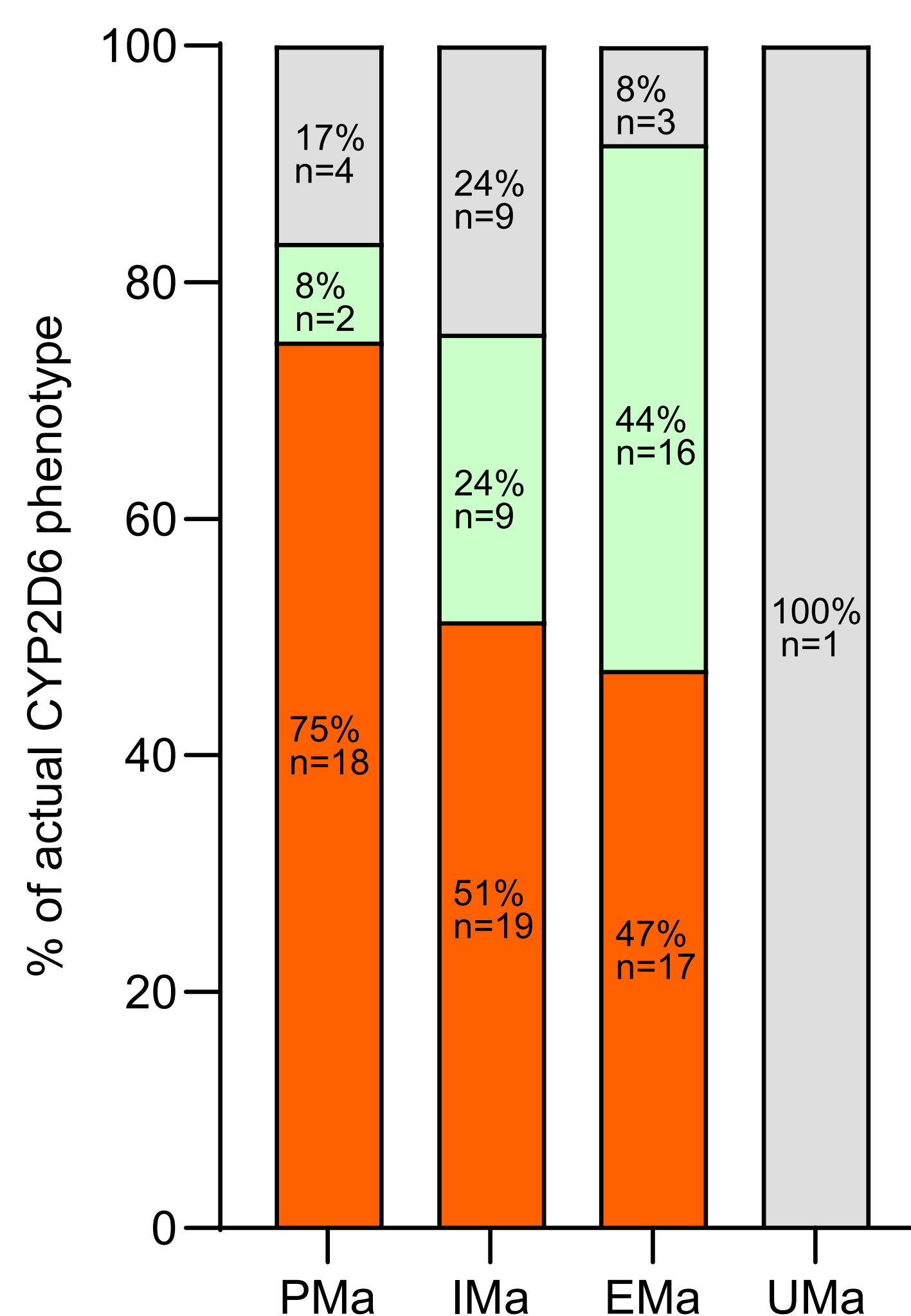


Figure 2: Proportion of patients with/without adverse drug reaction according to phenoconverted CYP2D6 phenotype, N = 98

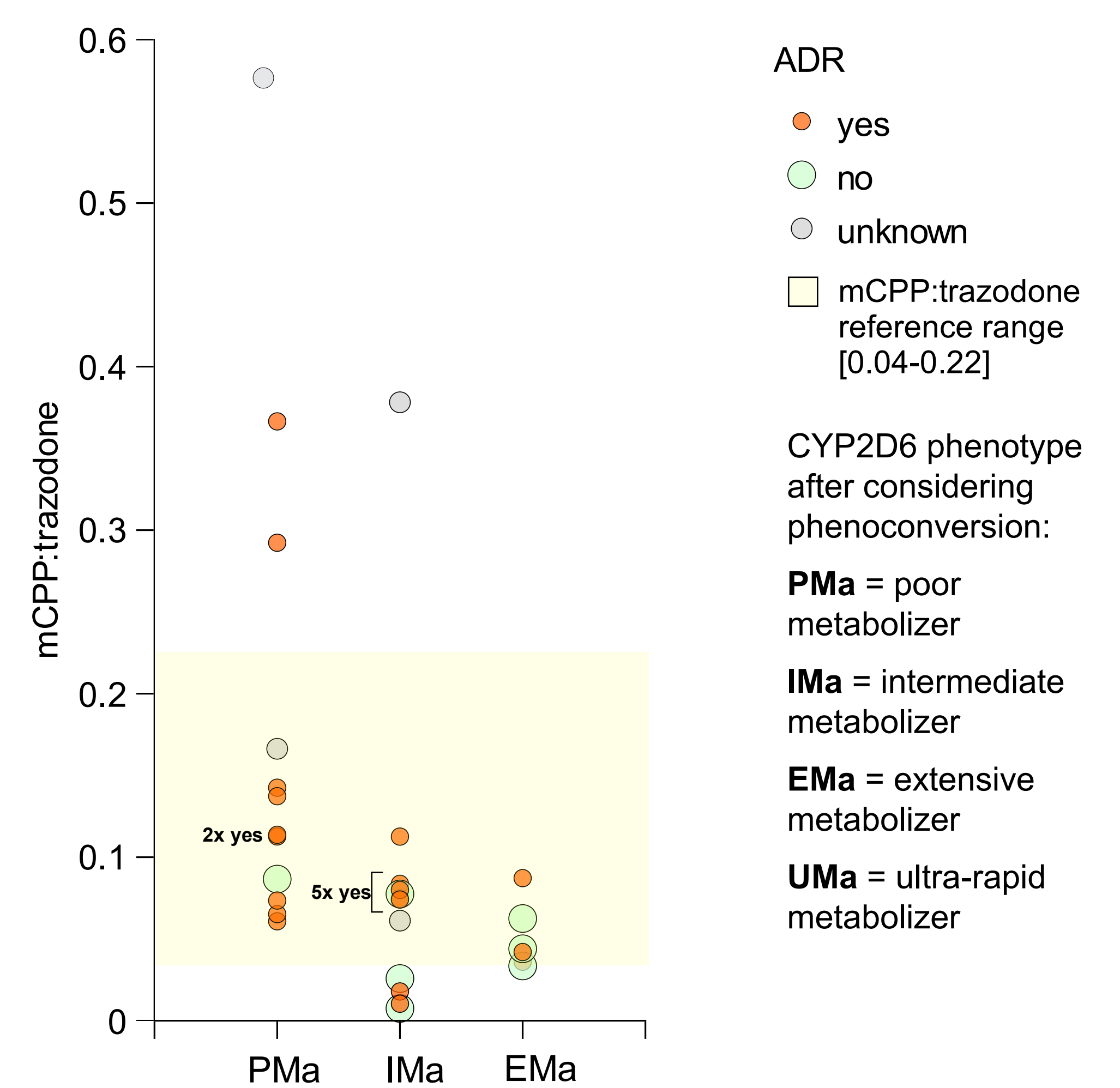


Figure 3: ratio of mCPP to trazodone serum level measurements with/without adverse drug reaction according to phenoconverted CYP2D6 phenotype, N = 31

- 98 patients taking trazodone
- more ADRs for CYP2D6 PMs compared to EMs ( $\phi = 0.394$ ,  $p = 0.004$ ) (fig. 2)
- no associations were found for genetic variants in CYP3A5 and ABCB1
- **CYP2D6 PMs were 9 times more likely to develop ADRs compared to EMs after adjusting for CYP3A5 phenotype, trazodone dose, and sex (OR 8.96; 95% CI = 1.67-48.08)**
- frequent ADRs: hyperhidrosis, tachycardia, tremor and anxiety
- 31 serum level measurements (fig. 3)
- higher mCPP:trazodone ratios for CYP2D6 PMs compared to EMs

### Literature:

- [1] Milosavljević F, et al. Eur Neuropsychopharmacol. 2024;81:43-52.
- [2] Skokou M, et al. eBioMedicine. 2024;101.
- [3] Shahzad G, et al. CMAJ. 2023; 14;195:E1499-1508.
- [4] Rotzinger S, et al. Drug Metab Dispos. 1998;26(6):572-575.
- [5] Kast RE. Acta Neuropsychiatr. 2007;19(3):220-221.
- [6] Rotzinger S, et al. Biol Psychiatry. 1998;44(11):1185-1191.



### Corresponding author

florine.wiss@spital.so.ch  
Institute of Hospital Pharmacy, Solothurner Spitäler,  
Olten, Switzerland  
Pharmaceutical Care Research Group, University of  
Basel, Switzerland